December 2006

Chemoprevention of breast cancer for women at hgh risk

Kathryn Chan
Thomas Jefferson University

Gloria J. Morris
Thomas Jefferson University, Gloria.Morris@jefferson.edu

Chemoprevention of Breast Cancer for Women at High Risk

Kathryn Chan, MD, and Gloria J Morris, MD, PhD

Corresponding author address:
Gloria J. Morris, MD, PhD
Department of Medicine, Division of Medical Oncology
125 South 9th Street
Suite 801 Sheridan Building
Philadelphia, PA 19107
Telephone (215)955-8874
Email: Gloria.Morris@jefferson.edu

I. Abstract:

Breast cancer remains the second most common cause of cancer death in the United States. Several studies have identified cohorts of women at higher than average risk to develop this disease. These are women who are exposed to high levels of endogenous or exogenous estrogens, those with a family history of breast cancer, and those who harbor benign breast disease or genetic mutations that predispose to breast cancer. In this population group, adapting a chemoprevention strategy to decrease the risk of developing overt disease is a strong consideration. To this end, tamoxifen is the most accepted agent to date. This article will describe high risk categories that predict future development of invasive breast cancer, will summarize the current available data to support the use of tamoxifen for chemoprevention, and will further discuss adverse effects of tamoxifen as well as measures to anticipate and monitor for possible adverse outcomes.

II. Introduction:

An estimated 214,640 American women will be diagnosed with breast cancer in 2006, according to American Cancer Society statistics (1). It is the second most common cause of cancer death and the main cause of death for women aged 45-55. Women recognized to be at higher risk than the average population for the development of breast cancer have historically been identified as those associated with exposure to higher (or longer) levels or circulating estrogens, including older age, early menarche and later menopause, nulliparity, older age at first full-term pregnancy, and history of current or past use of hormonal replacement therapy (containing estrogen and progesterone) (1). In addition, women considered at high risk include those with family history of breast cancer, personal history of previous breast biopsy(ies) or diagnosis of benign proliferative breast

disease, personal history of radiation exposure, and those who harbor specific genetic mutations (BRCA1, BRCA2, p53, or PTEN), Chemoprevention as a strategy to interfere with the development of breast cancer in women with high risk scenarios is emerging as a strong consideration for women's health. In this regard, tamoxifen has currently been the most widely accepted agent, patterning after well-established data from its use in the treatment and risk-reduction of breast cancer in the adjuvant setting.

III. Tamoxifen for prevention:

Several studies have sought to identify subsets of women who would be at highest risk for the development of breast cancer. The Gail Risk model has historically been used to predict the 5-year as well as lifetime risk of developing invasive breast cancer. This is a validated prediction model using five factors: current age, age at menarche, previous breast biopsies, age at first live birth, and family history of breast cancer in first-degree relatives (2-4). A 5-year risk of 1.66% or greater strongly promotes consideration for prevention strategies. The Claus model is an additional tool which can provide an estimate of future breast cancer risk in women with strong family histories of breast cancer (5).

There are four prominent studies reported in the literature comparing tamoxifen with placebo in the prevention of breast cancer for women considered at high risk (6). The American Breast Cancer Prevention Trial (P-1 study) sponsored by the National Surgical Adjuvant Breast and Bowel Project (NSABP) was a randomized trial of tamoxifen versus placebo in women considered at increased risk defined as: age older than 60, age between 35-59 with a Gail model prediction value at least 1.66%, or age 35 or greater with history

of lobular carcinoma in situ (LCIS). The trial was terminated early after a median follow-up of 48 months when interim analysis established a statistically significant benefit with tamoxifen (7). There was 49% relative risk reduction and 21% absolute risk reduction of invasive breast cancer among the cohorts on tamoxifen. Furthermore, an update of this study showed a 62% reduction of invasive breast cancer in the tamoxifen group but the incidence for ER-negative tumors was unchanged (8).

