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Case Report: NSAIDs and Obesity in Breast Cancer

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Case Report: NSAIDs and Obesity in Breast Cancer

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Abstract

Women have a one in eight lifetime risk of developing breast cancer. Risk factors for breast cancer include genetic predisposition, reproductive factors, environmental exposure and lifestyle. Preventative measures for breast cancer currently include screening with mammography and the promotion of a healthy lifestyle including maintaining a healthy body weight and reduction of risk factors for other chronic diseases such as diabetes. This paper discusses the case report of 46-year-old women being seen for preoperative evaluation for meniscus repair surgery. This patient has a family history of breast cancer and is taking the Non-steroidal anti-inflammatory drug (NSAID) ibuprofen for pain control. A literature review of Pubmed and CINHALL explored ties between the use of NSAIDs and breast cancer prevention. Insufficient data exists to recommend using and NSAID for the reduction of breast cancer risk at this time, further studies will be needed.

Keywords: Breast Cancer, Non-steroidal Anti-inflammatory Drug (NSAID)

Background

This paper will discuss the case of T. Smith, a 46-year-old woman with a familial history of breast cancer who is also taking a non-steroidal anti-inflammatory drug (NSAID) for pain control. It will look at the effect of NSAID use in the reduction of risk of breast cancer. The patient, T. Smith has multiple known risk factors. She has a familial history of breast cancer in her mother and maternal grandmother, she is also obese and has a history of smoking.

T. Smith is currently up to date on her screenings including mammography. She does understand the increased risk associated with familial diagnosis, obesity and tobacco use. T. Smith is currently using the NSAID ibuprofen 600 mg three times daily for the treatment of pain related to her knee injury. She is also taking acetaminophen 1000 mg three times daily for pain control and aspirin 81mg to reduce the risk of ACS and stroke.

A review of the literature was done to determine if taking NSAIDs on a regular basis has shown to provide a clinically significant reduction to the overall risk of breast cancer. If that is the case it could be recommended that T. Smith continue taking her NSAID medication, or change to another medication with the intent of reducing her risk of breast cancer.

Case Report

This case report looks at T. Smith, a 46 year-old women, who presents for a preoperative exam prior to knee surgery to repair a meniscus tear in her right knee. Vital signs are as follows :

BP 136/88 HR 78 T 98.5F SpO2 95% Height 5ft 6 in Weight 211

lb. BMI 34

Her history of present illness includes a recent diagnosis of meniscal tear in the right knee. This injury occurred after sustaining a fall approximately 6 months ago. She has surgery scheduled to repair this injury in 1 month. She has been taking acetaminophen 1000 mg three

times daily and ibuprofen 600 mg three times daily with some mild relief of symptoms noted. Her symptoms are worse with ambulation, she describes the pain as constant and aching.

Her medical history includes hypertension, diabetes type II and hypothyroidism. T. Smith is obese with a BMI of 34. She also has a history of squamous skin cancer on her neck. Her surgical history includes a hysterectomy, cesarean section following two normal pregnancies and a biopsy and resection of the area of squamous cell skin cancer on her neck.

T. Smith takes several medications. For her hypertension she is taking lisinopril 10 mg daily. For diabetes she is taking metformin 1000 mg twice daily and Rybelsus 7 mg daily. She is taking Synthroid 125 mg daily for her hypothyroidism. She takes Aspirin 81 mg once daily for secondary prevention of ACS and stroke. Finally, she is taking acetaminophen 1000 mg three times daily and ibuprofen 600 mg three times daily for knee pain.

Her family history includes hypertension, hyperlipidemia, prostate cancer and coronary artery disease in her father. He had cardiac catheterization with stent placement at age 55, he is living. In her mother there is a history of hypertension, breast cancer at 60 and obesity. Her maternal grandmother has hypertension and breast cancer. In her Paternal grandfather there was hypertension and melanoma and her paternal grandmother had a cerebral vascular accident at age 80. T. Smith does have two younger siblings who are both alive and well.

T. Smith works in education, she is married and has 2 children. She is current on her vaccinations and did receive an influenza vaccination for this season. She has a 20 pack year history of smoking but did quit several years ago. She does not vape and does not use smokeless tobacco. She drinks alcohol socially, less than once weekly. She has no personal or family history of complications with anesthesia. However, she is allergic to amoxicillin and morphine, the reaction to these medications is unknown. When asked, she denies any history of bleeding or

clotting disorders and denies any unusual bruising. She does endorse occasional shortness of breath with exertion.

Her exam is mostly unremarkable. There is some pain with palpation and with flexion and extension of her right knee. She is grossly neurologically intact with no obvious concerns for difficult intubation. Cardiac and respiratory exams within normal limits.

During her exam some basic lab work was ordered and an EKG obtained. The metabolic panel and complete blood count with differential were within normal limits. Her TSH was found to be 3.65, also within normal limits. The EKG obtained was slightly concerning. There was slight ST elevation noted in leads II, V4 and V5.

