Title

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Abstract

Breast Cancer remains a significant health issue, with roughly around 42,000 maternal deaths occurring each year. The relationship between exercise and breast cancer has been widely studied with substantial evidence suggesting that higher exercise can lower breast cancer proliferation. The meta analysis aimed to investigate the relationship between exercise activating the hormones and receptors of dopamine, insulin, and estrogen and breast cancer across different populations. We conducted a comprehensive search of electronic databases and included studies that reported the association between exercise and the hormones and their impact on breast cancer. Through this analysis, we were able to generate novel mechanisms for the hormones and were able to link exercise and breast cancer. Our findings suggest that an increase in exercise increased the levels of dopamine while lowering insulin and estrogen levels. These effects have a strong relationship with lowering breast cancer proliferation. Previous studies focused on generating already researched pathways to a higher degree. Our research incorporates previously researched pathways with the extension of introducing a new pathway that has not been researched thoroughly. Our research employs a meta-analysis of research papers and scientific data, which allows for a more comprehensive and rigorous examination of the research question and can help identify patterns and trends across studies.

Introduction

Breast cancer remains a significant global health issue, with 2.3 million women diagnosed with breast cancer and 685,000 deaths globally as of 2020 (World Health Organization, 2024). Physical activity has been consistently associated with reduced breast cancer mortality. In one cohort-based study, the relationship between physical activity and survival outcomes in high-risk breast cancer patients was explored (Cannioto, R. A, et. al, 2020).

The research focused on the influence of recreational physical activity (RPA), during prediagnosis and postdiagnosis, and outcomes in high-risk breast cancer patients. A total of 1340 high-risk breast cancer patients were enrolled, and detailed information on their physical activity levels, both before and after diagnosis, was collected through 4 DELCaP questionnaires, a self-administered epidemiological survey assessing demographic and lifestyle factors. The Physical Activity Guidelines for Americans (PAGAs) was the standard guideline for gauging relative activity levels. Participants who were engaged in RPA, at least once a week, were examined. Cox proportional hazards models were employed to determine the links between pre-diagnosis recreational physical activity (RPA) and the recurrence of the disease and mortality. Additionally, these models were utilized to evaluate the relationships reflecting the combined impact of RPA both before and after diagnosis on disease recurrence and mortality (Cannioto, R. A, et. al, 2020).

Patients meeting or exceeding the minimum PAGAs, both pre-diagnosis and post-diagnosis, exhibited over 50% reduction in the risk of breast cancer recurrence and mortality. Strikingly, even those who initiated PAGAs post-treatment demonstrated improved survival. Analysis revealed a consistent inverse relationship between RPA and mortality, with any regular weekly activity associated with a 63% reduction in mortality hazard.

The findings underscore the significant role of physical activity in breast cancer survivorship. However, the mechanisms linking physical activity and breast cancer risk and mortality are too broad. They include a decrease in the bioavailability of sex hormones, improved insulin sensitivity, decreased inflammation, improved adipokine milieu, improved immune surveillance, and improved DNA repair. In our meta-analysis, we aim to pinpoint the precise mechanisms through which elevated levels of exercise influence insulin, estrogen, and dopamine in breast cancer patients. This exploration is intended to explore the specific biologics of how exercise deters the proliferation of breast cancer.

Breast cancer, a predominant health concern among women in Western countries, has witnessed a significant improvement in survival rates over the past two decades. This advancement has resulted in a growing population of breast cancer survivors, whose quality of life and long-term health outcomes have become central in cancer care. In recent years, physical exercise has emerged as a promising intervention for improving the quality of life and physical outcomes for these individuals. The study "Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis" by McNeely et al. (2006), available from the National Center for Biotechnology Information (NCBI), aims to consolidate the evidence regarding the impact of exercise on breast cancer patients and survivors.

The systematic review and meta-analysis conducted by McNeely et al. (2006) explores the effectiveness of exercise interventions specifically for breast cancer patients and survivors, addressing a gap in research where previous studies have either included various types of cancers or employed nonrandomized, uncontrolled trials. This study focuses on randomized controlled trials (RCTs), considered the gold standard for clinical trials, to provide a more accurate estimation of the exercise intervention's effects.

McNeely et al. (2006) reviewed 136 studies, of which 14 met the inclusion criteria. The analysis revealed that despite the heterogeneity and relatively small sample sizes of these studies, exercise interventions led to statistically significant improvements in various key areas. These include enhanced quality of life, as measured by the Functional Assessment of Cancer Therapy–General and Breast scales, improved physical functioning, increased peak oxygen consumption, and reduced symptoms of fatigue. This study fills a critical gap by providing a more focused and reliable analysis of the benefits of exercise specifically for breast cancer survivors.

However, McNeely et al. (2006) highlights the need for larger trials with a greater focus on study quality and long-term benefits. This indicates a gap in current research, where the majority of studies fail to consider the long-term effects of exercise and potential adverse events. In addressing this gap, our paper proposes to investigate the effect of exercise on breast cancer. By focusing on this question, we aim to contribute to the understanding of sustainable exercise regimens and their prolonged impact on this population.

Dopamine Introduction

Dopamine, a pivotal neurotransmitter in the brain, plays a crucial role through its receptors, particularly the D1 and D2 types. These receptors are vital in modulating physiological properties and cellular signaling. As noted in a study, "the dopamine D1 and D2 receptors modulate physiological properties and cellular signaling" (Vučković et al.). The significance of studying these receptors is underlined by the fact that cancer cell proliferation is intricately linked to disruptions in the cellular signaling system.

The focus on D1 and D2 receptors is justified as they represent the primary subtypes within the D1-like and D2-like receptor families. This distinction is important because "D1-D5 are divided

into D1 like and D2 like" (National Center for Biotechnology Information), indicating their unique roles in signaling pathways. Furthermore, D1 and D2 receptors are known for their contrasting actions on intracellular signaling (Trantham-Davidson et al.).

The study of these receptors extends beyond dopamine's role as a neurotransmitter; it delves into how the activation of these receptors, potentially influenced by physical exercise, impacts various cellular pathways. Additionally, the interchangeable use of D1 and D2 with DRD1 and DRD2 in literature reflects the specific focus on these receptors. Understanding the roles of these receptors in cancer biology could lead to new therapeutic strategies and enhance our understanding of cellular signaling in oncogenesis.

Insulin Introduction

Insulin is a hormone produced within the pancreas and helps to regulate blood sugar levels. According to the American Diabetes Association, physical activity can help to lower blood sugar for up to 24 or more hours post-workout making the body more sensitive to insulin. (2024) It helps to improve insulin sensitivity in both normal and insulin-resistant people. Combining aerobic and resistance exercise significantly improves insulin sensitivity compared to modality alone.

