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A COMPREHENSIVE REVIEW OF BREAST FIBROADENOMA: PATHOPHYSIOLOGY, DIAGNOSIS AND TREATMENT

KHAN A[1], HAROUN BARAKA BB[2*], PANDEY A[3], KANNUR S[4] AND PORWAL M[5]

[1, 2*,3,4,5]Department of Pharmacology, KLE College of Pharmacy, Rajajinagar, Bangalore-560010, Karnataka, India

***Corresponding Author: Mr. Babiker Bashir Haroun Baraka: E Mail: bashirbaraka118@gmail.com**

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ABSTRACT

Overview of this study, as mentioned the outcome like diagnosis, treatment (pharmacological and non-pharmacological), and clear images to represent the types of fibroadenoma was a challenge. The previous study has described diagnosis and treatment, but our study mainly focuses on the types of diagnosis, pharmacological and non pharmacological treatments of fibroadenoma. Fibroadenoma a non cancerous breast tumour mostly found in women, but the frequency of fibroadenoma occurring in men is rare. A solid rubbery mass in nature and may vary in size and location. Mainly caused due to hormonal changes and gene mutation. The tumour may be a single or multiple masses present in one breast or both the breasts, strong family history leads to multiple tumours in the breast and mostly found in upper lateral quadrant. There are various ways to diagnose fibroadenoma namely: physical examination, clinical examination, imaging techniques and biopsy which give us the accurate diagnosis of the tumour. Based on the diagnosis report pharmacologically it can be treated via surgery and based on the histopathological assessment and nature of the tumour the procedure is decided. This article provides an overview about fibroadenoma, its types, symptoms, pathogenesis, diagnosis, treatment and management.

Keywords: fibroadenoma, breast, pathogenesis, diagnosis and treatments

INTRODUCTION

Fibroadenoma is an unusual but a short time appearance of solid tissue mass in the breast. Humans tend to undergo endocrinological changes that influence the normal development of the breast until puberty. But in some cases, fluctuations in the hormones results in fibroadenoma **[1]**. Fibroadenoma is a fibroepithelial tumour that is unilateral, painless and benign (non-cancerous) in nature, most commonly found in adolescent women and can be diagnosed at any age. Once formed they are marble-like mass in nature that consist of both epithelial and stromal tissues which is located under the skin of the breast. These rubbery masses are firm in nature and often vary in size **[2, 3]**. The prevalence rate of fibroadenoma is found to be 10% of the total female population worldwide **[3]**. The main aetiology is unspecified, but the hormone-dependent behaviour of this tumour gives the impression that unknown endocrine pathways can be the utmost probable cause of the benign lesions; that usually develops during adolescence and at young age that is simultaneous with breast development **[4]**. As it is hormone-dependent, the dimensions of the tumour tend to increase during hormonally active periods and later on decrease at the time of perimenopausal period. Apart from hormonal causes even body weight, race also are the risk factors **[5]**. Fibroadenomas tend to be too small to be felt, but some can be several inches huge. It can be diagnosed through clinical assessment which includes physical examination, patient history and imaging studies such as mammogram or ultrasound which provides vital information for initial evaluation **[6, 7]**. Accurate diagnosis and effective management of breast fibroadenomas rely on combining the clinical and pathological reports. Majority number of fibroadenomas need not be treated. But might be recommended to remove if they keep growing or change the shape of breast **[6, 7]**. Development of a carcinoma in a fibroadenoma is very rare unless there isn't a strong family history of breast tumours or breast cancer it is diagnosed on post-operative examination of excision biopsy **[8]**. Occurrence of breast disorders in puberty is mostly benign and rare. But still, they end up influencing the quality life of teenagers. Such disorders cause various abnormalities and irregularity in the breast development, cause infections and abscesses, nipple discharge, mastodynia and various other benign diseases that occur in the form of breast masses **[9]**. The previous study has shown the narrative review of fibroadenoma and all the results are concluded in this review. The recent review mainly focusing on types of diagnosis, pharmacological and non-

pharmacological treatment with explanation and images.

Types of fibroadenoma

1. **Simple fibroadenoma:** Simple fibroadenoma has very basic features such as oval or round in shape, the tumour maybe is hyperdense or isodense. There is no stromal atypia and no sparse mitotic activity **[10]**.

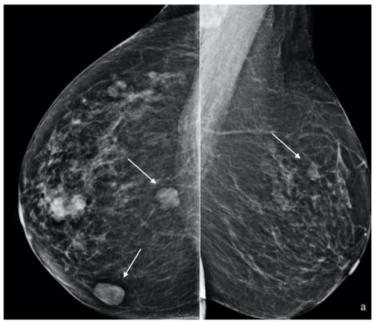

Figure 1: **Simple fibroadenoma**

2. **Complex fibroadenoma**

A variant of fibroadenoma it consists of more complex pathological features like a cyst >3mm, epithelial calcifications, sclerosis, adenosis. Presence of complex fibroadenoma increases the risk of breast cancer **[10]**.

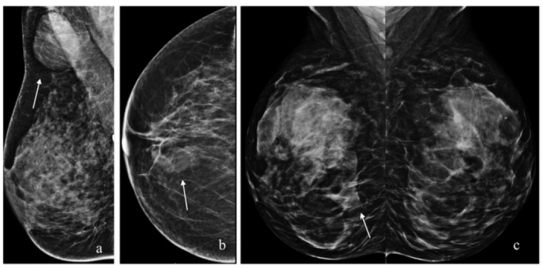

Figure 2: Complex fibroadenoma

3. **Juvenile fibroadenoma**

Juvenile fibroadenomas are quite rare, seen in adolescence (10-18yrs). It is restricted to a particular area, painless and grows rapidly which causes breast enlargement or asymmetry **[10]**.

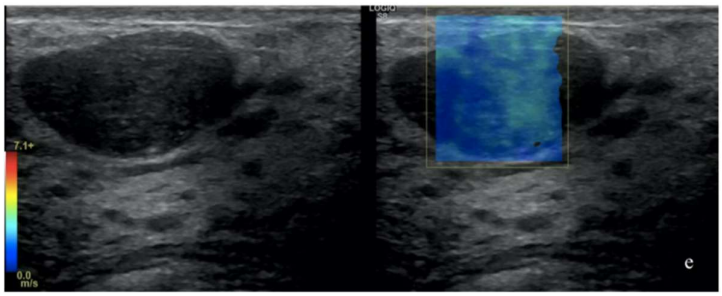

Figure 3: Juvenile fibroadenoma

4. Giant fibroadenoma

Giant fibroadenoma is a very rare variant. They are large >5cm often observed during the premenopausal period. Juvenile fibroadenoma becomes giant fibroadenoma due to rapid growth and the rapid growth causes breast enlargement and asymmetry **[10]**.