The patient states that she is up to date on all of her screenings including mammograms and colonoscopy. Additional education was provided regarding the importance of continuing these screenings as she is at increased risk for cancers due to family history and personal history of smoking. Regarding the abnormal EKG, T. Smith will be sent for a stress test prior to determining risk for surgery. Finally, the use of ibuprofen, ASA and diabetic medications prior to surgery was discussed. She was given instructions to go to the emergency department with any chest pain, shortness of breath or other symptoms concerning for ACS.

Literature Review

The first database used was Pubmed. This database looks at biomedical and life science literature from a variety of sources. Pubmed is based out of the National Institute of Health's National Library of Medicine. Pubmed was accessed using the University of North Dakota subscription. The search terms used for the initial search were "Breast Cancer" AND "NSAID". Limits placed on this search included articles from 2015-2020. Articles were only considered if they were looking at the adult population and were written in English. This search returned 291

articles. After review, 9 pertinent articles were found. Using this search the articles about topics associated with other uses for NSAIDs in breast cancer such as post-operative pain control were kept to a minimum.

The Cumulative Index to Nursing and Health Literature (CINAHL) database was also used, this data base was accessed using the University of North Dakota subscription. The search terms used were “Breast Cancer” AND “NSAID”. This search found many articles that were found using the previously mentioned database. Three additional, pertinent articles were found for use in the literature review. The limits set for the search included the date published (2015-2020), articles were only considered if they were less than 5 years old, English language and included an adult population.

The lifetime time risk of a woman developing breast cancer is 1 in 8 (approximately 13%) (Howlander et al., 2019). Modifiable risk factors for breast cancer reduction include lifestyle such as exercise and environmental exposures like radiation, tobacco and alcohol. There are also non-modifiable risks for breast cancer which include genetic predisposition and reproductive factors like age of menarche, age of first pregnancy and breast feeding. (Hawk, Maresso, & Brown, 2018). The following literature review looks at the effect of NSAIDs in the prevention of breast cancer.

While experimental studies have shown some promise in using NSAIDs to protect against breast cancer, epidemiologic studies have been less promising (Cairat et al., 2019). NSAIDs work on cyclooxygenase enzymes (COX-1 and COX-2) by inhibiting their activity. This inhibition allows for a reduction of inflammation and inhibition of platelet aggregation. Like colorectal cancer, breast cancer has been shown to have over expression of

COX-2. More research is needed to show a correlation between the use of NSAIDs and breast cancer prevention (Hawk et al., 2018).

A European cohort study within the European Prospective Investigation into Cancer and Nutrition (EPIC) (Cairat et al., 2019) used multiple models to show correlation between NSAID use with a reduction in breast cancer rates. Self-reported information on NSAID use was gathered in five of the countries part of the EPIC study. There were 140,981 women included in the analysis. Of these women, 7% were regularly using NSAIDs at baseline. After a follow-up period of 13 years, 7,379 cases of breast cancer were diagnosed. This study did not reveal a significant, consistent link between the use of NSAIDs and a reduction in the rate of breast cancer. This study did show a possible correlation between the use of hormone therapy and NSAIDs in the development of cancer, however that correlation was not examined in this trial (Cairat et al., 2019). Another study looked at a large cohort of Danish women diagnosed with breast cancer. The study analyzed the use of NSAIDs in the reduction of contralateral breast cancer. In this study there was no proof of a reduction of the rate of contralateral breast cancer in those who took NSAIDs regardless of COX selectivity (Bens et al., 2018).

Several trials looked specifically at the use of NSAIDs in the prevention of breast cancers that were hormone positive. The Spanish Multi-Case-Control study (Dierssen-Sotos et al., 2016) reports on the relationship between NSAIDs and breast cancer in 1736 women with breast cancer and 1895 healthy women. This study included all drugs indicated for the treatment of inflammatory diseases including Aspirin, acetic acid derivatives (diclofenac and Toradol), propionic acid derivatives (ibuprofen, naproxen) and Coxibs (celecoxib). The use of these drugs was measured in the number of years taken with groups being split into those who had taken the medication less than five years or five or more years. In this study there is a 24% reduction of

breast cancer risk with the use of NSAIDs (Dierssen-Sotos et al., 2016). Additionally, there were similar reductions with acetic acid derivatives, other propionic acid derivatives and Coxibs. These results were not seen with aspirin. These results were noted in hormone + or HER 2 + breast cancer (Dierssen-Sotos et al., 2016).

The California Teacher Study (Clarke et al., 2017) assessed the risk of breast cancer development in a cohort of over 50,000 public school professionals in relation to their self-reported use of NSAIDs (Clarke et al., 2017). This study showed an inverse association with the development of breast cancer in those who take three low dose aspirin tablets per week. Those taking other types of NSAIDs had a marginal decrease noted. These outcomes were consistent with other studies however this was the first study to look at low dose aspirin. Additionally, these outcomes were only consistent in women with hormone receptor positive/ HER2 negative cancers (Clarke et al., 2017).