Estrogen Introduction

As estrogen has been often linked to breast cancer development, it is crucial to study the mechanism of how estrogen affects breast cancer proliferation, including how to prevent this from occurring. In determining breast cancer risk, “a promising prognostic biomarker” is the discovery of estrogen receptors in a tumor as they are expressed in 70% of cases of breast cancer (Al-Shami et al., 2023).

Along with biomarkers for breast cancer risk, the preventive measures of this risk can be looked at through physical activity and exercise. For women who had more than 600 MET minutes of physical activity per week, equivalent to 150 minutes of physical activity per week at a moderate intensity, they had a lower risk of breast cancer by 3-14% than women who had less than 600 MET minutes per week (Kyu et al., 2016). Physical activity, at certain levels, can lower the risk of breast cancer as higher amounts of physical activity can reduce concentrations of estradiol (E2) and estrone (E1), which are also other factors for the risk of breast cancer development (Papadimitriou et al., 2020).

With estrogen being a biomarker for the risk of breast cancer as well as physical activity being able to reduce the levels of estrogen present, the mechanism between physical activity affecting estrogen concentrations and estrogen presence being a risk for breast cancer needs to be further examined.

Discussion and Pathways: Dopamine

D2 Receptor Primary Pathway

The connection between exercise and its positive impact on reducing breast cancer risk largely involves the activation of D2 receptors. In a study conducted in 2016, it was found that exercise, in this study a custom intensity structured training program, induces upregulation of striatal D2 receptors (Robertson et al., 2015). This study also looked at striatal D3 receptors, however, our paper focuses on D1 and D2 receptors primarily considering their implication in breast cancer explained previously. Similarly, the relationship

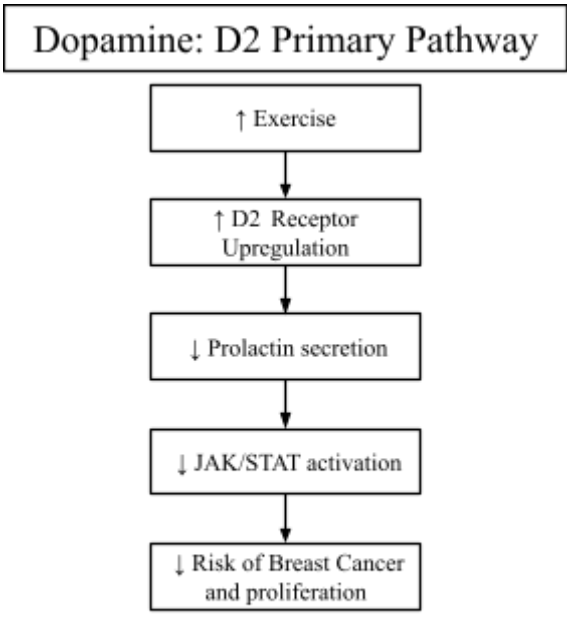

Figure 1. Primary D2 Receptor Pathway Hypothesized to reduce Breast Cancer via Exercise.

between exercise and D2 receptors is highlighted in Parkinson's engineered mice. It was calculated that the mice engineered to exhibit Parkinson's when subjected to extensive treadmill exercise depicted a 48.8% increase in striatal D2 receptors compared to the control engineered mice that did not exercise (Vučković et al., 2010). This data offers valuable insights into the potentially profound benefits of exercise, it is important to note that it could be somewhat overstated when considering that the brains of the mice engineered to have Parkinson's disease are already rather dopamine-depleted.

Following a meta-analysis of the role of D2 receptors in breast cancer (BC) specifically, it is evident that its activation inhibits cancer cell proliferation in BC patients (Grant et al., 2022). A 2023 study on breast cancer stated, "Dopamine or its receptor agonists seem to exhibit inhibitory effects on tumor growth in breast and several other cancer types. However, dopamine fails to diminish the proliferation and invasion of breast and colon cancer cells, indicating that factors such as tumor type, receptors expressed, and doses used play a role" (Jayachandran et al., 2023). This brings up some questions about the specific effects of dopamine D2 agonists as opposed to D2 antagonists and their effects on breast cancer due to the lack of research clarifying the contradicting effects discovered in different cancer types. Although some studies hinted at their findings that D2 antagonism through medication like Pimozide and others have shown anticancer activity in different contexts, they simultaneously highlight how its activation resulted in pro apoptotic effects in breast cancer tumors (Grant et al., 2022). Taking the example of Pimozide, it is known to decrease breast cancer proliferation (Strobl et al., 1990), a recent paper states that "Although these early studies hinted at a potential role for D2R antagonism in cancer development and treatment, there are some issues that should be considered in interpreting this data. In particular, the effects of the four antipsychotic drugs noted above required concentrations

two or more orders-of-magnitude higher than their KD" (Weissenrieder et al., 2019). This implies that the concentration of drugs were grossly magnified to produce the earlier discussed effects making it inapplicable in humans without producing dramatic and dangerous side effects.

Another study also raised the question of the possibility that prolactin-elevating dopamine antagonists that are currently used to treat psychotic disorders may initiate and promote breast cancer (Wang et al., 2002). Our hypothesized mechanism for D2 receptors relies on their role in decreasing prolactin. "DA/DRD2 signaling negatively regulates the transcription of PRL through its inhibition of the cAMP/PKA pathway" (Grant et al., 2022). The cAMP/PKA pathway and its correlation with breast cancer will be addressed in detail later in this paper. Prolactin is known to be notoriously overexpressed in breast cancer patients and is one of the most well researched neurotransmitters involved in BC research. Prolactin is involved in "breast cancer growth, metastasis, and chemoresistance" (Jayachandran et al., 2023). Prolactin seems to act through the growth promoting JAK-STAT pathway explained by Hathaway and her team, increasing the risk of breast cancer in pre-menopausal women (Hathaway et al., 2023). There is also substantial evidence that "The hormone is under the inhibitory control of the neurotransmitter dopamine, raising the question of whether dopaminergic drugs can improve breast cancer outcomes" (Jayachandran et al., 2023). However, the motivation behind our mechanism takes into the account the known side effects of dopaminergic anti-cancer drugs and their questionable efficacy. Instead our approach focuses on harmless natural techniques of physical exercise as a way to improve and/or prevent breast cancer.

