DR. PRIDVI KANDAGATLA (Orcid ID : 0000-0002-4252-617X)

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Patient and Provider Factors Associated with the Noninitiation of Tamoxifen for Young Women at High-Risk for the Development of Breast Cancer

Pridvi Kandagatla[1,2], Natalie N. Rizk[1], Danijela Dokic[3], Jeannie Kochkodan[4], Samantha Estevez[5], Megan Yankin[4], Sowmya Goranta[6], Katherine Huber-Keener[7], Jacqueline S. Jeruss[1]

[1]Surgery, University of Michigan

[2]Surgery, Henry Ford Hospital

[3]Medicine, Mercy Hospital

[4]University of Michigan School of Medicine

[5]Ob/Gyn, Zucker School of Medicine

[6]Internal Medicine, Michigan State University

[7]Ob/Gyn, University of Michigan

Correspondence:

Jacqueline S. Jeruss

Department of Surgery

University of Michigan

Ann Arbor, Michigan

jjeruss@med.umich.edu

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Abstract:

We sought to identify factors associated with disparities in tamoxifen utilization among young patients at high-risk for developing breast cancer. We identified 67 premenopausal, high-risk women ages 35-45, without surgical prophylaxis, who did not initiate tamoxifen. Factors associated with noninitiation were examined. 37% of patients had no documented provider-based discussion regarding initiation. Type of high-risk diagnosis was the only factor associated with a provider-based discussion ($p = 0.03$). For patients offered tamoxifen, primary reasons for noninitiation were perceived minimal benefit (66.7%), fertility concerns (16.7%), and concerns about side effects (7.1%). Implementation of comprehensive educational strategies regarding the benefits of tamoxifen should be facilitated to improve initiation among young high-risk patients.

Introduction

Breast cancer is the most common cancer affecting women across the world, and the leading cause of cancer-related death. Given the high incidence of breast cancer, effort has been placed on sensitive and specific screening strategies as well as the identification of high-risk patients. Through these strategies and implementation of antihormonal agents such as tamoxifen, prevention of breast cancer is possible. The NSABP P-1 Trial showed that the use of tamoxifen reduced the risk of estrogen-receptor positive breast cancer by 49% among high-risk patients.[1] As a result, tamoxifen is currently recommended as a chemo-preventative agent for women with an elevated breast cancer risk.[2,3] The current indications for tamoxifen as chemoprevention includes patients diagnosed with atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), a BRCA mutation, lobular carcinoma in situ (LCIS), flat epithelial atypia (FEA), or a strong family history.[4]

Given the long-term benefits of tamoxifen, young high-risk women may be a patient population that stands to obtain the greatest benefit. Despite this potential benefit, the number of eligible women, particularly young women, undergoing tamoxifen chemoprevention therapy is low.[5] The decision to initiate tamoxifen chemoprevention is complex, and multiple barriers and characteristics associated with the utilization of this therapy have been reported.[6,7] In this study,

we sought to identify factors associated with tamoxifen noninitiation among young patients with an increased risk for the development of breast cancer. With a thorough understanding of these deterring factors, providers may be able to help implement effective interventions to address these factors and increase tamoxifen initiation among young high-risk women.

Methods

Patient selection

With IRB approval, we identified women treated at Northwestern Memorial Hospital (Chicago, IL) who were younger than 46 years and received a high-risk diagnosis (BRCA mutation, LCIS, ADH, ALH, FEA, strong family history) between 2007-2012, for whom adjuvant tamoxifen was indicated, but was not initiated. Strong family history of breast cancer included first-degree female relatives. A total of 239 patients were identified. Patients who opted for surgical prophylaxis (bilateral mastectomy, bilateral oophorectomy), received a cancer diagnosis, or who initiated tamoxifen use were excluded (n=91). Additionally, women younger than 35 years (n=81) for whom tamoxifen was not indicated were excluded.

Chart review

Patient charts were reviewed for demographics, fertility concerns, and high-risk stratification. Collected data had been documented in the EMR through standardized formal Breast Cancer intake forms. Since the establishment of the Oncofertility program at Northwestern Memorial Hospital in 2007, a prompt was placed in the EMR, requiring oncologists to ask premenopausal patients about interest in fertility preservation prior to completing the medical record and the initiation of therapy. This information also was collected and compiled from providers' notes. Reviewing oncology notes and cross-referencing with pharmacies for patient's prescription data, tamoxifen use was also recorded. We examined the baseline demographic characteristics for the study patients and identified patient reasons for tamoxifen noninitiation. We also stratified the study patients by their high-risk diagnoses. A lack of documented discussion regarding tamoxifen indications or initiation were also noted. We performed Chi-Square tests with a significance value of 0.05 to identify patient factors associated with a lack of documented discussion regarding tamoxifen initiation.