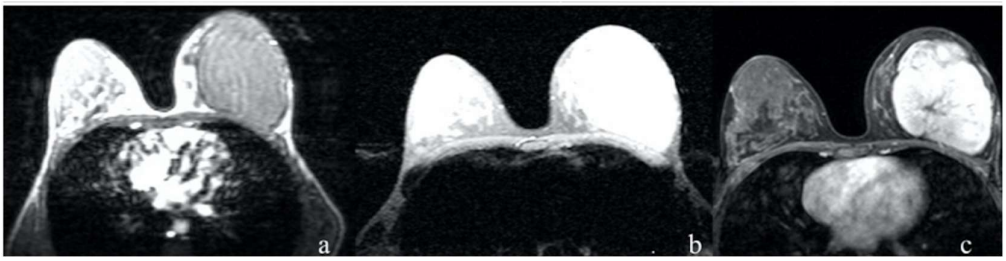

Figure 4: Giant fibroadenoma

5. Myxoid fibroadenoma

Myxoid fibroadenoma consists of huge amount of myxoid matrix content and hypocellular stromal content. They are non-cancerous tumour, develop occasionally and is related to carney complex (spotty skin pigmentation) **[10]**.

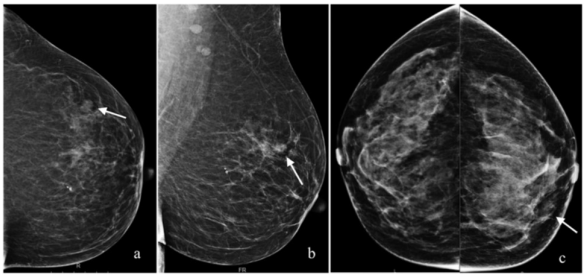

Figure 5: myxoid fibroadenoma

6. Cellular fibroadenoma

Cellular fibroadenoma has high stromal cellularity and lack of stromal atypia, it is found in young women and cellularity reduces with age **[10]**.

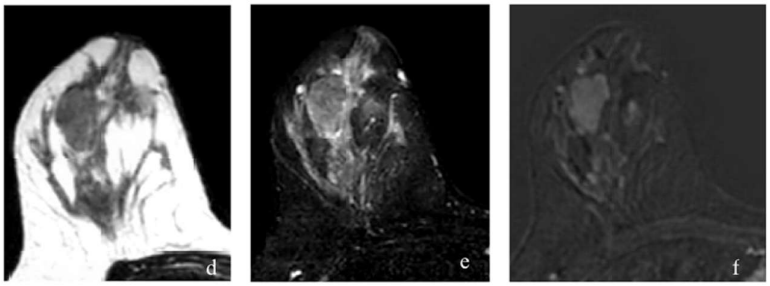

Figure 6: cellular fibroadenoma

Aetiology

Hormonal: Fibroadenoma is mainly caused due to more sensitivity of the breast tissue, due to increase in estrogen a female reproductive hormone. It tends to grow during pregnancy and shrink at the time of menopause **[2]**. Firstly, pregnenolone is synthesised from cholesterol, it is catalysed

by the cytochrome P450 side-chain cleavage enzyme (P450scc), the synthesised pregnenolone is then converted to progesterone by 3 b-hydroxysteroid dehydrogenase (3 b-HSD) in both theca and granulosa cells. Progesterone is transformed to androgens by cytochrome P450 17a-hydroxylase (P45017a) and 17 b-hydroxysteroid dehydrogenase (17 b-HSD), in the thecal cell and androgen is converted to estrogen in granulosa cell with the help of aromatase enzyme. Furthermore estrogen is synthesised in the theca cells i.e. ovary, placenta and corpus luteum. It is even synthesised by non-gonad organs i.e. brain, skin, heart and liver. And when this level of estrogen increases in the body it causes sensitivity in the breast tissue which leads to fibroadenoma **[12]**. It is more often found in younger women and it may shrink or regrow after a certain period of time **[11]**.

Gene mutation: Fibroadenoma is highly associated with gene mutations such as mediator complex subunit 12 (MED 12) and retinoic acid receptor alpha (RARA) out of which MED 12 somatic mutation occurs very frequently in these fibroepithelial tumours when compared to RARA mutation, based on the experiment that was conducted on Chinese population **[13]**.

Age of menarche: Younger women who tend to attend their menstruation at an early age (before 11yrs) are more liable to fibroadenoma when compared to the women who attain menstruation at a later age (after 14yrs). Early age to attain menstruation is caused due to various factors like environment, lifestyle, genes. But in the current scenario the age of menarche tends to occur early due to the changes in the consumption pattern, lifestyle and environment. The factors that led to early age of menarche are body mass index, diet, physiological status **[14]**.

Family history: There is a significant relation with family history and fibroadenoma, the people with strong family history of breast tumours are more liable to get the tumour when compared to the people without a family history. Once the tumour occurs there are chances that it may reappear in the same place or at a different place **[14]**.

Lifestyle: Lack of physical activity causes imbalance in the intake and output of the calories which leads to increased proliferation which elevates the risk of tumour, by sufficient physical activity the calories can be maintained. Not maintaining nutritional lifestyle with respect to food habits is also risky, consumption of fried food, smoked meat, food containing artificial sweeteners, preservatives, dyes and consumption of alcohol enhance the threat of tumour **[14]**.

Symptoms

- Fibroadenoma is a solid breast lump which causes minimal pain
- Round or oval in shape

- Easily movable
- Firm or rubbery
- Grows slowly, average length is 1 inch It may tend to get bigger overtime. There maybe are one or more than one lumps in both the breasts. Some tend to shrink overtime **[15]**.

Pathophysiology

Breast physiology: The breast is composed of epithelial and stromal elements. The epithelial element consists of two interconnected systems. The terminal duct lobular unit (TDLU) performs main secretory functions and large duct system does the collection and drainage during lactation. The stroma is composed of loose connective tissues and fat, located on both inter and intra lobular regions **[16]**.