The International Breast Cancer Intervention study (IBIS-I) also demonstrated substantial risk reduction for the development of breast cancer with the use of tamoxifen. This study conducted in the UK, Australia, New Zealand and other European countries accrued data from April 1992 to March 2001, and included women age 35-70 years considered to be at high risk for breast cancer on the basis of a positive family history or a personal history of atypical hyperplasia or lobular carcinoma in situ. A total of 7,152 participants were randomized in a double-blind fashion to either placebo or tamoxifen 20 mg per day for 5 years. With a median follow-up time of 50 months, there was a 32% reduction of risk of breast cancer in the experimental arm. In this trial, age, degree of risk and use of hormone-replacement therapy did not affect the reduction (9). There was a 31% reduction of risk in ER-positive invasive tumors with tamoxifen use but no demonstrated reduction in the risk for the development of ER-negative invasive tumors. There were no additional data to support any further benefits from the use of tamoxifen beyond 5 years.

Two other noteworthy European trials utilizing tamoxifen for breast cancer risk reduction have recently been reported. The Royal Marsden Hospital Trial evaluated 2471 women between ages 30 and 70 with a positive family history for breast cancer, but found no

significant difference between tamoxifen and placebo in the subsequent frequency of breast cancer observed (10). The Italian Tamoxifen Prevention study evaluated 5408 women between ages 35 and 70, all of whom had undergone previous hysterectomy. Also, those with a history of thromboembolism were excluded. Thus far, no difference in the rate of breast cancer events was detected between tamoxifen and placebo arms at median follow-up of 30 months (11). These European trials are smaller than the above mentioned NSABP and International trials, and did not include women with high risk benign lesions such as LCIS or ADH.

IV. High-Risk Benign Breast Lesions and Genetic Predisposition:

Recently, investigators have sought to define the types of benign breast disease at highest risk for the development of breast cancer. To this end, Hartman *et al* followed 9,087 women diagnosed with a benign breast disease at the Mayo Clinic over 15 years between 1967 and 1991 and estimated their risks for breast cancer for the spectrum of benign breast histopathologies identified **(see Figure 1)** (12). They established a relative risk of breast cancer of 4.24 over the general population for women with atypia as compared with normal cohorts, 1.88 relative risk with proliferative changes without atypia, and 1.27 relative risk for non-proliferative lesions (12), with significantly higher risk in younger individuals who were diagnosed with atypia **(see Figure 2).** They concluded that family history of breast cancer, defined as at least one first degree relative diagnosed with breast cancer before age 50 or two or more relatives diagnosed with breast cancer with one being a first-degree relative (12), portended an increased risk that was independent of the benign histology, as even nonproliferative lesions were then associated with increased

relative risk (**see Figure 2,** not statisticially significant). Importantly, they found no additional increase in risk for women with no family history and who had nonproliferative disease on breast biopsy (12).

Hershman *et al* analyzed the effectiveness of tamoxifen in the very high risk cohorts of women ages 35, 50 and 60 with Gail Risk model estimates of greater than 5%, and with atypical ductal hyperplasia, lobular carcinoma in situ, or having two or more first-degree relatives with breast cancer (13). They found that the greatest benefit of the use of tamoxifen was seen in the cohort with atypical ductal hyperplasia in whom survival benefits were prolonged by 202, 89, and 45 days respectively, depending on age, and was deemed a cost-effective maneuver in their care. These highlight the formal description of high risk- breast lesions which would be well-served with risk reduction strategies. Further historical data from the NSABP P-1 study have been used to examine the effect of tamoxifen treatment on the incidence of benign breast disease in women at high risk for breast cancer (14). The relative risk of breast cancer for patients with adenosis, cyst, duct ectasia, fibrocystic disease, fibroadenoma, fibrosis, hyperplasia, or metaplasia was estimated for participants who received either tamoxifen or placebo (14). Overall, tamoxifen reduced the risk of the development of breast cancer from these benign breast diseases by 28%, occurring predominantly in the subset of women younger than 50 years (14). This further strengthens the rationale for the use of tamoxifen as a chemopreventive strategy.

Another cohort of women at high risk for development of breast cancer are those with BRCA mutations. Carriers of both BRCA1 and 2 have an 80% lifetime risk for breast

cancer (15). These mutations also confer a risk of cancer in the opposite breast of approximately 3% per year (16). However, there are limited data on the benefits of tamoxifen in this situation to date (17,18). The P-1 trial had 19 participants with BRCA1/2 mutations who later developed breast cancer. Use of tamoxifen reduced disease in BRCA2 but not in BRCA1 carriers (17-19). Prophylactic surgery can certainly afford women who harbor BRCA1/2 mutations a substantial reduction of risk of breast cancer (20-23). For women who wish non-surgical methods of risk reduction, however, the small sample size of patients in studies with tamoxifen as chemoprevention limits the ability to support any conclusive evidence in this regard.