Results

We included a total of 67 patients in the study. The median age was 41 (range 35-45) and majority of the patients were white (62.7%). The preponderance of the patients in our study held a high-risk diagnosis of ADH (29.9%) followed by LCIS (17.9%) and BRCA 1 mutations (17.9%) (Table 1). Patients who had a high-risk diagnosis from biopsy proven pathology and family history were categorized by biopsy proven pathology. Patients who had only a family history of breast cancer and no pathologic or genetic diagnosis (n=3, 4.5%) were listed as "Family History." Of all of the patients with a high-risk diagnosis, the majority (68.7%) did have a family history of breast cancer. In the study population, 43.3% of patients opted to forgo genetic testing. Of the 38 patients that were tested, 17 (44.7%) had no genetic mutation, 9 (23.7%) had a BRCA 2 mutation, and 12 (31.6%) had BRCA 1 mutation. Most of the patients in our study did not have a breast MRI (70.1%), but had breast biopsy (65.7%). Table 2 shows comparisons between characteristics for patients that had a documented provider discussion regarding tamoxifen initiation and those that did not. There were no significant differences in patient demographics between the two groups. There was an association between patients with a tissue diagnosis (ADH/ALH or LCIS) and a documented provider discussion about tamoxifen (p=0.03).

Reasons for tamoxifen noninitiation:

Reasons for tamoxifen noninitiation were stratified into 5 categories (Figures 1A and 1B). The most common reason for noninitiation was a perception of little benefit (41.8%). Despite the indications for tamoxifen, 37.3% of patients did not have a documented discussion with a provider regarding treatment risks and benefits. Results were further stratified into reasons for declining tamoxifen among patients who had a documented discussion. The primary reason high-risk women (66.7%) declined tamoxifen was perception of little benefit. Declining tamoxifen for fertility concerns (16.7%) was the second most prevalent reason. A relatively low number of high-risk women declined tamoxifen secondary to concerns about side effects (7.1%).

Discussion

Considering the vast amount of data detailing the preventive benefit of tamoxifen for high-risk patients, it is concerning that the most common reason for underutilization in our study was perception of little benefit. A possible explanation could be a lack of information provided to high-risk patients. However, Fagerlin found that the perception of little benefit persisted even

after providing patients with a decision aid outlining the risks and benefits of tamoxifen for chemoprevention.[8] These findings were similar to those found by Port showing that educational sessions did not affect patients' decisions regarding tamoxifen.[9] These findings indicate possible discordant perceptions of tamoxifen benefit between patients and providers. While physicians are trained to practice medicine in an evidence-based manner, patients' decisions may not be as objective. Accordingly, Donnelly found that patients tend to be influenced by their social groups.[10] Donnelly also found that some women refused tamoxifen because it served as a constant reminder of their cancer risk.[10] Thus, though an ongoing risk of cancer may encourage some to actively participate in prevention strategies, some women may approach this concern differently. To this end, Holmberg found that patients did not rely solely on a quantitative risk-benefit analysis when making decisions.[11] Instead, they incorporated their life experiences and approached decision-making in a more personally meaningful manner. These factors can pose a challenge to providers, as the communication of quantifiable information may not be adequate to help patients make decisions regarding healthcare choices. A more tailored approach is warranted to ensure that the appropriate information is conveyed to the patient, which demands both clinical time and careful attention to individual patient concerns.

Fertility concerns are a unique aspect of the younger high-risk patient population that sets this cohort apart from older postmenopausal patients. For example, despite being viable strategies, embryo and oocyte preservation options were offered only about 39-43% and 62-63%, respectively, for eligible breast cancer patients.[12] Furthermore, contrary to data establishing safety of ovarian stimulation, 42.1% of surveyed providers agreed to or were neutral about the statement that ovarian stimulation for embryo/oocyte preservation was not safe.[12] In our study, 10.4% of all patients that did not initiate tamoxifen chemoprevention stated their reason was fertility concerns. Among those patients that had a documented discussion about tamoxifen with their provider, the proportion of patients reporting fertility concerns was 16.7%. This finding may be associated with information regarding the teratogenicity of tamoxifen and the years long time frame for tamoxifen treatment. Accordingly, a desire for future fertility is an independent predictor of delayed or noninitiation of tamoxifen among patients diagnosed with breast cancer.[13] These findings underscore the importance of education regarding options for fertility preservation for patients and providers confronting tamoxifen chemoprevention. A hiatus from tamoxifen to allow patients to become pregnant is also being studied.[14] Early referral to a

provider with specialization in reproductive endocrinology to facilitate the fertility preservation discussion is critical.