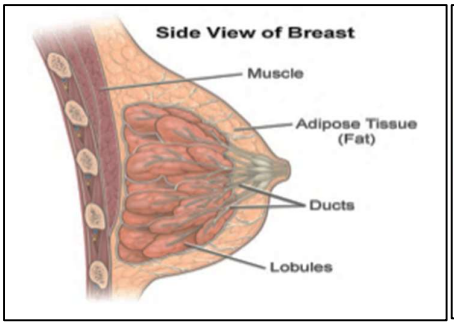

Figure 7: Normal breast

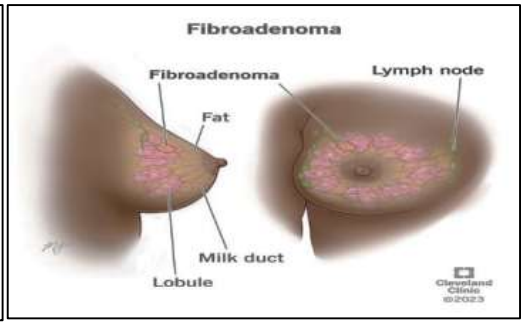

Figure 8: Breast with fibroadenoma

Pathogenesis: Fibroadenoma is a benign tumour commonly found in adolescent women, usually formed during the menarche age. They are formed by the rapid growth of the stromal and epithelial cells that originate from the duct lobular unit (epithelial structure within breast that produces milk during lactation) when components of fibroadenoma were analysed by polymerase chain reaction both the cells were found to be polyclonal, fibroadenomas are hyperplastic tumours, where there is abnormal growth of tissues which causes disturbance in the breast development. They are also stimulated by a hormone-receptor mechanism of estrogen and progesterone which happens mostly in pregnant women, during menstruation and premenopausal time. It is mostly formed as large one single mass, except in some cases there tend to be multiple masses. The mass may increase slowly without any and changes in the skin colour or pain. Some fibroadenomas respond to both growth hormone and epidermal growth factor receptors **[17, 18]**.

Gross pathology: Fibroadenoma is firm, painless, solid mass that is mobile in nature. Consists of a rubbery texture, white in colour, lobulated appearance with short slit places **[19]**.

Figure 9: Gross pathology after extraction

Microscopic pathology: Under microscope the following characteristics can be observed: Uniformly distributed epithelial cells in honey comb pattern, intact basement membrane, calcification may be present, presence of foam and apocrine cells, absence of mitotic figures, biphasic proliferation of stromal and epithelial components in two growth patterns pericanalicular growth pattern: stromal proliferation around epithelial structures. Intracanalicular growth pattern: stromal proliferation compressing the epithelial structures into clefts **[20]**.

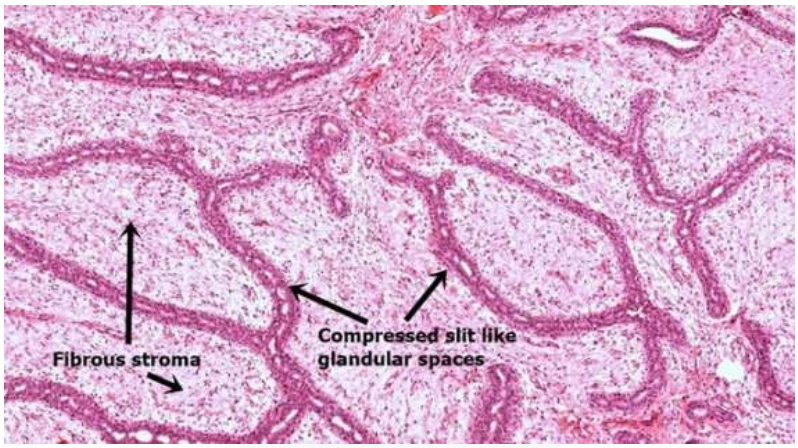

Figure 10: Microscopic pathology

Genetics: The mediator complex subunit 12 (MED 12) gene plays a major role in the transcription of the RNA polymerase II dependant genes **[17]**. Somatic mutation in the MED 12 gene causes genetic alterations and leads to development of fibroadenoma and the MED 12 mutations are present in stromal cells of the mammary gland and not in the epithelial cells **[21-23]**.

Case study of fibroadenoma: A study was conducted from august 2014 to 2016 on the patients who had breast lump or pain they were examined and evaluated. All the required data: name, age, marital status, background, symptoms, number of lumps, pre and post menstrual symptoms, location and size of the lumps was collected from the patients. All the specimens underwent

histopathological examination and all the cases were proven to be fibroadenoma that were considered in the study. A total to 80 cases were selected. The age group of these cases ranged from 10 – 60 years. Maximum cases were found in the age group 16 – 30 years followed by 31 – 45 years. Nearly 60 cases belonged to the urban background and 55 cases were of married women. The duration of the symptoms from 3 months to one year of a lump in the breast most of the fibroadenomas were found in the right breast. Lower quadrant was the main location of these lumps followed by upper lateral and 10 cases had lumps in both the breast. The tumours size varied from 3-5cms and 1-2cms. Giant fibroadenomas >5 cms were found in 15 cases. Based on the results, totally 12 cases were managed without any changes and the rest 68 cases underwent surgery with no major complications. 80% cases had a follow up for 6 months and none of them showed any signs of reoccurrence. None of the patients were on oral contraceptives **[24]**.

Table 1: Detailed review of the cases examined.

Patient characteristic	Diagnosis	Number of cases	Percentage
Age group (years)	0-15	2	2.5
	16-30	50	62.5
	31-45	18	22.5
	46-60	10	12.5
Background	Rural	20	25
	Urban	60	75
Marital status	Unmarried	25	31.25
	Married	55	68.75
Symptoms duration (months)	1-12	40	50
	13-24	12	15
	25-36	4	5
	37-48	14	17.5
	49-60	3	3.75
	61-72	7	8.75
Location	Left breast	30	37.5
	Right breast	40	50
	Bilateral	10	12.5
Quadrant	Upper lateral	22	27.5
	Upper medial	08	10
	Lower lateral	28	35
	Lower medial	04	5
	Central	08	10
	Multiple	10	12.5
Size (cms)	< 2	12	15
	3-5	43	53.75
	6-10	15	18.75
	10-20	10	12.5
Treatment	Conservative	12	15
	Excision	68	85