V. Guidelines for Chemoprevention

The National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) have established guidelines to offer women with high risk scenarios for the development of breast cancer the option of taking tamoxifen as chemoprevention after surgical options are considered (6). This risk assessment now includes evaluation for atypical hyperplasia or LCIS, and makes the recommendation for risk reduction therapy counseling for those patients who have a 5-year breast cancer risk of greater than or equal to 1.7% and a life expectancy of 10 years or greater. The duration of five years of treatment with tamoxifen for those patients who both desire risk reduction therapy as well as have no contraindication to tamoxifen, is extrapolated from the NSABP Breast Cancer Prevention Trial P-1 data.

VI. Following Patients on Tamoxifen

Physicians must also be cogniscant of the expected side effect profile of tamoxifen in order to anticipate symptoms, follow patients, and support women who are taking tamoxifen (24). Expected side effects include hot flashes, risk of deep venous thrombosis, retinopathy and cataract formation. Routine follow-up should include ophthalmologic examination for older individuals, and routine gynecologic examination including pelvic exam with Papanicolau screening. The overall rate of uterine sarcoma in the NSABP trials for women on tamoxifen (whether for prevention or in the adjuvant setting) was reported as 0.17/1,000 women-years or approximately less than 1 percent. The NCCN also highlights the need for prompt gynecologic evaluation of postmenopausal vaginal spotting or bleeding. Premenopausal patients may also benefit from bone mineral density screening as paradoxically, tamoxifen may induce bone loss in premenopausal women, but increase bone density in postmenopausal women (6). Patients should also be counseled to undergo monthly breast self-examination, and to avoid pregnancy during tamoxifen exposure. Discontinuation of tamoxifen is recommended on a short-term basis for patients undergoing elective surgery, and permanently for patients who suffer deep venous thrombois, pulmonary embolism, or stroke.

VII. Ongoing Studies

Ongoing studies evaluating other selective estrogen receptor modulators (SERMs) or aromatase inhibitors (AIs) for chemoprevention of breast cancer in women at high risk may provide other alternative strategies with different side effect profiles as compared

with tamoxifen. Raloxifene, also a SERM, differs from tamoxifen in that it bind to the estrogen receptor to block estrogen-mediated DNA transcription. Raloxifene is FDA-approved for the treatment and prevention of osteoporosis in postmenopausal women (25). The MORE trial (Multiples Outcomes of Raloxifene Evaluation) showed a significant reduction in postmenopausal osteoporosis as well as breast cancer incidence in women treated with raloxifene. In this trial, 7705 postmenopausal women with osteoporosis were randomized to placebo, 60 mg/day or 120 mg/day raloxifene for 3 years. After a median follow-up of 40 months, women treated with raloxifene enjoyed a significant reduction in fracture risk and an increase in bone mineral density as compared with those treated with placebo. In addition, the use of raloxifene showed as a secondary endpoint a reduction in the relative risk of the development of invasive breast cancer by 76% (95% CI, 0.13-0.44), with a decreased risk primarily in estrogen-receptor-positive cancers (26, 27). Side effects due to raloxifene were reported to include hot flashes, peripheral edema, leg cramps, and thromboembolic events [deep venous thrombosis (0.7% vs. 0.2% in placebo) and pulmonary embolism (0.3% vs. 0.1% in placebo), but no increase in the risk of endometrial cancers (26,27). Similarly, the CORE trial (Continuing Outcomes Relevant to Evista) continued to evaluate the effect of 4 additional years of raloxifene treatment on the incidence of invasive breast cancer in postmenopausal women with osteoporosis, with the risk reduced by 55% (HR=0.41; 95% CI, 0.21-0.71), and a reduction in the incidence of estrogen-receptor-positive breast cancers by 66% (HR=0.34; 95%CI, 0.18-0.66) (28). Adverse events were similar to those encountered in the MORE trial (28). These trials have stimulated the design of the NSABP STAR trial (Study of Tamoxifen and Raloxifene) which was initiated in 1999,

