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Is Tamoxifen Prophylaxis Effective in Reducing the Incidence of Breast Cancer in Women Who Are at High Risk?

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ABSTRACT

OBJECTIVE: The objective of this EBM review is to determine whether or not Tamoxifen prophylaxis is effective in reducing the incidence of breast cancer in woman who are at high risk.

STUDY DESIGN: Review of three English language primary studies published from 2005 to 2007.

DATA SOURCE: Three double-blind randomized control trials found using the PubMed and Cochrane database.

OUTCOME MEASURED: The primary outcome by all three studies included incidence of breast cancer.

RESULTS: Three double- blind randomized controlled trials were included in this review. Study by Powles et al showed statistically significant reduction in the incidents of breast cancer in the tamoxifen arm compared to placebo group. The second study by Cuzick et al showed the risk - reducing effect of tamoxifen appears to persist for at least 10 years. The third study by Fisher et al showed the rate of invasive breast cancer was reduced from 42.5 per 1000 women in the placebo group to 24.8 per 1000 in the tamoxifen group.

CONCLUSION: The result of three RTC's showed that use of tamoxifen prophylaxis for breast cancer provides risk-reducing effect in women at high risk.

KEY WORDS: tamoxifen prophylaxis and breast cancer, breast cancer prevention.

INTRODUCTION

Breast cancer is the most common cancer among American women. About 1 in 8 women in the United States will develop breast cancer. It is the second leading cause of death in women[4.] Most women that are affected by breast cancer do not have any family history of breast cancer, but women who does have an significant risk of developing breast cancer during their lifetime.

Woman that have family history often inherit BRCA1 and BRCA2 gene from either mother or father. Women with these mutations have a 55-65% risk of developing breast cancer by age of 70.[4] The focus of this study will be patients that are at high risk of breast cancer.

In 2014 there are about 232,670 new cases of invasive breast cancer and 10 % of all cancers are due to family history of breast or ovarian cancers or genes that are inherited from parents.[4] BRCA1 and BRCA2 is the most common cause of hereditary breast cancer. Patients with BRCA 1 mutations has as hight as 80% lifetime risk of developing cancer. For patients with BRCA 2 the risk is lower around 45 %. There are also other gene mutations that can lead to inherited breast cancer. These mutations are ATM, TP53, CHEK2, PTEN, CDH1 but they are much rarer and often do not increase the risk of breast cancer as much as the BRCA genes. [6] According to National Cancer Institute, it is estimated that 16.5 billion is spent every year on treating breast cancer in women. [5]

Some of the usual methods used to treat breast cancer is total mastectomy or modified radical mastectomy. Chemotherapy, radiation therapy and targeted therapy are some of the other options . In targeted therapy, monoclonal antibodies or tyrosine kinase can be used.

The topic of study is important to healthcare providers because preventive measures can be initiated such as using tamoxifen not only post breast cancer, but also as prophylaxis in women with high risk of developing breast cancer.

OBJECTIVE

The objective of this systemic review is to determine whether or not Tamoxifen prophylaxis is effective in reducing the incidence of breast cancer in woman who are at high risk.

METHODS

The three studies included in this review used specific criteria for selection of studies. The population included healthy women with high risk of developing breast cancer. All studies excluded any patients with breast cancer, prior invasive cancer, DVT, patients who have taken estrogen or progesterone therapy within 3 months of randomization or patients not in high risk. [1,2,3]

The intervention used in all three studies was Tamoxifen 20 mg/day . The treatment groups were compared to the control groups who were given placebo. The main outcome measured was incidence of breast cancer at 7 years, 96 months and 20 year follow-up. The studies were double blind, randomized and placebo controlled.

The study performed by Powles et al were given 20 mg/day or placebo for 8 years and were followed for twenty years. Treatment effect was assessed by the use of a Cox regression analysis and patient who developed breast cancer were identified. [3]

The study performed by Cuzick et al randomly assigned to receive either 20 mg/day or placebo for 5 years. Results were calculated at 96 months follow-up and all statistical tests were two-sided.[1]

In the study performed by Fisher et al the population was divided into two groups who were given either tamoxifen or placebo for five years. Estimates of the net benefit of tamoxifen therapy were compared by age, race and categories of predicted breast cancer risk. [2]

Key words used in the search were tamoxifen prophylaxis and breast cancer, breast cancer prevention. All articles were published in English and in peer-reviewed journals. Articles used in review were selected using search engines such as PubMed, Medline and Cochrane. All three articles were selected based on relevance to clinical question and if its outcome mattered to the patient (POEM). The studies that were used are randomized controlled studies and summary of statistics were reported using p-value, RRR, ARR and NNT.

Table 1 - Demographics & Characteristics of included studies

Study	**Type**	**# Pts**	**Age (yrs)**	**Inclusion Criteria**	**Exclusion Criteria**	**W/D**	**Interventions**
Powles[3]	Double Blind RTC	2,494	30-70	-Women with increased risk of breast cancer -At least one 1st degree relative who was <50 years when diagnosed -one 1 degree relative with bilateral breast cancer	-Women with a history of any cancers.	22	Tamoxifen 20mg/day
Fisher[2]	Double Blind RTC	13,388	35-59	- Women with increased risk - Women with negative mammogram	- If pt had taken estrogen or progesterone replacement therapy within 3 month of randomization.	181	Tamoxifen 20mg/day
Cuzick[1]	Double Blind RTC	7,145	35-70	-Women with at least twofold relative risk if they were 45-70 years of age, fourfold relative risk if they were 40-44 years of age, and tenfold risk if they were 35-39 years of age.	Women that had any previous invasive cancer or DVT.	6	Tamoxifen 20mg/day

OUTCOME MEASURED

The primary outcome measured was the incidence of breast cancer after tamoxifen prophylaxis was administered. IBIS -I trial measured outcome based on 96 month follow up after randomization. Relative risks were computed as the ratio of incidence rates and randomization was performed by telephone or fax at the IBIS center. Incidence rates were calculated by dividing the number of observed events by the number of women-years of follow-up, which continued until the development of breast cancer, death, or cutoff date for analysis. [1]

P-1 Study measured outcome by calculating rates of breast cancer and were compared by the use of risk ratios and 95% confidence interval. Estimate of the benefit from 5 years of tamoxifen therapy was then compared by age, race and categories. [2]

The primary outcome of Royal Marsden prevention trial was occurrences of breast cancer. Survival was assessed by the use of a Cox proportional hazards model, all tests were two-sided. [3]

RESULTS

Three double randomized controlled trials were analyzed in this review. All participants were healthy women with no evidence of breast cancer and with increased risk of developing one because of their family medical history of breast cancer. Patients with history of any cancer , deep vein thrombosis or pulmonary embolism were also excluded from the trial. [1,2,3]

In Powles, et al., 186 women developed invasive breast cancer, 82 that were on tamoxifen and 104 that were on placebo. This difference is not statistically significant (p=0.1). Results were reported at twenty-year follow-up. The absolute risk reduction (ARR) was calculated at 1.4% and the relative risk reduction (RRR) was 6.4%. In this study it was

determined that the number needed to treat (NNT) was 71 indicating that intervention is not effective. (Table 2)

Fisher et al., reported rates of breast cancer at 2.2% in tamoxifen group and 3.8% in the placebo group, respectively. These results were calculated at seven year follow-up. After 7 years results show that the difference in results is statistically significant (p= <.001). The risk ratio (ARR) was calculated to be 1.6% and the relative risk reduction (RRR) was 73%. This study determined that the number to treat (NNT) was 63. The effectiveness of tamoxifen was also assessed by comparing the rates of developing cancer each year during years 2-5. In the year 6 the reduction was 29% but in the year 7 it was only 14%.

Cuzick et al., reported that prophylactic effect of tamoxifen was fairly consistent for the entire follow-up period and no reduction of benefit was observed for up to 10 years after randomization. At 96 months after randomization, 142 (5.4 %) breast cancers were diagnosed in tamoxifen group and 195 (3.9%) in placebo group. This difference is also statistically significant (p=0.004). The ARR was calculated to be 1.5% and the RRR was 0.28 %. The number needed to treat (NNT) in this study was determined to be 66.

Table 2 -Efficacy of Tamoxifen prophylaxis in reducing the incidence of breast cancer.

Study	CER	EER	RRR	ARR	NNT	95%CI	p-value
Royal Marsden	7.8%	9.2%	17.9%	1.4%	71	0.58-1.04	0.1
National surgical adjuvant Breast and Bowel Project P-1 Study	2.2%	3.8%	73%	1.6%	63	0.46-0.70	0.001
IBIS-I Trial	5.4%	3.9%	-0.28%	-1.5%	-66	0.58-0.91	0.004

DISCUSSION

Tamoxifen is usually used to treat metastatic cancer, and to also treat breast cancer in certain patients after surgery. Now tamoxifen is also used in reducing the chances of breast cancer in women with high risk, such as family history of breast cancer. A major problem with tamoxifen is deciding whether benefit to the patient is greater than risk of taking it. [7] One of the problems with using tamoxifen in older people is that it was only studied in younger population, therefore it is unknown whether tamoxifen will work exactly the same way it does in younger adults. [8] In IBIS-I trial it was also discovered that tamoxifen therapy can increase risk of cardiovascular and thromboembolic events so as endometrial cancer. However, according to FDA tamoxifen is currently approved in use of preventing recurrence of breast cancer and it was concluded that tamoxifen benefits outweigh risk in women already diagnosed with breast cancer. The use of tamoxifen for prevention of breast cancer is currently used as an "off-label" and it is up to physician and the patient to make the determination whether they have enough confidence that the benefit would outweigh not only know risks but also the ones that are unknown at this time. [7]

CONCLUSION

According to Royal Marsden trial it was concluded that it was not statistically significant to demonstrate efficacy of tamoxifen in preventing invasive breast cancer in women at high risk. It did show significant reduction in the incidence of ER-positive breast cancer. There was also some limitations noted, this study was a single- institute, small study and participants were younger with stronger family history of breast cancer than those in other trials. [3]

Based on Cuzick et al., and Fisher et al., it can be concluded that tamoxifen prophylaxis is effective in reducing the incidence of breast cancer in women who are at high risk. According to Cuzick et al., the risk reducing effect appears to persist for at least 10 years , but the adverse effects do not continue after 5 year treatment period.

It was also indicated that the thromboembolic events and endometrial cancers were confined to the treatment period only. [1]

Future research should be designed to compare tamoxifen prophylaxis vs prophylactic mastectomy . The research should implement the efficacy and safety one over the other preventive measures.

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