Review Article Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.20185252-57

The Risk of Breast Cancer and the Role of Chemoprevention in Women With Atypical Ductal or Lobular Hyperplasia

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ARTICLE INFO

Received:
20 March 2018
Revised:
16 April 2018
Accepted:
28 April 2018

key words:
Atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), breast atypia, chemoprevention, risk reduction

ABSTRACT

Background: Women with atypical hyperplasia are about 4 times more likely to develop breast cancer compared with the general population. Atypical hyperplasia has been recommended to be used as a criterion for the inclusion of women in chemoprevention programs. Chemoprevention offers promise as a strategy for reducing the incidence of breast cancer in high-risk population.

Methods: A literature search was conducted in PubMed and Scopus databases using the search terms "breast atypia," "chemoprevention," and "risk-reducing therapy" for papers published from 1966 to Aug 2017. The search was limited to English-language papers and human studies. It yielded 114 search items. Article selection for possible inclusion was performed using the title and abstract. Finally, 12 studies were identified as eligible for inclusion in the review.

Results: The rates of atypical ductal hyperplasia (ADH) ranged from a low of 2 per 10000 mammograms in 1995 to a high of 6 per 10000 mammograms in 2011. Lobular neoplasia was an incidental finding in 0.5%–3.5% of core biopsies. True incidence of lobular neoplasia is unknown. Women with atypical breast lesions have a 5%–11% risk of developing breast cancer within 5 years and a 17%–26% risk of developing breast cancer within 10 years. The reported risk of breast cancer with atypical hyperplasia (ADH and ALH are often grouped together) is approximately 19% within 15 years. It is believed that the initiation of chemoprevention would be appropriate; if the 10-year breast cancer risk is 4% to 8%. Breast cancer risk reduction by chemoprevention is reported to be 32% to 55% in breast atypia.

Conclusion: According to our findings, patients with a diagnosis of ADH, ALH, or severe ADH should be considered for chemoprevention if they are at least 35 years of age and have no contraindications to treatment. Only 4%–20% of high-risk women decide to take chemoprevention, on average.

Introduction

One in eight women in developed countries is expected to develop breast cancer (BC) sometime in her lifetime.[1]

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It is controversial whether breast cancer arises from premalignant lesions. In 1985, Dupont and Page reviewed more than 10 000 benign breast biopsies and, based on strict pathologic criteria, divided them into three distinct categories: non-proliferative lesions, proliferative lesions without atypia, and atypical hyperplasias. They found that breast cancer risk in women with atypical hyperplasia was 4.4 times that of the general population,[2] and subsequent research lent support to that finding.[3,4] The reported risk of breast cancer for

women with atypical hyperplasia [atypical ductal hyperplasia (ADH) and lobular hyperplasia (ALH) are often grouped together] is approximately 19% within 15 years.[5] The propensity score demonstrated that 54.7% of cancers in women could have been prevented with the use of chemoprevention at a mean follow-up of 68 months.

The standard of care for ADH found on core biopsy remains excision. Following excision, patients with ADH should be referred for breast cancer risk assessment and risk reduction counseling. Routine excision following a core biopsy diagnosis of lobular neoplasia is not indicated in cases with radiographic-pathologic concordance.[6-9] Patients with a core biopsy diagnosis of lobular neoplasia (which includes ALH and classic LCIS), deemed concordant with imaging, should be counseled regarding the increased future breast cancer risk conferred by these lesions and the need for continued surveillance.

Age and estrogen exposure (early menarche, late menopause, nulliparity, use of exogenous hormones) are risk factors for breast cancer. High risk populations for breast cancer are considered to be women with ductal or lobular carcinoma *in situ*, women with a history of thoracic radiotherapy before the age of 30 years, women who have a 5-year breast cancer risk of ≥ 1.7%,[10] and women with atypical hyperplasia. According to the modified Wellings-Jensen model of breast cancer evolution, benign breast lesions such as ADH, a result of hyperplastic enlarged lobular unit formation, may evolve into ductal carcinoma *in situ* and, eventually, develop into invasive breast malignancy.[11, 12] Currently, women with atypical hyperplasia are not included in the guidelines for high-risk women, and it has been recommended that the updated versions include them.[1] Multiple models have been developed to help with prediction of breast cancer risk, including the Gail model,[13] the Tyrer-Cuzick model,[14,15] the Claus model[16], and several others.[17]

Chemoprevention uses pharmacologic or natural agents to prevent cancer development. Women aged 35 years and older who are at high risk of breast cancer (with a 5-year predicted risk for breast cancer of at least 1.66%) are recommended to take breast cancer risk-reducing agents such as tamoxifen.[18] A key driver of breast carcinogenesis is estrogen receptor α (ESR1) signaling. Consequently, agents that modulate ESR1 activity or deplete its ligand decrease breast cancer incidence.[19] Tamoxifen has previously been shown to reduce circulating IGF-1, a surrogate endpoint biomarker for phase II chemoprevention trials.[19] Tamoxifen significantly downregulates known estrogen response genes, such as *ESR1* and *SERPINA3,* but, notably, the *Ets* oncogene family transcription factor ETV4 was also significantly downregulated. Tamoxifen exerts a significant antiproliferative effect in some, but not all women, regardless of menopausal status.[5, 20] Tamoxifen has been shown to reduce the incidence of estrogen receptor-positive, but not estrogen receptor-negative, breast cancer.[1] NSABP P-1 trial recommended the use of atypical hyperplasia as a measure for the inclusion of women in chemoprevention programs.[21]

The purpose of this study was to review the literature on the risk of breast cancer based on ductal or lobular atypia to determine the effectiveness of chemoprevention in decreasing this risk. Information provided in this review will benefit health care providers who care for women at high risk for breast cancer by providing necessary information on development and delivery of breast cancer prevention. It will help readers of the chemoprevention literature to understand its strengths and weaknesses.

Methods

PubMed and Scopus databases were searched in August 2017 using the search terms "breast atypia," "chemoprevention," and "risk-reducing therapy." The search returned 114 results. After initial screening of titles and abstracts, 62 papers were identified for potential inclusion in the review. Reference lists of these papers were also reviewed for relevant articles. We identified 28 studies that addressed breast cancer chemoprevention in breast lesions with atypia. We searched for papers whose main goal was evaluation of breast cancer risk reduction in atypical breast lesions (ADH and ALH) by chemoprevention. Our search was limited to English-language papers and human studies. A total of 12 studies met all inclusion criteria.

Results

Incidence of Atypical breast lesions

The rates of ADH diagnosis ranged from a low of 2 per 10000 mammograms in 1995 to a high of 6 per 10000 mammograms in 2011.[22] Lobular neoplasia was an incidental finding in 0.5%–3.5% of core biopsies. True incidence of lobular neoplasia was unknown.[6-9]

Atypia as a cancer precursor

Women with atypical breast lesions have 5%–11% risk of developing breast cancer within 5 years and a 17%–26% risk of developing breast cancer within 10 years.[5] McEvoy and colleagues retrospectively evaluated the outcomes of the lesions in women under age 35 diagnosed with ADH, ALH, lobular carcinoma *in situ* (LCIS), and severe ADH from 1987 to 2010. They concluded that young women with atypical breast lesions were significantly more likely to develop breast cancer and recommended that they be followed closely.[23] A meta-analysis by Dyrstad et al found the summery risk estimate for developing breast cancer following

a biopsy showing atypical hyperplasia not otherwise specified was 3.93 (95% CI: 3.24–4.76).[24] A large cohort study at the Mayo Clinic also found a similar increased risk of breast cancer in women with atypical hyperplasia. They found that 30% of the women had developed breast cancer (*in situ* or invasive) 25 years after the atypical hyperplasia was confirmed by biopsy and that the number of foci of the hyperplasia was correlated with the risk of breast cancer.[4]

Cancer prevention in atypical lesions of the breast

Khan et al suggested that the use of antiestrogen agents such as tamoxifen might be an effective strategy for preventing breast cancer in women with benign breast disease (BBD) as patients with BBD who had estrogen receptor-positive epithelium were more likely to develop breast cancer later in life.[25]

Table1. Risk estimate of breast cancer after diagnosis of atypical lesion

Authors	Atypical lesion	OR	Cancer development	Mean (months)
Dyrstad *et al.*[24]	Atypical hyperplasia	3.24–4.76 (0.95 CI)		
	ADH	2.54–4.23 (0.95 CI)		
	ALH	2.81–5.47 (0.95 CI)		
Zhou *et al.*[27]	ADH	2.93 (0.95 CI)		
	ALH	5.14 (0.95 CI)		
Coopey *et al.*[5]	ADH		17.3%	120
	ALH		20.7%	120
	LCIS		26.7%	120
	Severe ADH		26%	120
	Atypical lesion (1658 patients without treatment)		184 (11.1%)	86
McEvoy *et al.*[23]	Atypical lesion (58)		7 (12%)	68

Tamoxifen treatment has also been shown to reduce the risk of BBD by 28% (RR = 0.72, 95% CI: 0.65–0.79) and the risk of biopsy by 29% (RR = 0.71, 95% CI: 0.66–0.77).[26]

Coopey and colleagues evaluated women's risk of breast cancer based on atypia type to determine the effectiveness of chemoprevention in decreasing the breast cancer risk.[5] They analyzed 2938 women diagnosed with atypical breast lesions and 2459 patients with atypia in 1999 and beyond. They reported that chemoprevention had significantly reduced breast cancer risk for all atypia types (P = 0.001). In terms of age at atypia diagnosis, women aged 50 years and older (age range: 50–93) had a statistically significant reduction in breast cancer risk with chemoprevention (P = 0.001, HR = 0.34). The hazard ratio for invasive cancer with chemoprevention compared with no chemoprevention was 0.48, suggesting a 52% reduction in risk with chemoprevention (P = 0.029). Similarly, the hazard ratio for ductal carcinoma *in situ* with chemoprevention compared with no chemoprevention was 0.45, suggesting a 55% risk reduction with chemoprevention (P = 0.024). They calculated that if all women diagnosed with atypia in 1999 and beyond took chemoprevention, they could have prevented 69 out of the observed 126 (54.7%) cancers that occurred during that time period. They concluded that the breast cancer risk in atypical breast lesions could be reduced by an estimated 50% at 5 years (from 8.3% to 4.1%) and 65% at 10 years (21.3% to 7.5%) using chemoprevention.[5]

Four large trials with long-term follow-up have been conducted to evaluate the efficacy of tamoxifen treatment in preventing breast cancer in high-risk women: the Royal Marsden tamoxifen prevention trial, National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (NSABP-P1), an Italian study, and the International Breast Cancer Intervention Study I (IBIS-I).

The NSABP-P1 (1992–1997) included a total of 13954 patients, of whom 13388 (95.9%) were randomly assigned to receive, in a double-masked manner, 20 mg/day of either tamoxifen or placebo for 5 years. The incidence of breast cancer, both invasive and noninvasive, was reduced significantly as a result of tamoxifen administration. The number of cancer events in the placebo group was almost twice as many as that in the tamoxifen group. The number of invasive breast cancer cases was 175 in the placebo group vs 89 in the tamoxifen group (P < 0.00001), corresponding to a 49% reduction in the overall risk. Women who were ≥ 60 years old at randomization experienced a greater tamoxifen-associated reduction in breast cancer incidence compared with those who were < 50 at randomization (55% vs 44%). Subgroup analyses revealed that chemoprevention had reduced the risk of breast cancer by 56% among women with a history of LCIS and by 86% in women with a history of atypical hyperplasia.[18]

The Royal Marsden trial randomized 2471 eligible high-risk women to take either placebo or tamoxifen (20 mg daily) for eight years. Upon

Table 2. Chemoprevention effect on breast cancer risk reduction in breast atypia

Study		No.	Person-Years	Observed events	Expected events	RR	95% CI
Mayo-cohort[4]	Overall atypia group	331	4543	66	17	0.388	3.00–4.94
NSABP-P1[18]	Women assigned to tamoxifen	6681	26154	89		0.51	0.39–0.66
	Women assigned to placebo	6707	26247	175			
Boston[5]	Atypia group Without chemoprevention	1658		184 (11.1%)	21.3%		
	Atypia group assigned to chemoprevention	615		36 (5.8%)	7.5%	HR:0.48	55% reduction
RMPT[20]	Atypia group assigned to chemoprevention	2471				32% reduction in risk	

follow-up evaluation after a median of 18.4 years from randomization (years after the 8 years of tamoxifen was complete), the researchers noticed a 32% reduction in ER/PR-positive primary breast cancer incidence, a demonstration of the consistent "carryover protective effect" of long-term estrogen deprivation therapies used to treat or prevent breast cancer.[20]

In a meta-analysis by Ropka and associates, patients' decision about breast cancer chemoprevention was evaluated. They reviewed 9 studies that had reported the hypothetical uptake, i.e., the rate of participants' showing interest in getting chemoprevention medication, and 5 reporting real uptake, namely, acceptance of chemoprevention medication (mean uptake rates: 24.7% and 14.8%, respectively). Using logistic regression, they found significant correlation with type of decision (hypothetical versus real, OR: 1.65; 95% CI: 1.26–2.16), educational or decision support intervention (provided vs not, OR: 0.21; 95% CI: 0.17–0.27), and cohort risk for breast cancer (high-risk vs general population, OR: 0.65; 95% CI: 0.56–0.75). Increased uptake was consistently correlated with perceived vulnerability, and reduced uptake was correlated with concern for adverse effects.[28]

Discussion

In this study, we reviewed published studies evaluating the association of biopsy-proven atypical lesions of the breast with the risk of developing breast cancer. Proliferative BBD with atypia confers a relative risk for future breast cancer of 4.[1, 24] The mean duration from initial diagnosis of BBD to diagnosis of breast cancer was 9.4 years.[25] As the screening methods improve, the diagnosis of atypical lesions at an early stage increases, and this relative risk is shown to be even higher in more recent studies. There are reports indicating that women with atypical breast lesions have a 5%–11% risk of developing breast cancer within 5 years and a17%–26% risk of developing breast cancer within 10 years. For LCIS, prior studies have found a 4% risk of breast cancer at 5 years, a 7%–13% risk at 10 years, and a17%–28% risk at 15 years.[5]

The Mayo Clinic study also found a similar increased risk of breast cancer in women with atypical hyperplasia. They found that 30% of the women had developed breast cancer (*in situ* or invasive) 25 years after the atypical hyperplasia was confirmed by biopsy and that the number of foci of the hyperplasia was correlated with the risk of breast cancer.[4]

A recently published consensus statement on the use of preventive therapy for breast cancer recommends that the initiation of chemoprevention would be appropriate if the 10-year breast cancer risk is 4%–8%.[29] It is estimated that up to 50% of breast cancers could be prevented among women at least 35 years old at elevated risk using currently available chemoprevention strategies.[23] The American Society of Clinical Oncology recommends discussion of chemoprevention with women who have an increased 5-year risk for breast cancer and endorses consistent use of benign breast biopsy morphology for risk classification.[30] According to our findings, patients with a diagnosis of ADH, ALH, LCIS, or severe ADH meets this criterion and should be considered for chemoprevention if they are at least 35 years old and have no contraindications to treatment. Contraindications to treatment with tamoxifen include the following: history of deep venous thrombosis, thrombotic stroke, pulmonary embolus, known inherited clotting trait, transient ischemic attack, and pregnancy.[5] Furthermore, the risk to benefit ratio of chemoprevention needs to be individualized for each patient based on menopausal status, presence of a uterus, and other comorbidities.

Most women elect not to take chemoprevention agents despite the overall risk reduction established. Only 4%–20% of high-risk women decide to take chemoprevention, on average.[5] Contributing factors to this decision include fear of potential side effects, physicians' not recommending it, and patients' perception that their breast cancer risk is not that high.[28]

Atypical hyperplasia is associated with a significant increase in the risk of developing breast cancer. This necessitates the development of management strategies such as risk-reducing therapies for women with benign breast lesions with atypia. There is still much room for improvement. Physicians should counsel patients with ADH and ALH, especially those with a life expectancy of ≥10 years, about the effectiveness of chemoprevention in decreasing their breast cancer risk. These women are considered to be at increased risk for breast cancer and must receive tailored counseling on how they might decrease their risk of breast cancer. Furthermore, the risk to benefit ratio of chemoprevention needs to be individualized for each patient.

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