and has enrolled 20,000 postmenopausal women at high risk for the development of breast cancer (29,30). At this writing, data from this trial is expected and is to be presented at the 2006 American Society of Clinical Oncology meeting. Unpublished results suggest that the numbers of invasive breast cancer events were similar with both drugs, but the incidence of ductal carcinoma in situ was lower on tamoxifen (31). Additionally, the development of uterine cancers, deep venous thromboses, and pulmonary embolism were lower with raloxifene as compared with tamoxifen (31). Trials utilizing other SERMs chemoprevention are ongoing (6). These include the Raloxifene for Use in the Heart (RUTH) study (32) in which breast cancer risk is assessed and the HOT study, in which low-dose tamoxifen added to HRT seeks to guage risk reduction (33).

The use of aromatase inhibitors have thus far been demonstrated as reducing risk of recurrence of breast cancer and reducing the risk of contralateral breast cancer in the adjuvant setting with the superiority of anastrozole over tamoxifen borne out in the ATAC trial (Arimidex, Tamoxifen, and the Combination), specifically in the subset of women with hormone-receptor-positive breast cancer (34,35). The International Breast Intervention Study-2 (IBIS-2) is currently ongoing, and seeks to evaluate breast cancer risk reduction in 10,000 women with the use of anastrozole versus placebo (9).

VII. Conclusions:

Chemoprevention can be considered for breast cancer risk reduction in women with high risk benign but proliferative breast lesions, with tamoxifen as the current standard of care. More limited data suggests tamoxifen can be considered in women who harbor BRCA1/2

mutations. Risks and side effects profile of tamoxifen treatment must be heavily weighed on an individual bases, and risk models must be presented to the patient, along with therapeutic plan for frequent mammograms, physical exams, and appropriate ancillary follow-up. Future studies of the contribution of other SERMs and aromatase inhibition in breast cancer risk reduction are awaited.

Figure Legends:

Figure One:

Histologic Presentation of Benign Breast Disease. **Panel A** *illustrates nonproliferative fibrocystic with the formation of microcysts among normal architecture of the breast tissue and associated with interlobular fibrosis.* **Panel B** *illustrates proliferative hyperplasia without atypia as compared with a normal lobule on the left side.* **Panel C** *also shows moderate proliferative hyperplasia without atypia, with. duct partially distended by hyperplastic epithelium in the lumen.* **Panel D** *illustrates florid proliferative ductal hyperplasia without atypia, with a "crowded, jumbled-appearing" epithelial proliferation within the duct.* **Panel E** *shows atypical ductal hyperplasia characterized by a combination of architectural complexity, partially formed secondary lumens, mild nuclear hyperchromasia.* **Panel F** *shows atypical lobular hyperplasia with monotonous cells filingl the lumens of partially distended. [From Hartmann et al, NEJM 2005; 353:229-37. Reproduced with permission from the New England Journal of Medicine, MMS Reference Number: PS-2006-2368, MMS Invoice Number: RY-2006-2368.]*

Figure Two:

Interaction Profiles for Risk-Factors and Benign Breast Disease, with Comparison of the Number of Events Observed with the Number Expected. **Panel A** *shows events accounting for histologic disease compared with age;* **Panel B** *shows events compared with age and family history;* **Panel C** *shows events compiled with respect to histologic type and family history. CI denotes confidence interval, NP nonproliferative disease, PDWA proliferative disease without atypia, and AH atypical hyperplasia.* [*From Hartmann et al, NEJM 2005; 353:229-37. Reproduced with permission from the New England Journal of Medicine, MMS Reference Number: PS-2006-2368, MMS Invoice Number: RY-2006-2368.*

References:

1. Jemal A, Siegel R, Ward E, et al. Cancer Statistics, 2006. CA Cancer J Clin. 2006; 56: 106-130.

2. Gail MH. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. Journal of the National Cancer Institute 1989; 81: 1879-86.

3. Gail MH. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. JNCI 1999; 91: 1829-46.

4. Spiegelman D, Colditz GA, Hunter DL et al. Validation of the Gail et al model for predicting individual breast cancer risk. JNCI 1994; 86:600-607.