Another aspect of patient perceptions about tamoxifen identified in our study was the concern about side-effects. Bober found a decrease in tamoxifen initiation among women of all ages concerned with side-effects.[15] Donnelly found the perceived impact of side effects to be a common theme among young patients accepting or declining tamoxifen.[10] Interventions to minimize the side effects of tamoxifen utilizing medications such as venlafaxine could decrease discontinuation rates and help alleviate patient concerns regarding side-effects.[16]

In terms of patient-physician communication, more than a third of the patients did not have a documented discussion with their provider regarding tamoxifen. A physician-led discussion is a major contributor to initiation of tamoxifen among patients, as the physician recommendation of tamoxifen has been associated with initiation.[15] This effect also occurs at the primary care level, as a study by Taylor and Taguchi found the opinion of the family physician to play a role in the patients' decision to start tamoxifen.[17] A lack of discussion by physicians may also be the result of a lack of provider knowledge.[18] Kaplan found that a deficit in training was a barrier in tamoxifen prescription.[19] That work also found that breast cancer risk reduction practices varied significantly based on the specialty of the primary treating provider.[19] Collectively, these findings indicate areas for standardization of information and improved medical education regarding the nature of physician discussions, bias, and inherent perceptions about the risk/benefit associated with tamoxifen.

Patient decision-making is a complex process, and physicians must ensure that the patient's decision is informed. For this purpose, a multi-disciplinary approach may be warranted in the management of young high-risk patients. Concerns over fertility or side-effects could be alleviated through a comprehensive discussion and education. Through a team approach including oncologists, surgeons, and oncofertility specialists, many concerns about tamoxifen could be addressed. We propose an algorithm for the management of these patients that may help fill the gaps in communication between providers and patients (Figure 3). Patient decision-making is a highly individualized process. Providers should be equipped to discuss evidence-based data while also offering a patient centered approach to care to ensure that patients are enabled to make most informed decisions possible.

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High-Risk Diagnosis	
ADH	20 (29.9%)
ALH	7 (10.4%)
BRCA1+	12 (17.9%)
BRCA2+	9 (13.4%)
Family Hx	3 (4.5%)
FEA	4 (6.0%)
LCIS	12 (17.9%)
Family History of Breast Cancer	
Positive	46 (68.7%)
Negative	21 (31.3%)
Family History of Ovarian Cancer	
Positive	16 (23.9%)
Negative	51 (76.1%)
Genetic Mutation Status	
BRCA1+	12 (17.9%)
BRCA2+	9 (13.4%)
No Genetic mutation	17 (25.4%)
Declined Genetic testing	29 (43.3%)
History of Breast Biopsy	
Yes	44 (65.7%)
No	23 (34.3%)
History of Breast MRI	
Yes	20 (29.9%)
No	47 (70.1%)

Table 1: **High-risk breast cancer diagnosis**

		Discussed	No Documented Discussion	p-value
n (%)		42 (62.7%)	25 (37.3%)	
Mean Age (SD)		41.3 (2.9)	40.7 (3.2)	0.44
Diagnosis				**0.03**
	ADH/ALH	19 (47.6)	8 (36.0)	
	BRCA 1+/2+	8 (14.3)	13 (48.0)	
	Family History	3 (9.5)	0 (4.0)	
	FEA	2 (7.1)	2 (8.0)	
	LCIS	10 (21.4)	2 (4.0)	
Race (%)				0.47
	White	23 (54.8)	19 (76.0)	
	Black	4 (9.5)	2 (8.0)	
	Asian	2 (4.8)	0 (0.0)	
	Other	4 (9.5)	2 (8.0)	
	Declined	9 (21.4)	2 (8.0)	
Ethnicity (%)				0.41
	Hispanic	8 (19.0)	2 (8.0)	
	Non-Hispanic	28 (66.7)	20 (80.0)	
	Declined	6 (14.3)	3 (12.0)	
Marital Status (%)				0.67
	Single	11 (26.2)	5 (20.0)	
	Married	28 (66.7)	17 (68.0)	
	Separated/Divorced/Widowed	3 (7.1)	3 (12.0)	
Alcohol Use (%)		25 (59.5)	16 (64.0)	0.72
Smoking (%)				0.65
	Never	30 (71.4)	21 (84.0)	
	Former	8 (19.0)	3 (12.0)	
	Current	3 (7.1)	1 (4.0)	
	Unknown	1 (2.4)	0 (0.0)	
Insurance (%)				0.26
	None	14 (33.3)	6 (24.0)	
	Private	27 (64.3)	16 (64.0)	
	Public	1 (2.4)	3 (12.0)	
Family History (%)				0.61
	None	13 (31.0)	8 (32.0)	
	1st Degree Relative	18 (42.9)	8 (32.0)	
	Non-1st Degree Relative	11 (26.2)	9 (36.0)	
Anxiety (%)		7 (16.7)	4 (16.0)	1.00
Obesity (%)		4 (9.5)	4 (16.0)	0.46
Nulliparous (%)		24 (57.1)	13 (52.0)	0.50