D2 Receptor Secondary Pathway

The activation pathway of dopamine has shown significant promise in the context of breast cancer. The pathway demonstrates how increased exercise, elevated dopamine levels, and

specific anti-cancer drugs can decrease VPF/VEGF signaling, reducing angiogenesis and impeding breast cancer proliferation. In this pathway, exercise is the initiating factor, kick-starting the cascade by stimulating dopamine release and influencing downstream signaling pathways. As stated by García-Chico et al. (2023), "Physical activity is related to reduced breast cancer mortality and recurrence in breast cancer patients, as well as fewer/less severe adverse effects following its treatment". Elevated dopamine levels, induced by exercise, play a pivotal role as they interact with specific anticancer drugs, forming a crucial connection that modulates Vascular Permeability Factor/Vascular Endothelial Growth Factor (VPF/VEGF) signaling. The synergy between exercise-induced dopamine release and certain medications significantly attenuates VPF/VEGF signaling, central to angiogenesis.

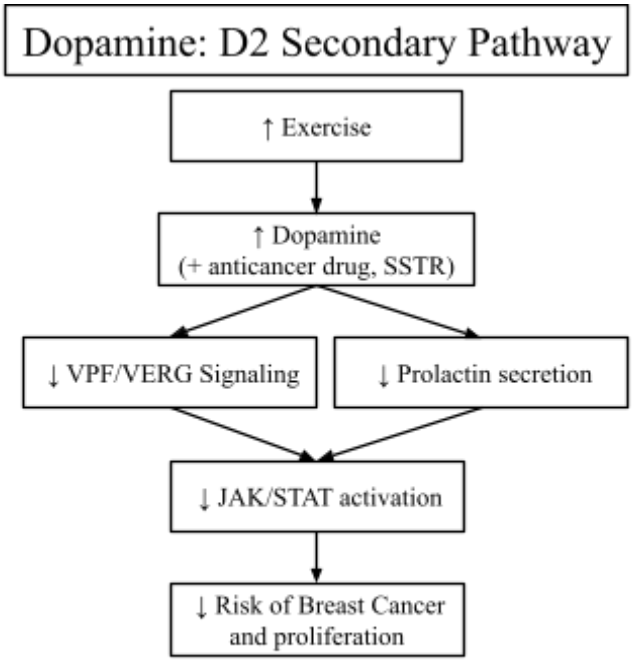

Figure 2. Secondary D2 Receptor Pathway Hypothesized to reduce Breast Cancer via Exercise.

Research findings from multiple studies support the components and interactions within this pathway. Garcia-Chico et al. (2023) reinforced the significance of physical activity in addressing breast cancer hallmarks. They noted that, "...following a healthy lifestyle, particularly engaging in regular physical activity or physical exercise, might reduce the risk of developing the disease". Additionally, Buss et al. (2021) emphasized the positive impact of exercise on crucial breast cancer hallmarks, potentially linked to dopamine activity. They indicate that, “...exercise may be able to attenuate cancer-induced impairments in muscle (mitochondrial)

function and the development of cancer cachexia" (Buss et al., 2021). Xu et al. (2022) explored exercise's potential influence on Reactive Oxygen Species (ROS) levels and chemoresistance in breast cancer, possibly mediated by dopamine-related pathways. The authors indicate that , "...targeting ROS systems has a great potential to treat cancer patients with chemoresistance" (Xu et al., 2022). The collective findings highlight the intricate relationship between exercise, dopamine, anti-cancer drugs, and VPF/VEGF signaling in breast cancer progression and treatment.

Jo et al.(2022) elucidate the importance of HDAC6 suppression to curb autophagy-associated cancer drug resistance. The authors state that, “the HDAC6 inhibitor can enhance the sensitivity of cancer cells to anti-cancer drugs by inhibiting autophagy”(Jo et al. 2022). Also, Kim et al.(2016) highlighted the HDAC3/CAGE axis and its targeting of EGFR signaling. The authors note that, "Through its interaction with tubulin β3, HDAC3 regulates the response to anti-cancer drugs" (Kim et al., 2016). The pathway involving exercise-induced dopamine release and VPF/VEGF signaling modulation offers insights into potential breast cancer treatments. By understanding how exercise affects critical signaling pathways, we can develop targeted therapies to impede tumor growth and metastasis.

Research in the future should investigate these differences in detail, which could result in the elaboration of more accurate interventions for the treatment of breast cancer. Understanding the complex dynamics of this pathway is crucial for revising therapeutic options and advancing breast cancer studies.

D1 Receptor Pathway

While the D2 pathway hypothesis is well supported by already researched papers in the field, there is a tertiary pathway that concealed that this section forms a hypothesis around. It is

studied that in breast cancer, DRD1 expression has been linked to advanced disease and poor prognosis however counter-intuitively, DRD1 agonists are used as breast cancer medication (Grant et al., 2022). "D1R is overexpressed in a significant number of primary breast tumors, characterized by having an aggressive phenotype and predicting a shorter survival time for patients" (Ben-Jonathan et al., 2019). However, unexpectedly, the D1R agonists increased intracellular cGMP levels, activating the cGMP/protein kinase G (PKG) pathway as opposed to the cAMP/PKA system as we would expect. The cGMP/PKG pathway can directly activate apoptotic events (Ben-Jonathan et al., 2019), thus supporting the use of D1 activators to treat breast cancer.

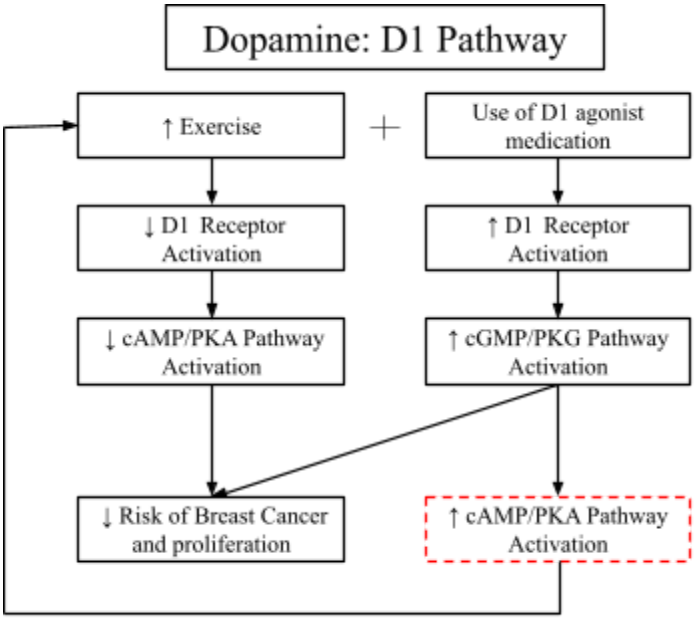

Figure 3. D1-Exercise Pathway Hypothesis in reducing Breast Cancer.