5. Claus EB, Risch N, Thompason WD. Autosomal dominant inheritance of early onset breast cancer: Implications for risk prediction. Cancer 73: 643-651, 1994.

6. Chlebowski RT, N Col, EP Winer, et al. American Society of Clinical Oncology Technology Assessment of Pharmacologic Interventions for Breast Cancer Risk reduction including tamoxifen, raloxifene, and aromatase inhibition. Journal of Clinical Oncology 20(15): 3328-3343, 2002.

7. Fisher B. Tamoxifen for the prevention of breast cancer: a report of the national surgical adjuvant breast and bowel project P-1 study. JNCI 1998; 90: 1371-88.

8. Fisher B. Tamoxifen for the prevention of breast cancer: current status of the national surgical adjuvant breast and bowel project P-1 study. JNCI 2005; 97: 1652-62.

9. Cuzick J, Forbes J, Edwards R, Baum M, Cawthorn S, Coates A, Hamed A, Howell A, Powles T; IBIS investigators. First results from the international breast cancer intervention study (IBIS-1): a randomized prevention trial. Lancet 2002; 360: 817-24

10. Powles T, R Eeles, S Ashley, et al. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomized chemoprevention trial. Lancet 1998; 352: 98-101.

11. Veronesi U, P Maisonneuve, A Costa, et al. Prevention of breast cancer with tamoxifen : Preliminary findings from the Italian randomized trial among hysterectomised women. Lancet 1998; 352: 93-97.

12. Hartmann LC. Benign breast disease and the risk of breast cancer. The New England Journal of Medicine 2005; 353:229-37.

13. Hershman D. Outcomes of tamoxifen chemoprevention for breast cancer in very high risk women: a cost effectiveness analysis. Journal of Clinical Oncology 2002; 20: 9-16.

14. Tan-Chiu E. Effects of tamoxifem on benign breast disease in women at high risk for breast cancer. JNCI 2002; 95: 302-7.

15. Antoniou A. Average risk of breast and ovarian cancer awssociated with BRCA1 and BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. American Journal of Human Genetics 2003; 72: 1117-30.

16. Metcalfe K. Contralateral brest cancer in BRCA1 and BRCA2 mutation carriers. JCO 2004.; 22: 2328-35.

17. Peshkin NF, C Isaacs. Evaluation and management of women with BRCA-1/2 mutations. Oncology 2005; 19(11):1451-1459.

18. Narod SA, JS Brunet, P Ghadirian, et al. Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Hereditary Breast Cancer Clinical Study Group. Lancet 2000; 356 (9245):1876-1881.

19. King MC. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: the national surgical adjuvant breast and bowel project NSABP-P-1) breast cancer prevention trial. JAMA 2001; 286: 2251-56.

20. Struewing JP, P Watson, DF Easton, et al. Prophylactic oophorectomy in inherited breast/ovarian cancer families. J Natl Cancer Monogr 1995; 17:33-35.

21. Rebbeck TR, AM Levin, A Eisen, et al. Breast Cancer Risk After Bilateral Prophylactic Oophorectomy in BRCA1 mutation carriers. J Natl Cancer Inst 91: 1475-1479, 1999.

22. Rebbeck TR, HT Lynch, SL Neuhausen, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med 2002; 346:1616-1622.

23. Olson JE, TA Sellers, SJ Iturria, LC Hartmann. Bilateral oophorectomy and breast cancer risk reduction among women with a family history. Cancer Detect Prev 2004; 28(5): 357-360.

24. Elmore JG, G Gigerenzer. Benign Breast Disease – The Risks of Communicating Risk. The New England Journal of Medicine 2005; 353(3): 297-299.

25. Raloxifene for postmenopausal osteoporosis. The Medical Letter on Drugs and Therapeutics 1998; 40:29.

26. Ettinger B, Black DM, Mitlake BH et al. Reduction of vertebral fracture risk in post-menopausal women with osteoporosis treated with raloxifene: Results from a 3-year randomized clinical trial. JAMA 1999; 28: 637-645.

27. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: Results from the MORE randomized trial. JAMA 1999; 281:2189-2197.

28. Martino S, Cauley JA, Barrett-Connor E, et al; CORE Investigators. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. Journal of the National Cancer Institute 2004; 96(23): 1751-1761.