Based on the case study conducted majority of the diagnosed cases belonged to the age group 16–30 years which maybe be due to hormonal dependency, lactation and menopause time that may lead to lump formation. It is more common in teenagers and in urban background when compared to rural due to more literacy and media sources that increases the awareness regarding the screening of the breast. Early marriage is one among the main reasons that most of the married women were diagnosed. The fibroadenoma was almost equally distributed in both the breasts, but more lumps were found in the left breast than right, upper lateral quadrant is a common location based on the findings. Fibroadenoma is often detected during self examination or medical examination it is a solid breast mass of 1-2 cms and may vary in size up to 18cms. Fibroadenomas larger than 5cms are termed as giant fibroadenomas that is usually found in pregnant and lactating women, and when found in adolescent girls it is termed as juvenile fibroadenoma which is rapidly growing mass in the breast. Patients with multiple fibroadenoma had a very strong family history of breast tumours unlike women with single fibroadenoma. Surgical removal of the tumour was preferred for treatment in majority of cases, as 1/3 of the cases underwent long periodic monitoring which caused anxiety and discomfort in patients. Fibroadenoma excision through peri-areolar incision (FETPI) is the technique used and the incision is done in the acceptable area only, later on the scar can be camouflaged by using the areolar skin. Women with no family history did not have greater risk of breast cancer when compared to women with a family history, the risk is very low in women under the age of 35 years. So it is recommended for the younger generation to undergo frequent clinical evaluations **[24]**.

Diagnosis: Any variation in the breast mass should be medically evaluated. When the patients undergo medical evaluation it includes collection of complete medical reports, family histories, previous breast related issues, symptoms observed, information about the mass i.e. its location, duration, changes in size, any pain or discharge, mobility, any nipple discharge or palpitation in the lymph nodes **[25]**.

1. **Physical examination:** Patients tend to appear normal, vital signs are normal but there is firmness in the breast, it is non-tender, single mass or multiple masses, smooth in nature, mobile and rubbery which needs to be clinically examined **[25]**.

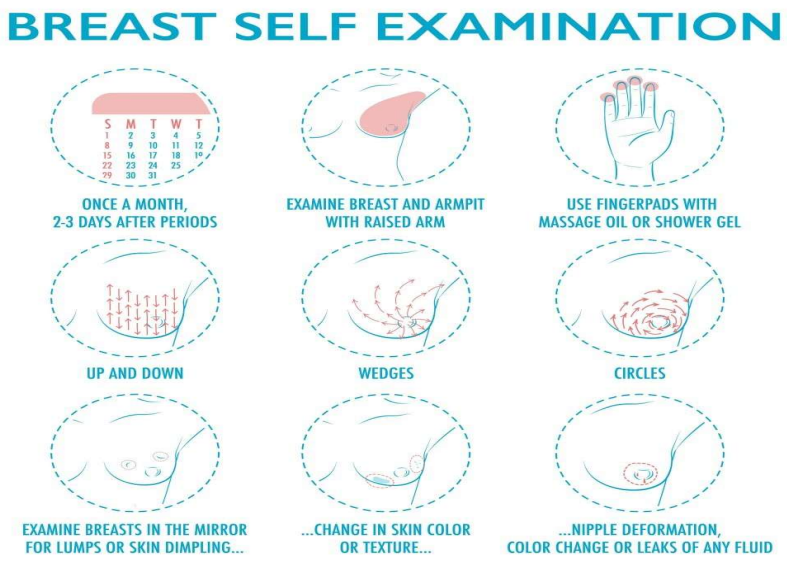

Figure 11: Self Breast Examination

2. Clinical examination

Evaluation of breast mass: evaluation of the breast is done where they examine the size, shape, location and mobility, which is used for the further diagnosis **[26]**.

Variation in the breast appearance: evaluation of variation in the breast i.e. skin refraction, changes in the shape, any visible alterations or nipple discharge may offer some unusual clues for the diagnosis and may not be a symptom of fibroadenoma which aids to the further diagnosis **[27]**.

Evaluation of axillary lymph node: the lymph nodes are assessed in the axillary region to see if there are any palpable or enlarged lymph nodes **[28]**.

3. Imaging techniques

Mammography: Also known as mammogram uses X-rays to make an image of the breast tissue; it detects the borders of fibroadenoma and sets it apart from the other tissues to get a better scan, used mostly in elderly women or those with thick breast tissue. Sometimes this technique finds out the calcifications present within the fibroadenoma. Fibroadenomas may appear to be solid masses that consist of smooth margins **[29, 30]**.

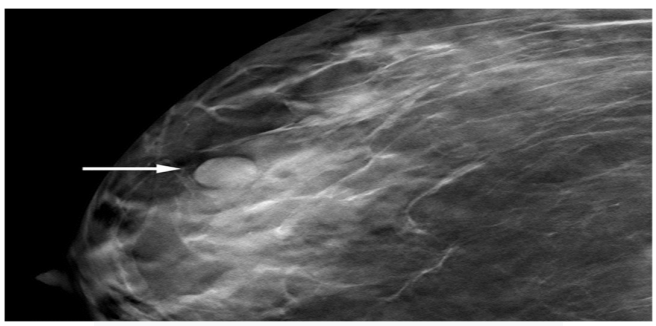

Figure 12: Mammogram of breast fibroadenoma

Ultrasound: It is a diagnostic technique where the sound waves make echoes that form pictures of the tissues and organs on the computer screen known as sonogram. Fibroadenoma usually appears as a dark mass on ultrasound it is displayed with well defined margins for identification. It is used in younger women and this imaging technique gives a real time visualization of the tumour **[31, 32]**.

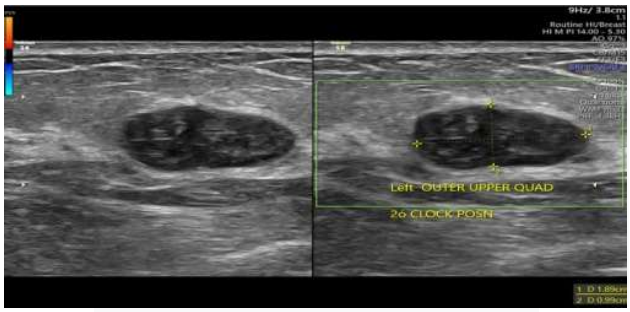

Figure 13: Ultrasound of breast fibroadenoma

Magnetic resonance imaging (MRI): Magnetic image resonance technique, an imaging method that provides detailed images of every organ, bone, muscle, blood vessels and almost every internal structure of human body. It is used in particular cases where the diagnosis is uncertain, this technique excels in evaluating the degree of disease, gives diagnostic accuracy and identifies multiple masses in the breast **[33, 34]**.