With regards to the cAMP/PKA pathway, it is involved in breast cancer cell migration implying pro-cancer activity (Caretta & Mucignat-Caretta, 2011). Protein Kinase A (PKA) primarily acts through its binding with cAMP thus establishing the cAMP/PKA pathway that is suggested to participate in the onset and progression of many cancerous tumors (Caretta & Mucignat-Caretta, 2011). D2-like receptors involved in the two pathways explained above, are coupled with specific proteins to suppress cAMP, thus inhibiting PKA. On the other hand, D1-like receptors, according to their original classification, are coupled with specific proteins to increase cAMP and stimulate PKA (Ben-Jonathan et al., 2019). However, to address

contradicting findings showing that D1 receptor activation decreases cAMP like in the case of D1 agonist Fenoldopam, it is hypothesized that this effect "is likely secondary to the elevated cGMP, which activates cAMP-hydrolyzing PDEs, underlying the reciprocal relationships between the two cyclic nucleotides" (Ben‐Jonathan et al., 2019). A recent mice study showed that cGMP was significantly elevated in breast tumors by Fenolodopam while cAMP was only mildly elevated. The cGMP/PKG pathway is less researched but its affection of "suppressing cell invasion, stimulating apoptosis and increasing chemosensitivity" (Caretta & Mucignat‐Caretta, 2011), make it crucial to breast cancer research. In addition, again counterintuitive to the opposite activity of D1-type versus D2-type receptors, both receptors seem to be capable of inhibiting the research of prolactin (Schoors et al., 1991). One study also suggested that it is the absence of D1 receptors that triggers prolactin release (Cocchi et al., 1987). One limitation to note here is the recency of these studies. The foundation of classifications of D1 and D2 type receptors was established in the 1970's and although it holds today, "the signaling cascades which are activated by the various DARs are much more variable and complex"[13](Ben‐Jonathan et al., 2019), thus pointing out the need for further research.

Although there are a minimal number of human studies on the effects of exercise on D1 receptors, addiction mice studies have found that mice that performed aerobic exercise had lower D1 receptor binding and higher D2 receptor binding in striatal regions (Robison et al., 2018). Another study shows that exercise selectively upregulated D2 receptor proteins but had no effect on the D1 receptor protein levels (Vučković et al., 2010).We hypothesize that physician exercise coupled with D1 agonist drugs can help lower those slightly elevated cAMP levels, lowering cancer cell proliferation combined with the tremendous benefits through the two D2 receptor pathways explained above.

Conflicting Research and Discussion

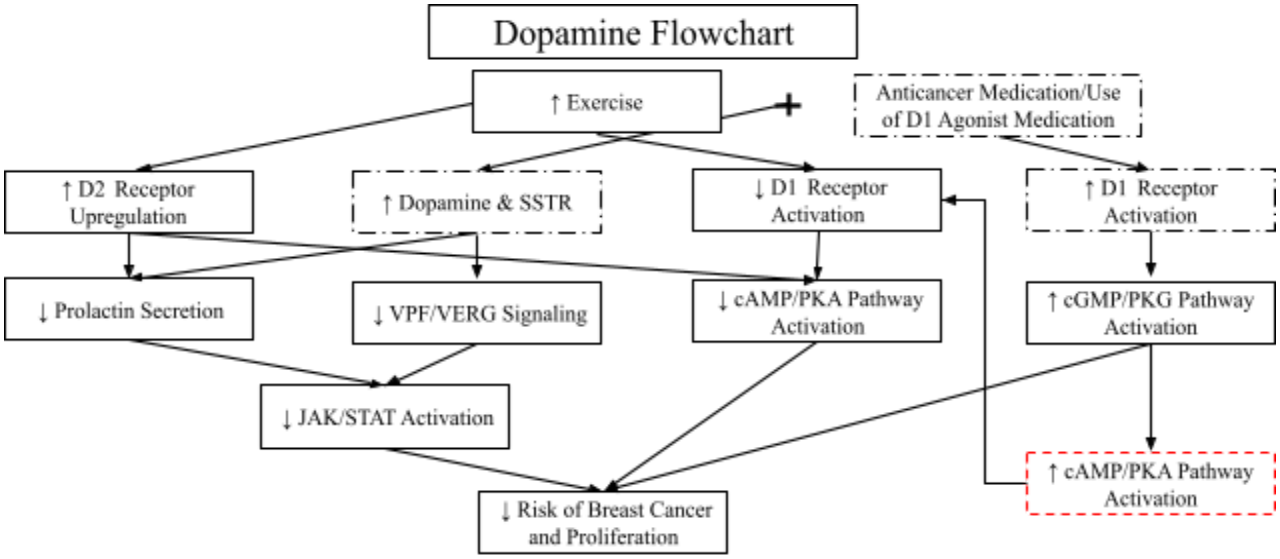

Figure 4. Dopamine Pathway in Reducing Risk of Breast Cancer and Proliferation via Exercise. Note that the pathway highlighted in Fig. 2. above works in combination with anticancer medication. Individual pathways are highlighted in Figures 1-3.

The meta analysis of the papers we found on the topic led us to the development of this novel pathway involving exercise and dopamine receptors. However, it is transparent that there is substantial scope for more research on the specific steps in each of the pathways to emerge with clear undisputed results in specifically breast cancer patients. It is clear however that the effects of physical exercise on dopamine have the potential to mediate breast cancer proliferation through both the D1 and D2 pathways in counterintuitive ways. Breast cancer medication that acts on these pathways is not only conflicting, but also produces debilitating side-effects on the body, however, our mechanism safely reduces breast cancer tumor growth and proliferation through exercise. Without a doubt, this mechanism does not apply to later stages of breast cancer where patients might not be physically capable to engage in exercise, however minimal it may be. However, in early stages, our research shows how exercise must be implemented in the care plan of breast cancer patients. It is also important to note that bidirectional associations have been made between dopamine and exercise (Marques et al., 2021), meaning that consistent

exercise can prove to be beneficial in the long term as well. The combined pathway shown above also highlights the complexity of the different factors involved in breast cancer and the need to do more research on the effects of each sub-pathway on different tumor types within the breast cancer umbrella.

Discussion and Pathways: Insulin

EMT and MAPK Pathway

Exercise plays a large role in lowering insulin production within the body and can improve the overall health of a person. Specifically, exercise increases insulin sensitivity ensuring the muscle cells are better at collecting glucose by using any available insulin. Those with type 2 diabetes often face the opposite called insulin resistance which is caused when the muscles and liver do not respond normally leading to many detrimental effects. Therefore, it is important to practice exercise daily to ensure optimal function of the body and to reduce overall insulin levels to also ensure lower breast cancer proliferation. EMT stands for Epithelial to Mesenchymal Transition and is a cellular process responsible for the formation and development of organs from embryonic cells. Dysregulation of EMT is frequently found alongside biologically aggressive cancers such as breast cancer. It promotes invasion, metastasis, and poor survival. (Yee, 2020) The EMT process during the beginning stages of cancer is highly dynamic, implying it can be reversed. There is little research on the lifestyle choices that can regulate EMT but miRNA is known to control EMT by regulating its transcription factors. (Huang, 2022) Lifestyle factors such as diet, physical activity, smoking, and alcohol consumption may all affect the miRNA machinery and several other factors. (Panico, 2021) Hyperinsulinemia also promotes tissue inflammation by activating PI3K/AKT-signaling and NFkB which is one of the main regulators. These factors then increase inflammatory cytokines and chemokines which directly

promote tissue inflammation and angiogenesis. This further increases the insulin resistance of muscle and the cycle continues. Diabetes and inflammation are connected, regular physical activity releases a flood of anti-inflammatory chemicals into the body leading to increased insulin sensitivity. This also helps to reduce chronic inflammation that causes damaged cells and may eventually lead to tissue death. (Pahwa, 2023) Insulin activated both MAPK and PI3K/AKT-signaling promoting both cellular motility and cancer cell invasion. Under nutrient-rich conditions, IGF-1 (Insulin Growth Factor) binds to a receptor on the MAPK to activate the process. MAPKs are enzymes that respond to extracellular stimulation and convert extracellular stimuli into a wide range of cellular responses. (Cargnello, 2011) AKT is known to disrupt cellular polarity, reorganize the cytoskeleton, and contract the cellular body leading to cellular motility. Angiogenesis is a key factor in cancer initiation and is how the body forms new blood vessels facilitating a nutrient-rich environment for the tumor to signal for more blood. There are angiogenesis inhibitors and anti-angiogenic herbs to successfully prevent tumor growth. (Sagar 2006) Vitamin D can also act as a potent anti-angiogenic factor, especially during the earlier stages. (Kalkunte, 2005)

Discussion

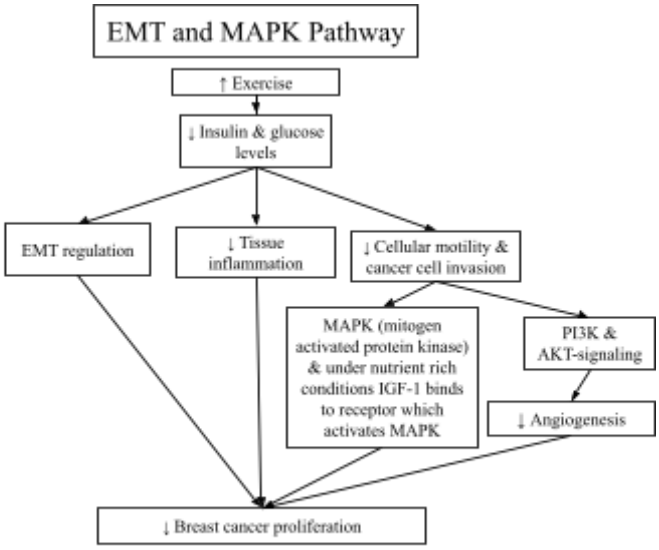

Figure 5. EMT and MAPK Pathway of Insulin

Breast cancer growth can be actively prevented by practicing a daily lifestyle and incorporating healthy routines. It is important to exercise regularly early on to increase insulin sensitivity which not only impacts breast cancer proliferation but has ties to many other conditions. Despite

diabetes and insulin resistance being distinct diseases, insulin signaling is central in regulating the progression of both. It is key to prevent insulin resistance during treatment and before diagnosis to prevent the possible growth of breast cancer. While it is not standard to care for insulin after diagnosis it is important to screen women with a higher glycemic index for the potential risk during regular check-ups for women. Insulin's importance in the progression of cancer should be paid more attention to while screening by cancer physicians given the large impact.

Insulin Growth Factor Pathway

The evidence surrounding the effect of exercise on breast cancer proliferation is considered strong, and upon analysis, the insulin/insulin growth factor-1 (IGF-1) pathway is one of the mechanisms driving this. IGF-1 is an important factor in breast cancer proliferation as it is a known mitogen that promotes cellular proliferation and prevents apoptosis in breast cancer patients (de Boer, M. C, et. al, 2017). IGF-1 levels were investigated in one randomized clinical trial that researched the effects of implementing both aerobic and resistance exercise in survivors of breast cancer over 16 weeks. The researchers found that the exercise plan,

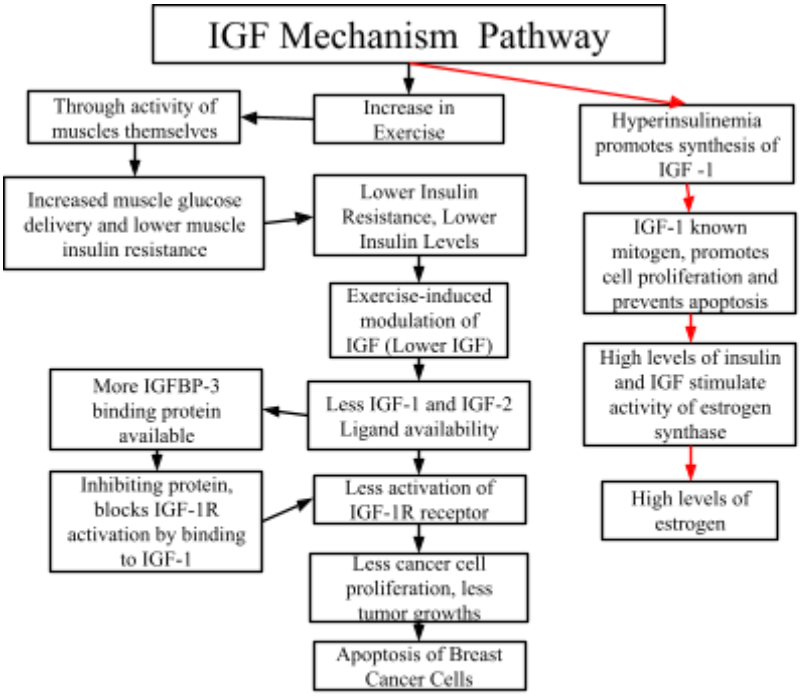

Figure 6. IGF-1 mediating breast cancer proliferation

conducted under close supervision, resulted in a reduction in insulin resistance and biomarkers hypothesized to mediate the relationship between obesity and breast cancer, including IGF-1 (Dieli-Conwright, C. M, et. al, 2018). There are many mechanisms through which physical activity may decrease muscle insulin resistance, such as increased glucose transporter protein and increased activity of glycogen synthase. However, these mechanisms are achieved mostly through the activity of the muscles themselves (de Boer, M. C, et. al, 2017). The activity of the muscles leading to a decrease in insulin resistance is important because that means less insulin is needed to regulate one's blood-sugar levels, but also less insulin will activate the IGF-1 pathway. The IGF-1 pathway is activated by the IGF-1, IGF-2, and insulin ligands, resulting in mitosis and inhibiting apoptosis (CD Creative Diagnosis et. al, n.d). Lower levels of insulin and IGF-1 allow the IGF binding proteins 1-6 (IGFBP 1-6) to regulate IGF-1 levels by binding to free IGF-1 and inhibiting activation of the pathway (CD Creative Diagnosis et. al, n.d). Lower levels of insulin and IGF-1 are preferable for lowering breast cancer proliferation, but also because hyperinsulinemic levels contribute to the overstimulation of estrogen synthase, promoting cell-cycle progression in breast cancer cells (CD Creative Diagnosis et. al, n.d).

Despite the clinical trial's results, there is conflicting research that denies that IGF-1 levels decrease due to exercise. In one 12-month randomized clinical trial, the experimental group underwent moderate aerobic exercise while the control group underwent a stretching program. They found that IGF-1 concentrations did not change statistically significantly, in both exercisers and controls while IGFBP-3 decreased slightly in exercisers and controls, and the difference between the two groups was not statistically significant (McTiernan, A, et. al, 2005). The main difference between this study and the 16-week clinical trial is the employment of

exercise plans, the 16-week clinical trial used a mix of resistance and aerobic training under supervision for more total time being physically active.

Discussion

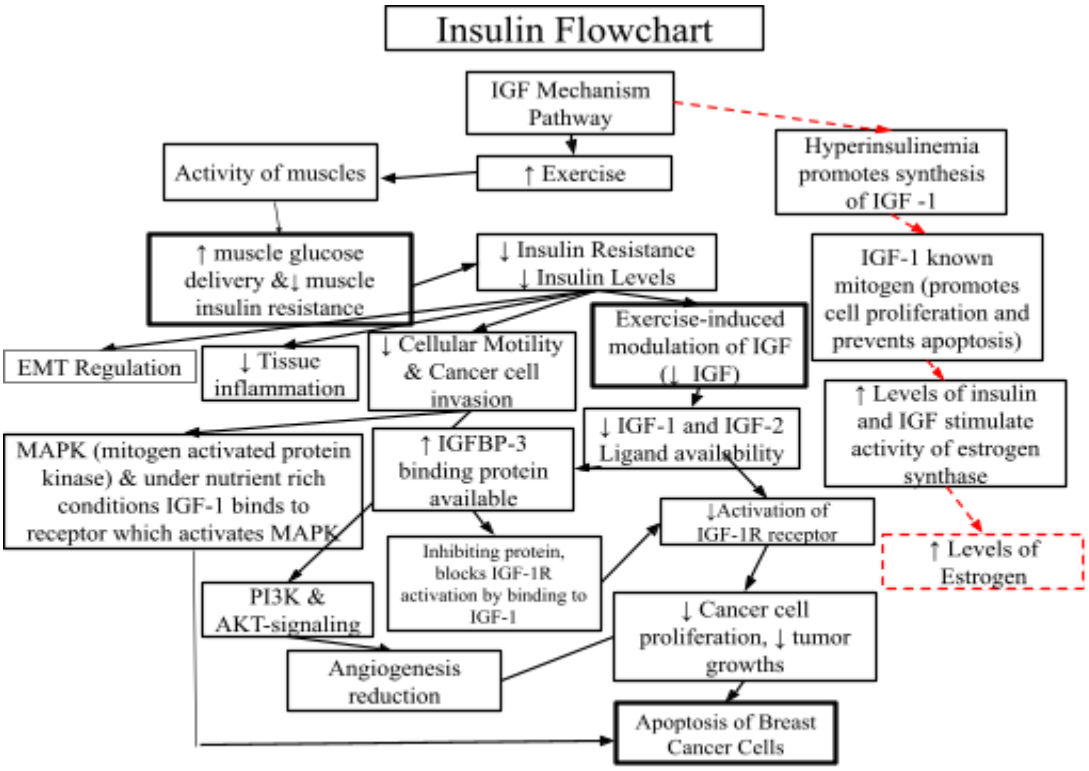

Figure 7. Combined Insulin flowchart decreasing breast cancer proliferation

The intricacies surrounding the impact of physical activity on the insulin/IGF-1 signaling pathway in the context of breast cancer call for a more nuanced interpretation of the available evidence. While the initial clinical trial demonstrated a reduction in insulin resistance and associated biomarkers, including IGF-1, conflicting findings from a separate 12-month trial prompt a reconsideration of the relationship between exercise and IGF-1 modulation. This dichotomy prompts an important question: could the duration of physical activity play a pivotal role in determining its effectiveness in influencing IGF-1 levels? In light of these conflicting findings, future research should prioritize investigating the optimal duration and intensity of physical activity required to achieve meaningful reductions in IGF-1 levels among breast cancer

patients and survivors. Longitudinal studies, encompassing diverse exercise regimens and durations, can provide a more comprehensive understanding of the temporal patterns of IGF-1 modulation. Researchers may also consider exploring the potential dose-response relationship between exercise duration and IGF-1 levels, acknowledging that a one-size-fits-all approach may not be suitable for every individual. For now, preliminary evidence supports the implementation of physical activity, considering its effect on the insulin/IGF-1 signaling pathway, in treatment plans for breast cancer patients as well as survivors.

Discussion and Pathways: Estrogen

Effects of Estrogen on Breast Cancer

In order to understand how exercise can impact the development of breast cancer, it is important to note the process through which estrogen hormones affect the risk of cancer. To start, the literary review "Endogenous estrogens—breast cancer and chemoprevention" by Starek-Świechowicz, Beata et al. provides an overview of estrogen metabolism and its relation to breast cancer (Starek-Świechowicz et al., 2021). Estrogen and its metabolites have different molecular structures and functions, and thus different metabolic pathways have varying effects on the possible occurrence of breast cancer. Firstly, the main starting points include Estrone (E1) and Estradiol (E2), known as parent estrogens. These two hormones are easily convertible to one another through enzymes, and occur in differing ratios based on menopausal status. E1 and E2 then undergo hydroxylation—the addition of hydroxyl group—into one of three main pathways, forming either 2-hydroxyestrone (2-OHE), 4-hydroxyestrone (4-OHE), or 16α-hydroxyestrone (16α-OHE). Each one of these metabolic pathways possesses different characteristics relating to breast cancer, which will be investigated more thoroughly in this section. Continuing, 2-OHE and 4-OHE can be further metabolized into either 2-methoxyestrone (2-MeOH) and

4-methoxyestrone (4-MeOH) respectively, or form electrophilic quinones (Starek-Świechowicz et al., 2021).

Before researching the individual pathways of estrogen metabolism, E2—one of the main parent estrogens—has been linked to the development of breast cancer, as seen in the paper "Postmenopausal plasma sex hormone levels and breast cancer risk over 20 years of follow-up" by Zhang, Xuehong et al. The study described in the paper included two blood draws from a large group of healthy women, with 32,826 subjects in 1990 and 25,947 of those still healthy in 2000 (Zhang et al., 2013). By the year 2010 a total of 707 cases of breast cancer were recorded, whose hormone levels were compared with the two controls selected per case (Zhang et al., 2013). Analyzing data from both blood draws shows that cases of breast cancer exhibited significantly higher levels of estradiol, both 10 and 20 years prior to the actual diagnosis of cancer. Subjects in the highest quartile of estradiol showed an approximate 1.4-2.0 fold increase in incidences of breast cancer compared with the lowest quartile.

As estrogen is broken down, one of its possible pathways it can take starts with 2-hydroxylation. According to Starek-Świechowicz, Beata et al. (2021), as estrogen is taken down this 2-pathway, its metabolites actually exhibit anticarcinogenic properties, contrary to its aforementioned parent hormone. 2-OHE is said to have less potency than parent estrogen, reducing cell proliferation. In addition to its chemical structure, this also has to do with the fact that 2-OHE is broken down at a faster rate, compared with other metabolic pathways. Schneider, J et al. (1982) found in their paper "Abnormal oxidative metabolism of estradiol in women with breast cancer" that half-maximal oxidation took 5.0 hours in breast cancer patients, compared with 7.1 hours for 16α-OHE, meaning 2-OHE estrogen is active for less time. Moreover, as

2-OHE is further metabolized to 2-MeOH, it begins to display apoptotic behavior with tumor cells to prevent cancer proliferation (Starek-Świechowicz et al., 2021).

Additionally, estrogen can metabolize through the 4-pathway, resulting in metabolites of different strengths and chemical abilities relating to breast cancer risk. One research article titled, "Relative imbalances in estrogen metabolism and conjugation in breast tissue of women with carcinoma: potential biomarkers of susceptibility to cancer" by Rogan, G. Eleanor et al. includes the hypothesis that 4-OHE broken down into its electrophilic quinone form creates depurinating adducts with DNA; in other words, 4-pathway metabolites are theorized to bond with DNA, causing potentially cancerous mutations. Rogan et al.'s study provides evidence towards the malignant effect of the 4-pathway through a study of 28 women with ductal carcinoma, compared with 49 women with solely benign breast disease as a control. Breast biopsies of each subject revealed statistically significant increases in 4-OHE in cases of carcinoma—13.3 pmol/g tissue compared with a control of 3.4 pmol/g tissue—as well as increased levels of quinone conjugates, indicating that 4-pathway quinones were linked to cancer cases (Rogan et al., 2003).

Lastly, estrogen that undergoes 16α-hydroxylation proves to demonstrate potent cell proliferation and is potentially linked with the production of breast cancer. As previously mentioned, 16α-OHE is shown to be active for a longer amount of time than 2-OHE. Furthermore, a study by Swaneck, G E, and J Fishman researches in depth the mechanism by which 16α-OHE proliferates cancer growth. By using MCF-7 human breast cancer cells in glass discs, the study determined that after 100 hours, the amount of 16α-OHE bound to nuclear estrogen receptors increased by 4 times, while levels of E2 binding also decreased accordingly (Swaneck et al. 1988). This suggests that 16α-OHE causes a permanent and unregulated activation of estrogen receptors in the cell nucleus. Although the paper also suggests the

possibility of 16α-OHE DNA adducts similar to 4-pathway quinones, direct evidence is not currently available and more research is still needed in this respect. The study by Schneider, J et al. (1982) connects this research on 16α-OHE to human subjects by taking blood samples from 33 women with breast cancer and 10 women with no adverse health conditions. The cancer cases presented with significantly higher levels of 16α-OHE—approximately a 50% increase compared with controls—in addition to a significantly decreased ratio of 2-OHE to 16-OHE (Schneider et al., 1982).

Effects of Exercise on Estrogen

By looking at how exercise can affect estrogen hormones, it can help to better visualize the pathway of how exercise impacts estrogen, thus affecting the development of breast cancer.

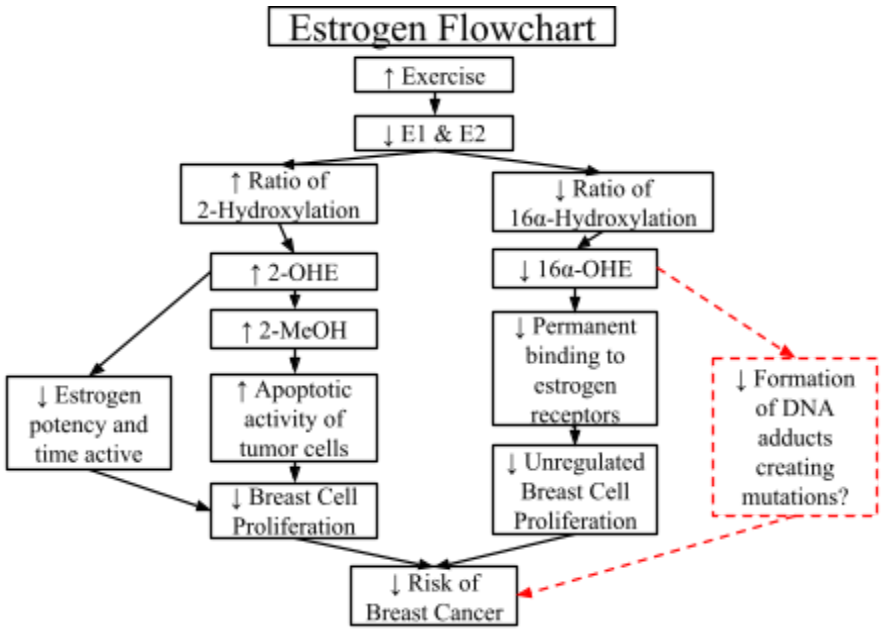

Figure 8. Estrogen decreasing breast cancer proliferation

The main parent estrogens, E1 (estrone) and E2 (estradiol), as mentioned previously, can be metabolized into estrogen metabolites. Specifically, E2 is a parent estrogen that has appeared in higher levels in breast cancer cases, making it of interest in understanding the impact physical activity might have on it. In the aforementioned estrogen metabolites, 2-OHE has shown possible apoptotic activity of tumor cells, suggesting that higher

levels of 2-OHE could prevent breast cancer proliferation. For 4-OHE and 16α-OHE, which have been shown to be present in high levels for cases of breast cancer, the effect of exercise on these metabolites can also help to demonstrate the impact of exercise on breast cancer risk.

Prior to discussing the association between exercise and estrogen metabolites, the effect of exercise on the parent estrogens mentioned should be discussed. For E2 (estradiol), exercise has been shown as a potential factor in decreasing levels of these forms of parent estrogens. In a study conducted by Matthews, Charles E. et al. titled "Effects of exercise and cardiorespiratory fitness on estrogen metabolism in postmenopausal women" women in the exercise group, with an average of 178 minutes of exercise per week for the course of one year, had an overall decrease of 10% in levels of E2 (estradiol) compared to women in the control group. This demonstrates the association between exercise and decrease in estradiol. Furthermore, a decrease in estradiol could lead to a decrease in the metabolization of itself into metabolites like 16α-OHE, which is present in high levels in patients with breast cancer (Matthews. et al., 2018). On the other hand, the impact of exercise on E1 (estrone) levels appears to be different than that of exercise on levels of E2. According to Smith, Alma J. et al., in their study "The Effects of Aerobic Exercise on Estrogen Metabolism in Healthy Premenopausal Women", for the 153 women in the control group, there was a decrease in the levels of E1 that was significant. However, for the 165 women in the exercise group, they did not experience the same significant decrease in levels of E1 (Smith et al., 2013). For E1 and the effect of exercise on its concentration, there needs to be further research dedicated to understanding the impact of physical activity on this parent estrogen, estrone. As physical activity has a positive association with a decrease in levels of E2, estradiol, there could be similar results for physical activity and E1, estrone.

Turning to the 4-pathway metabolite, 4-OHE, there is a need for more research focusing on this specific metabolite. Smith et al. have noted in their study that there were no significant changes in the concentrations of 4-OHE for women who were in the exercise group or for women in the control group. Similarly, Matthews, Charles E. et al. found that physical activity did not change the level of the 4-hydroxylation pathway in "Association between Physical Activity and Urinary Estrogens and Estrogen Metabolites in Premenopausal Women". For the 4-pathway metabolite, there appears to be no impact from physical activity as of where the research is now. Thus, more research focusing on this metabolite needs to be conducted in order to study the impact of exercise on 4-OHE.

Moreover, when looking at the association between exercise and estrogen metabolites, the ratio of 2-OHE/16α-OHE as well as individual levels of 2-OHE and 16α-OHE is important to cover. For the ratio of 2-OHE/16α-OHE, Ursin, Giske et al. have noted in their study "Urinary 2-hydroxyestrone/16α-hydroxyestrone ratio and family history of breast cancer in premenopausal women" that "the lower the ratio the higher the risk" is for breast cancer. Inversely, this suggests that a larger ratio indicates a lower risk for breast cancer as more 2-pathway metabolites are present compared to 16-pathway metabolites. The concentration of 2-OHE metabolites was found to have a positive correlation with physical activity as discussed in "The relationship between physical activity and 2-hydroxyestrone, 16α-hydroxyestrone, and the 2/16 ratio in premenopausal women (United States)" by Bentz, Ann T. et al., indicating that exercise could increase levels of 2-OHE. As 2-OHE has been discussed above to be active for less time than 16α-OHE, the metabolization of parent estrogen into the 2-pathway instead of the 16-pathway could potentially prevent the cell proliferation of breast cancer cells. Adding on, for the 16-hydroxylation pathway, Matthews, Charles E. et al. concluded in "Association between

Physical Activity and Urinary Estrogens and Estrogen Metabolites in Premenopausal Women" that women who were most physically active experienced a "15% lower level of 16-hydroxylation pathway", including the level of 16α-OHE metabolites. The studies by Bentz et al. and Matthews et al. demonstrate a positive association between physical activity and increased concentration of 2-OHE metabolites, and physical activity and a decrease in concentrations of the 16-pathway metabolites, respectively. In the study, by Smith et al. (2013) the 165 women in the exercise group were assigned aerobic exercise for 5 days per week, for 30 minutes. The women in the exercise group had a significant increase in the ratio of 2-OHE/16α-OHE whereas the women in the control group instead had a decrease that was non-significant in the ratio of 2-OHE/16α-OHE (Smith et al., 2013). This study directly looks at the ratio of the metabolites, 2-OHE/16α-OHE, and an increase in the ratio suggests either an increase in levels of 2-OHE or a decrease in levels of 16α-OHE. As mentioned previously, a higher concentration of 2-OHE has potential to prevent cell proliferation while high concentrations of 16α-OHE have appeared in patients with breast cancer. Thus, a lower level of 16α-OHE and a higher level of 2-OHE could be interpreted as to reduce the risk of breast cancer proliferation, through physical activity.

Conclusion

Exercise presents itself as a viable treatment aid for breast cancer patients and breast cancer prevention. The mechanisms displayed shed light on the breast cancer-exercise connection through dopamine, estrogen, and insulin pathways. Through their exploration, we were able to highlight novel findings that further elaborate this connection. It can be concluded that elevated levels of exercise can lead to higher levels of dopamine as well as lower levels of estrogen and insulin levels which contributes to a lower rate of breast cancer. Future studies

should investigate whether aerobic resistance, a combination of both, as well as their respective time duration, is the most effective for optimal levels of estrogen, dopamine, and insulin growth factor. It would also be imperative to further the combined role of exercise and breast cancer medication as a way to bring optimal treatment for breast cancer patients.

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