Table 2: Physician Discussion of Tamoxifen Initiation.

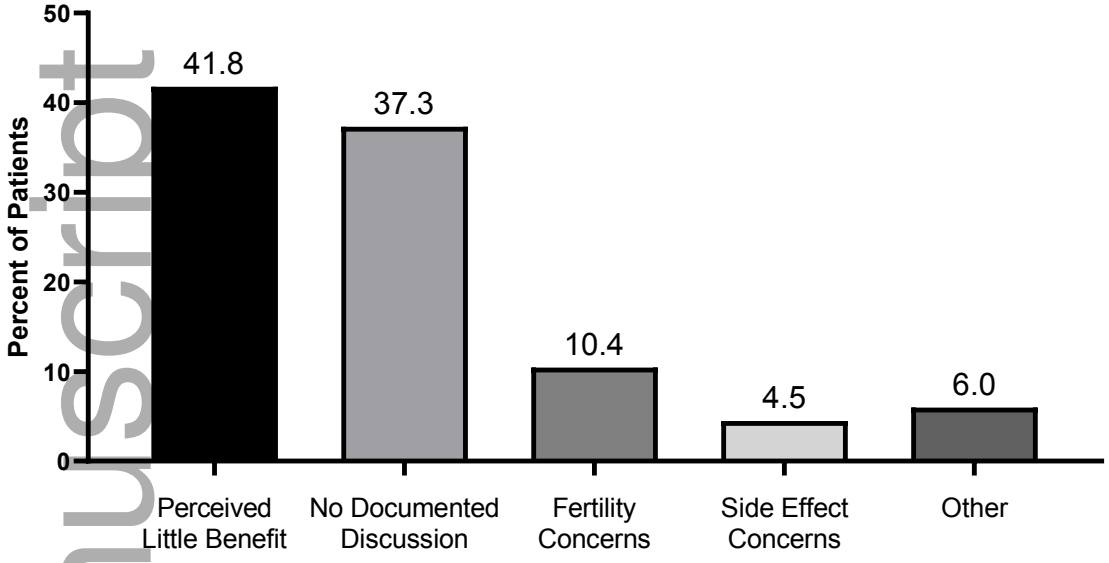

Figure 1A: Reasons for Tamoxifen Noninitiation

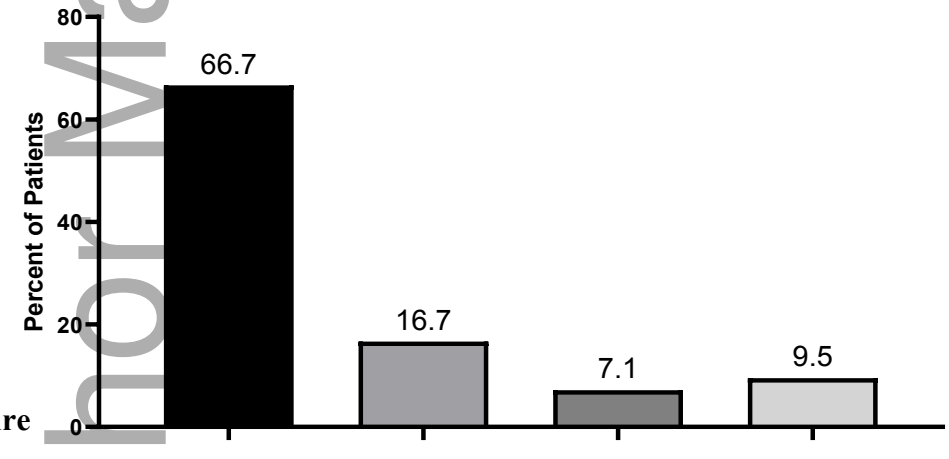

Figure 1B: Reasons for Tamoxifen Noninitiation After a Documented Discussion with a Healthcare Provider.