Other studies have more thoroughly examined the link between genetics and breast cancer and the possible influence of NSAIDs. One cohort study looked at a group of women aged 18 to 71. Women either used aspirin, a COX-2 inhibitor, ibuprofen and other NSAIDs or Acetaminophen at regular intervals. This study also took into consideration the risk associated with familial history or breast cancer including BRCA1 and BRCA2 carriers (Kehm et al., 2019). Findings showed 39% and 37% reduced risk of breast cancer in the prospective and combined cohorts using Aspirin. Those using a COX-2 inhibitor show a 61% and 71% reduced risk of developing breast cancer. Other NSAIDs and acetaminophen were not associated with any reduced risk. Additionally, there was no alteration in risk associated with use of these medications and the consideration of familial history or genetic factors (Kehm et al., 2019).

A prospective study of women who have a sister with breast cancer assessed the use of NSAIDs with their lifetime risk of developing cancer. When looking at the use of non-Coxib and non-aspirin NSAIDs and their overall risk no evidence of reduction in post-menopausal women (Kim et al., 2015). However, in premenopausal women there was a small but significant reduction in the risk for breast cancer in those taking NSAIDs or Aspirin (Kim et al., 2015).

A systematic review looking at several large studies (Sutton et al., 2015), examined the outcomes of women taking NSAIDs or aspirin after diagnosis with breast cancer. This review examined a large body of literature regarding the mortality of women with breast cancer following surgical intervention. The study looked at the use of NSAIDs in the treatment of these women (Sutton et al., 2015). The studies did not reveal any significant reduction of mortality related to breast cancer. However, it was noted that there was little data looking at specific dosages and the specifics of the patients in question. This review highlighted the need for large, randomized trials in looking more in depth at this topic (Sutton et al., 2015).

Data from two retrospective institutional studies (Desmedt et al., 2018) examined the use of NSAIDs in the intraoperative period for primary cancer surgery related to the risk of recurrence of the breast cancer. The patients involved in these studies were women considered to have elevated body mass index (BMI) of greater than or equal to 25. During surgery the patients were given either Toradol or diclofenac for pain control and to attempt to reduce the amount of opioid pain medications used (Desmedt et al., 2018). With the used of diclofenac there was no change in rates of cancer recurrence. In patients who received intraoperative Toradol there was a clinically significant reduction in the rate of distant cancer recurrence (Desmedt et al., 2018).

Another population based, case-controlled study looking at just over 5,000 women addresses the concern for inflammation causing increased rates of cancer (Cui et al., 2014). This study found that there was a reduction in the risk of getting breast cancer in women taking NSAIDs. The risk reduction was most notable when the individual was also taking a low dose aspirin. Additionally, the risk reduction was more significant for overweight women (Cui et al., 2014).

Two invitro studies (Bowers et al., 2014), which looked at the sera of breast cancer patients analyzed the daily use of an NSAID that provides COX-2 inhibition. This study looked at how the use of this medication can reduce the risk of recurrent estrogen positive breast cancer in women specifically those who may be at an increased risk as a result of an increased BMI. This retrospective study found that women with a BMI of 30 or more, taking an NSAID had a 52% less chance of having recurrent breast cancer with an additional 28 months noted before recurrence. This study also examined the serology of normal weight women and those who are overweight. These results show an increase risk of breast cancer in overweight women (Bowers et al., 2014).

While there are promising studies that show a potential benefit in NSAID use correlating to breast cancer risk reduction, there is not sufficient data available to recommend using NSAIDs for the prevention of breast cancer at this time. More research is needed before making additional conclusions about the use of NSAIDs in this way. These trials could assess dosage and have specific parameters in place for the type of patient and breast cancer being assessed. It can also be concluded that aspirin has also had mixed results in the prevention of breast cancer in certain populations. These trials are needed to further demonstrate the efficacy of each drug, which dosages should be given and to which type of patient.

Learning Points

- Modifiable risk factors should remain a priority for health care providers in reducing breast cancer risk in women. These factors include physical activity and a sedentary lifestyle, being overweight or obese, some forms of hormone replacement therapy when used for over 5 years during or after menopause and drinking alcohol. Other reproductive factors include not becoming pregnant until after age 30, not breast feeding and not having a full term pregnancy. Providers should give adequate teaching in these topics and provide resources as needed to support women who would like to pursue change in any of these areas.
- Current literature does not recommend using NSAIDs or aspirin to reduce the risk of breast cancer. While some data does seem encouraging most of the existing data that remains inconclusive. What we can conclude from the above information is that genetic predisposition and obesity can increase a woman's risk of developing breast cancer. Additionally, the existing trials do not show specific data regarding which NSAIDs and which dosages could be recommended for this use.
- Further research is needed to determine if the use of an NSAID could be used to reduce breast cancer risk. These studies need to be large and randomized. Additionally, they should look at specific dosages of drugs on certain populations of women in order to determine whether or not it is truly effective in reducing risk.

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