29. Vogel VG. Follow-up of the breast cancer prevention trial and the future of breast cancer prevention efforts. Clin Cancer Res 2001; 7:4413s-4418s; discussion 4411s-4412s.

30. Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Wolmark N. The study of tamoxifen and raloxifene: preliminary enrollment data from a randomized breast cancer risk reduction trial. Clin Breast Cancer. 2002; 3(2):153-9.

31. Raolxifene (Evista) for breast cancer prevention in postmenopausal women. The Medical Letter on Drugs and Therapeutics 2006; 48(1234).

32. Mosca L, Barrett-Connro E, Wenger NK, et al. Design and methods of the Raloxifene Use for the Heart (RUTH) study. Am J Cardiol 2001; 88: 392-395.

33. Decensi A, Galli A, Veronesi U. HRT opposed to low-dose tamoxifen (HOT study): rationale and design. Recent Results Cancer Res 2003;163:104-11; discussion 264-6.

34. Baum M BA, Cuzick J, Forbes J, Houghton JH, Klijn JG, Sahmoud T; ATAC Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomized trial. Lancet 2002; 359(9324): 2131-2139.

35. Baum M BA, Cuzick J, Forbes J, Houghton JH, Klijn JG, Sahmoud T; ATAC (Arimidex, Tamoxifen Alone or in Combination) Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. Cancer 2003; 98(9): 1802-1810.

Figure
One:

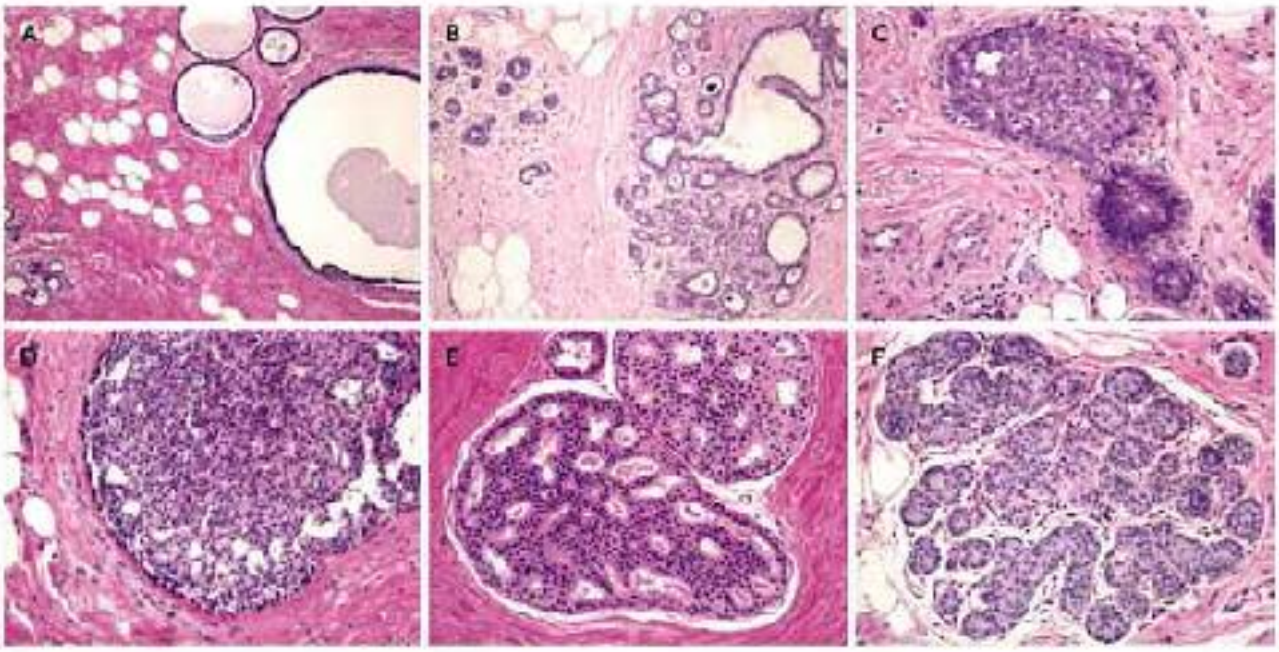

Figure Two: