Estimating the Risks and Benefits of Tamoxifen Chemoprevention for Breast Cancer in Brazil

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ABSTRACT

Background

According to the National Surgical Adjuvant Breast and Bowel Project (NSABP-P1), tamoxifen can prevent 49% of invasive breast cancers in patients who have a five-year risk of 1.67% or more. Because tamoxifen is associated with side effects (endometrial cancer and stroke), it is necessary to weight the risks and benefits of using tamoxifen for prevention of breast cancer. The aim of this paper is to calculate a risk-benefit index based on the Brazilian population to assess the feasibility of Tamoxifen as a chemopreventive agent.

Results

Results showed that with increasing age, the greater the five-year risk of breast cancer would have to be for a positive risk-benefit index. This shows that more risk exists in older women with the use of tamoxifen, precisely because of the values of incidence and mortality of the assessed diseases that increase with age in the population.

Conclusion

This study presents a methodology to determine the benefits and risks associated with chemoprevention with tamoxifen in the Brazilian population.

Keywords: Breast Neoplasms, Tamoxifen, Chemoprevention

BACKGROUND

Breast cancer is the most prevalent cancer in women worldwide and in Brazil (1). Chemoprevention has the potential to be a major approach to reducing the incidence of breast cancer among high-risk populations (2-4). The Breast Cancer Prevention Trial (BCPT) was a randomized, placebo-controlled study that evaluated the effects of tamoxifen (20mg once daily for up to 5 years) on a population of women at high risk for Breast cancer (7). To be eligible for the study, women had to be over 60 years old or have a projected 5-year risk of invasive breast cancer equal to or greater than that of an average 60-year-old woman (1.66%).

In 1998, the National Cancer Institute (NCI) and the National Surgical Adjuvant Breast and Colon Project (NSABP-P1) released data from the BCPT demonstrating that treatment with tamoxifen reduces the risk of invasive breast cancer (7). Based on this study, the U.S. Food and Drug Administration (FDA) approved tamoxifen as a preventive agent for breast cancer.

Data from the BCPT showed a 49% reduction in invasive breast cancer. There was also a 50% reduction in the risk of noninvasive breast cancer, and in the incidence of fractures, including hip fractures, in individuals receiving tamoxifen. However, some women on the BCPT have also experienced life-threatening side effects from the use of tamoxifen, such as endometrial cancer, pulmonary embolism, stroke, and deep venous thrombosis. Tamoxifen increases the risk of endometrial cancer by 2.53 times, the risk of ischemic stroke by 1.59 times and the risk of pulmonary embolism by 3.01 times (7).

The variety of side effects due to the use of tamoxifen makes the decision of chemoprevention a complex issue. A well-made decision depends on the risk profile of each woman and their preferences and expectations in their treatment. The assessment between benefits and side effects of tamoxifen depends on age and other factors, such as the underlying risk of breast cancer and history of hysterectomy.

Gail et al. (6) proposed a risk-benefit index to weigh the risks and benefits of chemoprevention with tamoxifen. They showed that tamoxifen would be more beneficial for younger women with an increased risk of breast cancer. They also demonstrated that tamoxifen was not suitable for older patients with a low risk for breast cancer.

The indication of chemoprevention for breast cancer should be evidence-based and reflect the situation of the population served. The objective of this study is to calculate a risk-benefit index based on a Brazilian database in order to evaluate the viability of using tamoxifen for chemoprevention in Brazilian women defined as high risk for breast cancer.

METHODS

The methodology used was based and reproduced according to the work developed by Gail et al (6). This study defines a risk-benefit index for the use of tamoxifen for chemoprevention of breast cancer in high-risk patients based on incidence rates and population mortality.

To calculate a risk-benefit ratio for the use of tamoxifen different data sources were used. There are no data on the exact chemopreventive effects of tamoxifen for Brazilian women, as there is no prospective, controlled and randomized study with the use of tamoxifen for chemoprevention of breast cancer in the Brazilian population.

To define the preventive effects of tamoxifen it was assumed that its effect on Brazilian women was the same as on American women. The relative risks of breast cancer, hip fracture, endometrial cancer, and ischemic stroke were used from the NSABP-P.1.study (5). Relative risks with a 95% confidence interval are presented in Table 1.

The data of incidence were collected from the database of the Ministry of Health - SUS Hospital Information System (SIH / SUS) in the year 2010. Incidence data on endometrial cancer, hip fracture and ischemic stroke were compiled, both for the white race and for the black race. The results of the mortality rates were also extracted from the database of the Ministry of Health - SUS Hospital Information System (SIH / SUS) in 2010.

To assess the risks and benefits of tamoxifen chemoprevention, the methods of Gail et al.(6) were followed. The benefits of tamoxifen are the prevention of both invasive breast cancer and hip fracture. The risks of using tamoxifen are considered as endometrial cancer and stroke (Figure 1). To summarize the risks and benefits of using tamoxifen in a single number, the risk-benefit index was defined according to Equation 1 (Figure 2).

To calculate the expected number of cases of invasive breast cancer prevented over a 5-year period, the estimated risk in 5 years of invasive breast cancer was multiplied by the relative risk reduced by tamoxifen. The relative risk used was that obtained in the NSABP-P1 study of 0.51. This data shows that if 100 women use Tamoxifen 49 cases of invasive breast cancer will be prevented.

To calculate the expected number of hip fractures, endometrial cancer and ischemic stroke, we used Equation 2 (Figure 3), which is the same method as that of Gail et al (6). In Equation 2, the hazard rate is determined by the incidence rate multiplied by the relative risk of the NSABP-P1 study (Table 1). In individuals not treated with tamoxifen, the relative risk is equal to 1, so that the hazard rate is the same as the incidence rate. The mortality rates from other causes were calculated by subtracting the specific mortality rate from the general mortality rate.

In the same way as the study by Gail et al, it was assumed that the magnitude of each case of breast cancer, hip fracture, endometrial cancer and ischemic stroke were the same. If the risk - benefit index is negative, it shows that tamoxifen has more

risks than benefits, however, if its value is positive, it is concluded that the benefits in its use prevail.

RESULTS

The data obtained according to Equation 2 are shown in Table 2 and Table 3. The results of the estimated numbers of hip fractures, endometrial cancer and ischemic strokes are organized between the treated groups (hazard ratio based on Relative risk of the NASBP study) and not treated with tamoxifen (hazard ratio equal to the incidence rate).

According to the data, it was observed that the expected numbers of hip fractures and ischemic strokes in women not treated with tamoxifen increased with age, both for the white race and the black race. The expected number of endometrial cancer was highest in the sixth decade of life.

The calculated numbers of expected injuries in 5 years for hip fracture were lower for treatment with tamoxifen, while the numbers calculated for endometrial cancer and ischemic stroke were higher for tamoxifen treatment. This trend was true for all age groups. In the age range of 50-59 years, the calculated number of hip fractures decreased practically by half with tamoxifen treatment, both for white race and for black race among Brazilian women.

The risk-benefit index calculated according to Equation 2 is shown in Table 4 (white race) and Table 5 (black race), organized by age group and risk of developing invasive breast cancer in 5 years. In the tables, the shaded area shows a positive risk-benefit index, that is, in which the benefits of using tamoxifen outweigh the risks.

DISCUSSION

Regarding the 5-year risk of breast cancer and the risk-benefit index, it was observed that with increasing age, the risk of breast cancer in the 5-year period would have to be higher in order to obtain a positive risk-benefit index. This demonstrates that the greater the age, the more risks there are with the use of tamoxifen, precisely because of the incidence and mortality values of the evaluated diseases that increase with age in the population.

The data in Tables 4 and 5 show that in the Brazilian population the risks of using tamoxifen are greater than the benefits in older women, both for the white race and for the black race. This conclusion was also obtained in Korean and North American studies (6,7). The Korean study presented the result that only women younger than 40 years had a positive risk-benefit for the use of tamoxifen, while according to the American study patients younger than 50 years old had more benefits than risks.

Limitations of this study are that the side effects of tamoxifen were estimated from the BCPT study of NSABP-1, in which 96.5% of the sample consisted of white women. Estimates determined in this study were based on the assumption that risks and benefits of using tamoxifen for black women would be the same as for the white race, but this may not be entirely true since the reference study did not obtain an equal sample number for the different ethnicities. The Gail et al study assumed that the injuries evaluated as risks of tamoxifen had the same magnitude of effect on the risk-benefit index, however each event has different mortality and cost. In addition, the magnitude of each event is subjective and each woman has different concerns regarding tolerable side effects.

CONCLUSION

The decision to use tamoxifen to reduce the risk of breast cancer is complicated by the presence of several potential risks that should be weighed against the potential beneficial effects. In this paper, a methodology was presented to determine the benefits and risks associated with chemoprevention with tamoxifen.

The credibility of chemoprevention as a rational approach to prevent breast cancer has been supported by the results of several clinical trials conducted in populations of high risk for the development of breast cancer. Future work should include research and development of tools that accurately identify ideal candidates for chemoprevention strategies and that establish the risks and benefits of prevention treatments for breast cancer.

ABBREVIATIONS

- BCPT: Breast Cancer Prevention Trial
- NCI: National Cancer Institute
- NSABP-P1: National Surgical Adjuvant Breast and Colon Project
- FDA: U.S. Food and Drug Administration
- SIH / SUS: Ministry of Health - SUS Hospital Information System

DECLARATIONS

- Ethics approval and consent to participate: Not applicable

  Formal ethics approval was not required according to national guidelines. It is determined that research that uses public accessible information will not be registered or evaluated by formal ethics approval, pursuant to Law no. 12,527, of November 18th, 2011; which can be found at: http://conselho.saude.gov.br/resolucoes/2016/Reso510.pdf

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FIGURE LEGENDS

Table 1 – Assumed relative risks from NSABP-P1 study

Injury	Relative risk	95% CI
Breast Cancer	0,51	0,39-0,66
Hip Fracture	0,55	0,25-1,15
Endometrial cancer	2,53	1,35-4,97
Ischemic stroke	1,59	0,93-2,77

NSABP-P1 = National Surgical Adjuvant Breast and Bowel Project P1; CI= Confidence interval

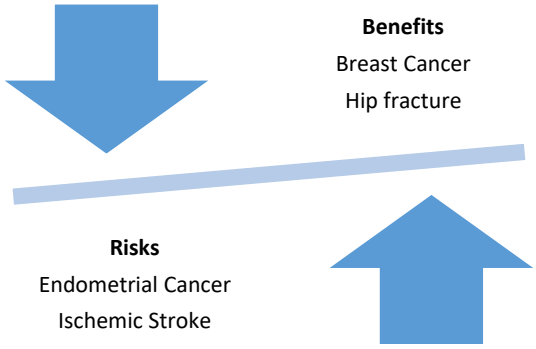

Figure 1. Weighing the risks and benefits of tamoxifen chemoprevention for Brazilian women

Figure 2. (Equation 1)

Risk-Benefit Index = *(expected number of invasive breast cancer prevented + expected number of hip fracture prevented) – (expected number of endometrial cancer + expected number of ischemic stroke)*

Figure 3.

$$(\boldsymbol{Equation\ 2})\ Expected\ number\ of\ injury\ over\ 5\ years = hazard\ rate\ /\ (hazard\ rate + mortality\ rate\ from\ other\ causes) \times [1 - exp\{-5 \times (hazard\ rate + mortality\ rate\ from\ other\ causes)\}]$$

Table 2 – Calculated numbers of injuries expected in 5 years among 10,000 Brazilian women - White Race

Injury	Age group				
	35-39	40-49	50-59	60-69	70-79
Tamoxifen Untreated					
Hip Fracture	1,14	1,65	4,09	13,08	21,83
Endometrial Cancer	1,98	3,85	4,65	7,16	4,96
Ischemic stroke	2,64	6,71	15,57	36,01	40,79
Tamoxifen Treated					
Hip Fracture	0,63	0,91	2,25	7,20	12,01
Endometrial cancer	5,01	9,74	11,75	18,10	12,53
Ischemic stroke	4,19	10,68	24,79	57,46	65,11

Table 3 – Calculated numbers of injuries expected in 5 years among 10,000 Brazilian women - Black Race

Injury	Age Group				
	35-39	40-49	50-59	60-69	70-79
Tamoxifen Untreated					
Hip Fracture	0,91	1,10	2,23	5,59	8,92
Endometrial Cancer	2,68	4,04	3,16	4,06	2,69
Ischemic stroke	2,58	6,06	13,63	29,01	31,75
Tamoxifen Treated					
Hip Fracture	0,50	0,60	1,23	3,07	4,91
Endometrial Cancer	6,78	10,21	7,99	10,27	6,82
Ischemic stroke	4,11	9,64	21,66	46,09	50,44

Table 4 –Risk-benefit index for tamoxifen chemoprevention among 10,000 Brazilian women – White Race

5-year risk (%)	Age Group				
	35-39	40-49	50-59	60-69	70-79
0,05	-6,12	-17,05	-31,85	-65,91	-63,18
0,1	-3,67	-14,60	-29,40	-63,46	-60,73
0,2	1,23	-9,70	-24,50	-58,56	-55,83
0,3	6,13	-4,80	-19,60	-53,66	-50,93
0,4	11,03	0,10	-14,70	-48,76	-46,03
0,5	15,93	5,00	-9,80	-43,86	-41,13
1,0	40,43	29,50	14,70	-19,36	-16,63
1,5	64,93	54,00	39,20	5,14	7,87
2,0	89,43	78,50	63,70	29,64	32,37
2,5	113,93	103,00	88,20	54,14	56,87
3,0	138,43	127,50	112,70	78,64	81,37
3,5	162,93	152,00	137,20	103,14	105,87

*shaded area shows a positive risk-benefit index, that is, in which the benefits of using tamoxifen outweigh the risks

Table 5 – Risk-benefit indices for tamoxifen chemoprevention among 10,000 Brazilian women – Black Race

5-year risk (%)	Age group				
	35-39	40-49	50-59	60-69	70-79
0,05	-7,93	-16,79	-25,97	-50,84	-49,90
0,1	-5,48	-14,34	-23,52	-48,39	-47,45
0,2	-0,58	-9,44	-18,62	-43,49	-42,55
0,3	4,32	-4,54	-13,72	-38,59	-37,65
0,4	9,22	0,36	-8,82	-33,69	-32,75
0,5	14,12	5,26	-3,92	-28,79	-27,85
1,0	38,62	29,76	20,58	-4,29	-3,35
1,5	63,12	54,26	45,08	20,21	21,15
2,0	87,62	78,76	69,58	44,71	45,65
2,5	112,12	103,26	94,08	69,21	70,15
3,0	136,62	127,76	118,58	93,71	94,65
3,5	161,12	152,26	143,08	118,21	119,15

*shaded area shows a positive risk-benefit index, that is, in which the benefits of using tamoxifen outweigh the risks