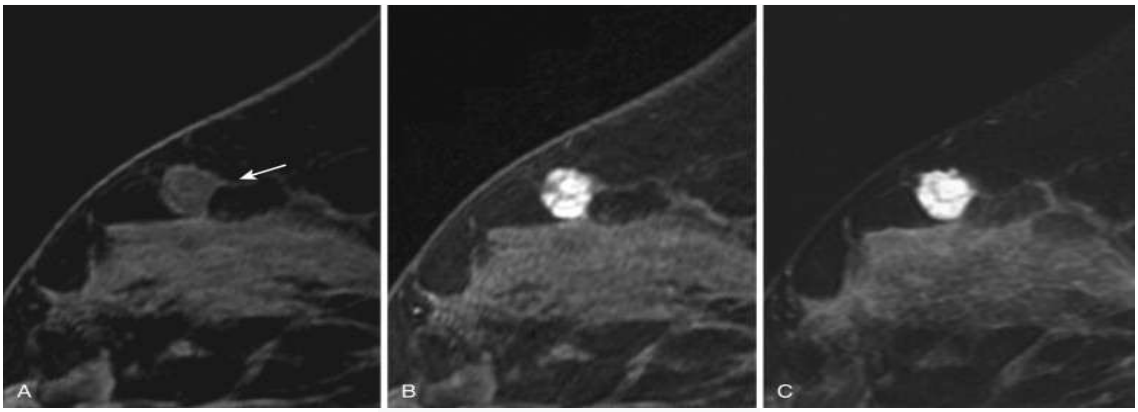

Figure 14: MRI of breast fibroadenoma

4. Biopsy for histopathological assessment

Fine needle biopsy (FNA): A type of biopsy in which a very thin needle and syringe is used to remove sample of cells, tissue, fluid or the lump in the body and later examined under the microscope. It is used to assess the breast lump and confirm whether it is benign or malignant. It is majorly used for the assessment to simple fibro adenoma only and is helpful in the initial diagnostic process **[35]**.

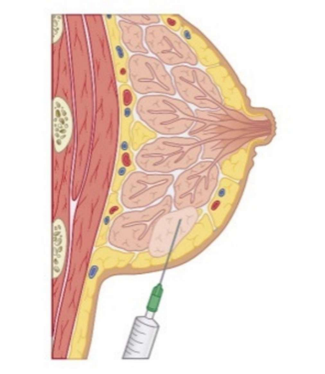

Figure 15: FNA biopsy

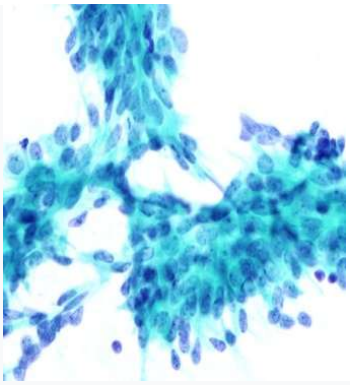

Figure 16: FNA under microscope in PAP stain

Core needle biopsy (CNB): It is a needle biopsy, a thin hollow tube needle is used to extract the cells/sample from the body. Used for the removal of larger tissues, it yields an required amount of tissue sample for histological examination. This technique helps in precise diagnosis and thorough evaluation of the lump **[36]**.

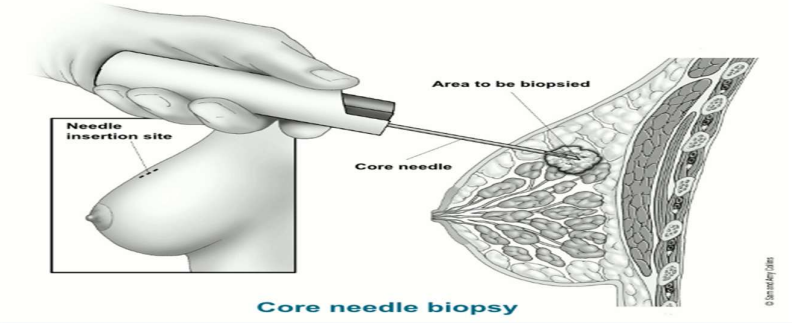

Figure 17: Core needle biopsy

Excisional biopsy: When the fibro adenoma is very larger and exhibits complex features or maybe malignant in nature this method is used to completely remove the fibroadenoma for histopathological assessment. It is the most suitable process in comparison with FNA and CNB, it is indispensable and the diagnosis is crucial **[37]**.

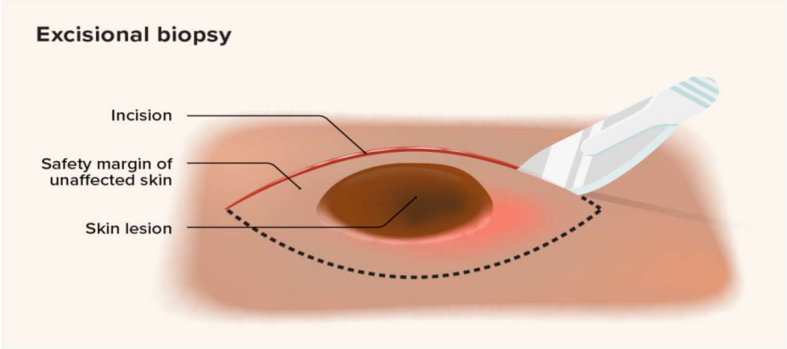

Figure 18: Excisional biopsy

Treatment

In most of the cases fibroadenoma doesn't require treatment. They usually diminish and dissipate over time; unless they consist of other breast tissues and are large in size they should be surgically removed. Based on the outcome of the imaging techniques, histopathological data and clinical evaluation further treatment decisions are made **[38]**.

Pharmacological treatments

Drugs

Evening primrose oil: consists of gamma-linolenic acid, which affects the prostaglandins metabolism and when studied further for the benign breast treatment, it showed its results on the tumours less than 3cm, where the fibroadenoma reduced in size and showed better effect **[39, 40]**.

Tamoxifen: as fibroadenoma is hormone dependant mainly estrogen, anti – estrogenic compounds were studied. A selective estrogen receptor modulator (SERM) tamoxifen is studied for treating fibroadenoma where is reduces the size and chances of further development of fibroadenoma, but the rate of shrinkage is not studied **[41, 42]**.

Centchroman: this is also an SERM, used to treat fibroadenoma. Based on the study conducted around 12.1% is the rate of disappearance and 60% had reduction in size. SERMs have side effects: leg cramps, headache, depression, menstrual irregularity, flushes and endometrial hyperplasia **[43]**.

Metformin: it is a drug with approved safety profile and tolerability. Based on the study conducted it was found that metformin has better effects for the treatment of multiple fibroadenomas and for small masses **[43]**.

Surgical interference

Lumpectomy: a type of breast surgery where the fibroadenoma and a small amount of surrounding tissue is removed. The removed tissue undergoes histopathological evaluation to confirm its benign nature. This method is used when the fibroadenoma is large in size, causing uncertainty or discomfort. Tissue of the breast are retained and minimal scars **[44]**.

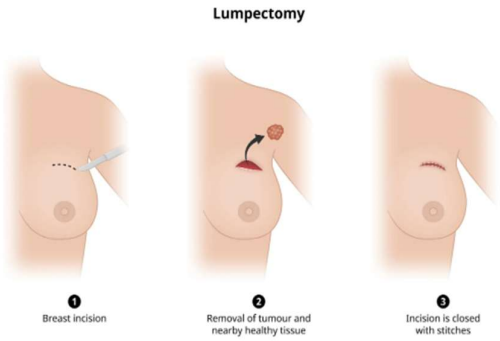

Figure 19: Lumpectomy of breast fibroadenoma

Excisional biopsy: the fibroadenoma is completely removed, it is similar to lumpectomy. The fibroadenoma is removed and sent for histopathological evaluation of its benign nature. This method is appropriate in the cases where the patients seek evidence of the fibroadenomas nature **[45]**.

Cryoablation: This procedure involves freezing of the fibroadenoma using a cryoprobe a metal device that is used with the help of ultrasound assistance to freeze the tumour and spares the tissue around it. It is used in certain cases, when the size of fibroadenoma is small and accessible, it even depends on the location and size. An advantage of this method is it causes minimal invasiveness and very little scaring and short period of time for recovery when compared to other surgical methods **[46]**.

Figure 20: Cryoablation of breast fibroadenoma

Emerging minimal invasive treatments

Ultrasound guided vacuum assisted biopsy (VAB): It is a minimal invasive technique that targets and removes the fibroadenoma under the ultrasound guidance with accuracy. A vacuum assisted device is used to obtain required amount of samples of the fibroadenoma, which are sent for histopathological assessment. It has minimal scarring and minimal recuperation time and less post procedure discomfort compared to other methods **[47]**.

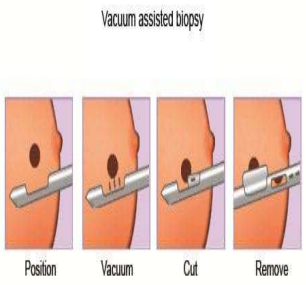

Figure 21: Vacuum assisted biopsy

Figure 22: Vacuum assisted biopsy machine

Radiofrequency ablation (RFA): In this method the fibroadenoma is heated and destroyed using the radiofrequency energy. It is used for small fibroadenomas, it is a targeted procedure guided by imaging and precision while preserving the healthy tissue. VAB and RFA are the same for minimal scaring and invasiveness. But RFA has a quicker recovery period **[48]**.

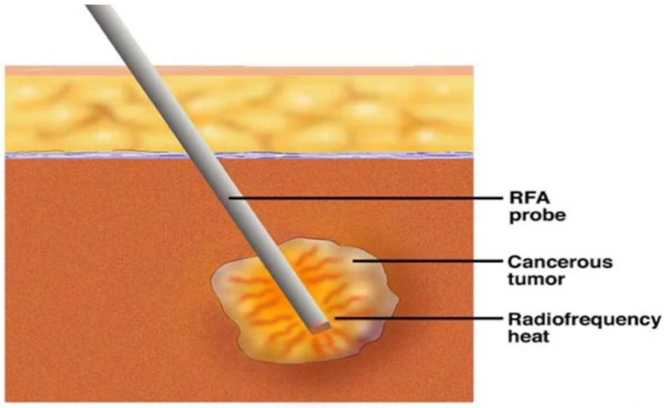

Figure 23: Radiofrequency ablation

Non-pharmacological treatments

Examine and regular monitoring: For small fibro adenomas immediate treatment is not necessary. It is recommended to have a regular watch where the breast is clinically examined, imaging studies are done, changes are monitored i.e. size, shape, mobility or behaviour. After close observation based on the based on the development or changes further assessment is done **[49]**.

Patient education: Patients are to be provided with all the information about fibroadenoma: its benign nature, impact on the health of breast, potential for stability, risks, the surgeries, recovering time **[50]**. Educating the patients on fibroadenoma helps them to make a right decision and they even get to know the importance of reporting any new changes or symptoms related to the tumour. This open communication helps in better management **[51]**.

Physiological impact: Fibroadenomas also have a psychological impact on the patients. It is the duty of the health care providers to take care of the patients by addressing their fears and anxiety and even provide them with counselling if needed. And be attentive towards their concerns, as physical and emotional well-being is a significant aspect in the treatment of fibroadenoma **[52]** (52).

Physical activity: Physical activity i.e. walking, exercise lessen the threat of rapid development of the damaged tissue. One of the earliest steps for the growth of breast disease. And also doesn't encourage the multiplying of the damaged tissue. So it is essential to maintain a consistent physical activity for healthy lifestyle **[53]**.

Diet: The possibility of fibroadenoma reduces by following a dietary pattern consisting of whole lot of fruits, leafy vegetables, and fibrous food **[54]**. Food consisting of high fat dairy products, preservatives, junk food and consumption of alcohol should be avoided **[55]**.

CONCLUSION

In conclusion, fibroadenoma is a breast tumour mostly found in adolescent women. It is made of stromal and epithelial cells. And

mainly caused due to hormonal imbalance and genetic mutation, family history does play a significant role. It is a solid mass that is hard and mobile in nature that can be initially diagnosed by physical examination or by any abnormalities in the breast such as presence of hard mass and slight pain in breast which is further diagnosed using various imaging and biopsy techniques which gives us more precise information regarding its location, shape, size and confirmation about its malignant nature based on which further treatment is conducted. In imaging techniques mammography is used in elderly women, ultrasound in younger women and MRI is used when the diagnosis is not clear. For histopathological assessment fine needle biopsy is done to examine simple fibroadenoma, excisional biopsy is done when the fibroadenoma is larger and has to be completely removed, core needle biopsy is used for precise diagnosis. It can be surgically treated by lumpectomy where the fibroadenoma is removed with minimal scaring and in cryoablation the tumour is freezed without harming the surrounding tissue, it is used to treat small tumours and has less scaring and shorter recovery period in comparison to other methods. Some emerging minimal invasive techniques are ultrasound guided vacuum assisted biopsy and radiofrequency ablation; this method has faster recovery period. Based on a case study that was conducted in the year 2016, it was concluded saying majority of the patients diagnosed with fibroadenoma belonged to the age group 16-30yrs, in the course of puberty and lactation time. And it is often found in the left breast and sometimes in multiples if there is strong family history of breast tumours, upper lateral quadrant is the common location. Not all fibroadenomas need to be treated surgically. Some tend to shrink overtime, but some tend to reoccur if not treated properly. Adapting healthy and fit lifestyle from the formative years help we overcome most of the health issues. For further studies case study's that include lactating mothers also need to be taken under consideration.

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REFERENCES

[1] Restrepo R, Cervantes LF, Swirsky AM, Diaz A. Breast development in pediatric patients from birth to puberty: physiology, pathology and imaging correlation. Pediatr Radiol. 2021;51(11):1959-1969.

[2] Chen Z, Zhang Y, Li W, Gao C, Huang F, Cheng L, Jin M, Xu X, Huang J. Single cell profiling of female breast fibroadenoma reveals distinct epithelial

cell compositions and therapeutic targets. Nat Commun. 2023;14(1):3469.

[3] Ahmad A, Najeeb E, ul Haq MB, Bashir H, Uzair M, Mamoon N. Ductal carcinoma in situ and invasive carcinoma originating in a Fibroadenoma with concurrent benign phyllodes tumor: A case report. International Journal of Surgery Case Reports. 2024

[4] Motamedi M, Moini A, Maajani K, Maleki-Hajiagha A, Alipour S. Infertility Does Not Increase the Rate of Breast Fibroadenoma. J Reprod Infertil. 2023;24(1):58-62.

[5] Thapa S, Phulware RH, Kumar A, Kishore S. Cytomorphological Features of Complex Fibroadenoma Breast. J Cytol. 2023;40(4):220-222.

[6] Ramala SR Jr, Chandak S, Chandak MS, Annareddy S. A Comprehensive Review of Breast Fibroadenoma: Correlating Clinical and Pathological Findings. Cureus. 2023 5;15(12):e49948.

[7] Salati SA. Breast fibroadenomas: a review in the light of current literature. Pol Przegl Chir. 2020;93(1):40-48.

[8] Mareti E, Vatopoulou A, Spyropoulou GA, Papanastasiou A, Pratilas GC, Liberis A, Hatzipantelis E, Dinas K. Breast Disorders in Adolescence: A Review of the Literature. Breast Care (Basel). 2021;16(2):149-155.

[9] Basara Akin I, Balci P. Fibroadenomas: a multidisciplinary review of the variants. Clin Imaging. 2021;71:83-100.

[10] Li J, Humphreys K, Ho PJ, Eriksson M, Darai-Ramqvist E, Lindström LS, Hall P, Czene K. Family History, Reproductive, and Lifestyle Risk Factors for Fibroadenoma and Breast Cancer. JNCI Cancer Spectr. 2018;2(3):pky051.

[11] Lee M, Soltanian HT. Breast fibroadenomas in adolescents: current perspectives. Adolesc Health Med Ther. 2015 ;6:159-63.

[12] Xie SN, Cai YJ, Ma B, Xu Y, Qian P, Zhou JD, Zhao FG, Chen J. The genomic mutation spectrums of breast fibroadenomas in Chinese population by whole exome sequencing analysis. Cancer Med. 2019;8(5):2372-2379.

[13] Fitri, A. E., Daan Khambri and Afriwardi (2022) "Risk Factor Analysis of Fibroadenoma Mammae In Adolescent Girls In 2021", *Science Midwifery*, 10(2), pp. 1788-1792. Available at: https://midwifery.iocspublisher.org/index.php/midwifery/article/view/545

[14] Greenberg R, Skornick Y, Kaplan O. Management of breast fibroadenomas. J Gen Intern Med. 1998;13(9):640-5.

[15] Beacon health system. Fibroadenoma. 2022.

https://www.beaconhealthsystem.org/library/diseases-and-conditions/fibroadenoma?content_id=CON-20305538

[16] C. Michael Gibson. Fibroadenoma pathophysiology. 2020. https://www.wikidoc.org/index.php/Fibroadenoma_pathophysiology

[17] Al-Shami K, Awadi S, Khamees A, Alsheikh AM, Al-Sharif S, Ala' Bereshy R, Al-Eitan SF, Banikhaled SH, Al-Qudimat AR, Al-Zoubi RM, Al Zoubi MS. Estrogens and the risk of breast cancer: A narrative review of literature. Heliyon. 2023;9(9):e20224.

[18] Estrogens and the risk of breast cancer: A narrative review of literature, Heliyon, 9(9), 2023, e20224, ISSN 2405-8440.

[19] Mitchell, Richard; Kumar, Vinay; Fausto, Nelson; Abbas, Abul K.; Aster, Jon (2011). Pocket Companion to Robbins & Cotran Pathologic Basis of Disease (8th ed.). Elsevier Saunders. pp. 550. ISBN 978-1416054542.

[20] Williams HJ. Educational Case: Fibroadenoma of the Breast. Acad Pathol. 2018;5:2374289518790926.

[21] Piscuoglio S, Murray M, Fusco N, Marchiò C, Loo FL, Martelotto LG, Schultheis AM, Akram M, Weigelt B, Brogi E, Reis-Filho JS. MED12 somatic mutations in fibroadenomas and phyllodes tumours of the breast. Histopathology. 2015;67(5):719-29.

[22] Darooei M, Khan F, Rehan M, Zubeda S, Jeyashanker E, Annapurna S, Shah A, Maddali S, Hasan Q. MED12 somatic mutations encompassing exon 2 associated with benign breast fibroadenomas and not breast carcinoma in Indian women. J Cell Biochem. 2019;120(1):182-191.

[23] Lim WK, Ong CK, Tan J, Thike AA, Ng CC, Rajasegaran V, Myint SS, Nagarajan S, Nasir ND, McPherson JR, Cutcutache I, Poore G, Tay ST, Ooi WS, Tan VK, Hartman M, Ong KW, Tan BK, Rozen SG, Tan PH, Tan P, Teh BT. Exome sequencing identifies highly recurrent MED12 somatic mutations in breast fibroadenoma. Nat Genet. 2014;46(8):877-80.

[24] Purushothaman Rangaswamy, Shaikh Afzal Rubby. Clinical study on fibroadenoma of the breast. International surgery journal, 3(4): 1-4.

[25] Cerrato F, Labow BI. Diagnosis and management of fibroadenomas in the adolescent breast. Semin Plast Surg. 2013;27(1):23-5

[26] Ravi, C., Rodrigues, G. Accuracy of Clinical Examination of Breast Lumps in Detecting Malignancy: A Retrospective Study. Indian J Surg Oncol 3, 154–157 (2012).

[27] Henderson JA, Duffee D, Ferguson T. Breast Examination Techniques. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024 -. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459179/

[28] Pinheiro DJ, Elias S, Nazário AC. Axillary lymph nodes in breast cancer patients: sonographic evaluation. Radiol Bras. 2014;47(4):240-4.

[29] Joshi P, Sharma R.Benign Lesions on Screening Mammography: Increasing Diagnostic Confidence in a Hitherto Unscreened Population.J Clin of Diagn Res.2017; 11(9):TC14-TC17.

[30] Li H, Zhang S, Wang Q, Zhu R. Clinical value of mammography in diagnosis and identification of breast mass. Pak J Med Sci. 2016;32(4):1020-5.

[31] Gokhale S. Ultrasound characterization of breast masses. Indian J Radiol Imaging. 2009;19(3):242-7.

[32] Malherbe K, Tafti D. Breast Ultrasound. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024 -. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557837/

[33] Gunduru M, Grigorian C. Breast Magnetic Resonance Imaging. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024 -. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539727/

[34] Cloete DJ, Minne C, Schoub PK, Becker JHR. Magnetic resonance imaging of fibroadenoma-like lesions and correlation with Breast Imaging-Reporting and Data System and Kaiser scoring system. SA J Radiol. 2018;22(2):1532.

[35] Casaubon JT, Tomlinson-Hansen S, Regan JP. Fine Needle Aspiration of Breast Masses. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024 -. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470268/

[36] Łukasiewicz E, Ziemiecka A, Jakubowski W, Vojinovic J, Bogucevska M, Dobruch-Sobczak K. Fine-needle versus core-needle biopsy - which one to choose in preoperative assessment of focal lesions in the breasts? Literature review. J Ultrason. 2017;17(71):267-274.

[37] Neville G, Neill CO, Murphy R, Corrigan M, Redmond PH, Feeley L, Bennett MW, O'Connell F, Browne TJ. Is excision biopsy of fibroadenomas based solely on size criteria warranted? Breast J. 2018;24(6):981-985.

[38] Kevin fox. Fibroadenomas of the breast: causes, symptoms and treatment. Benign breast conditions. 2024

https://www.breastcancer.org/benign-breast-conditions/fibroadenoma

[39] Bayles B, Usatine R. Evening primrose oil. Am Fam Physician. 2009 Dec 15;80(12):1405-8. PMID: 20000302.

[40] Kollias J, Macmillan RD, Sibbering DM, Burrell H, Robertson JF. Effect of evening primrose oil on clinically diagnosed fibroadenomas. The Breast. 2000;9(1):35-6.

[41] Tan-Chiu E, Wang J, Costantino JP, Paik S, Butch C, Wickerham DL, Fisher B, Wolmark N. Effects of tamoxifen on benign breast disease in women at high risk for breast cancer. Journal of the National Cancer Institute. 2003;95(4):302-7.

[42] Viviani RS, Gebrim LH, Baracat EC, De Lima GR. Evaluation of the ultrasonographic volume of breast fibroadenomas in women treated with tamoxifen. Minerva ginecologica. 2002;54(6):531-5.

[43] Alipour, S., Abedi, M., Saberi, A. et al. Metformin as a new option in the medical management of breast fibroadenoma; a randomized clinical trial. BMC Endocr Disord 21, 169 (2021).

[44] Breast-conserving surgery (lumpectomy). American cancer society. 2021 https://www.cancer.org/cancer/types/breast-cancer/treatment/surgery-for-breast-cancer/breast-conserving-surgery-lumpectomy.html

[45] Neville G, Neill CO, Murphy R, Corrigan M, Redmond PH, Feeley L, Bennett MW, O'Connell F, Browne TJ. Is excision biopsy of fibroadenomas based solely on size criteria warranted? Breast J. 2018;24(6):981-985.

[46] Niu L, Wu B, Xu K. Cryosurgery for breast fibroadenomas. Gland Surg. 2012;1(2):128-31.

[47] Buğdaycı O, Kaya H, Arıbal E. Ultrasound Guided Therapeutic Excisional Vacuum Assisted Biopsy in Breast Fibroadenomas. J Breast Health. 2017;13(2):74-76.

[48] Nguyen T, Hattery E, Khatri VP. Radiofrequency ablation and breast cancer: a review. Gland Surg. 2014;3(2):128-35.

[49] Elmore JG, Armstrong K, Lehman CD, Fletcher SW. Screening for breast cancer. JAMA. 2005;293(10):1245-56.

[50] Bergus GR, Levin IP, Elstein AS. Presenting risks and benefits to patients. J Gen Intern Med. 2002;17(8):612-7

[51] Williams HJ. Educational Case: Fibroadenoma of the Breast. Acad Pathol. 2018;5:2374289518790926

[52] Srivastava V, Meena RK, Ansari MA, Kumar D, Kumar A. A Study of Anxiety and Depression in Benign Breast Disease. J Midlife Health. 2020;11(4):200-209.

[53] Jung MM, Colditz GA, Collins LC, Schnitt SJ, Connolly JL, Tamimi RM. Lifetime physical activity and the incidence of proliferative benign breast disease. Cancer Causes Control. 2011;22(9):1297-305

[54] Nelson ZC, Ray RM, Wu C, Stalsberg H, Porter P, Lampe JW, Shannon J, Horner N, Li W, Wang W, Hu Y, Gao D, Thomas DB. Fruit and vegetable intakes are associated with lower risk of breast fibroadenomas in Chinese women. J Nutr. 2010;140(7):1294-301

[55] Fibrocystic Breast Disease Diet. Lybrate. Aug 2020. https://www.lybrate.com/topic/fibrocystic-breast-disease-diet