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Effect of Estrogen on Insulin Resistance: Focus on Carcinogenesis, Tumor Growth, and Other Pathological Aspects

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ABSTRACT

Estrogen plays a pivotal role in regulating metabolic processes, particularly in maintaining insulin sensitivity. However, its imbalance, as observed in conditions like menopause or polycystic ovary syndrome (PCOS), contributes to insulin resistance, which is a key driver of various pathological states, including carcinogenesis and tumor growth. This narrative review explores the complex interaction between estrogen, insulin resistance, and associated pathological aspects, with a focus on cancer development. Estrogen influences insulin signaling pathways, while insulin resistance fosters a pro-tumorigenic environment, especially in hormone-sensitive cancers like breast and endometrial cancer. Furthermore, the review discusses the impact of estrogen-insulin resistance interactions on other pathological conditions, such as cardiovascular diseases, non-alcoholic fatty liver disease (NAFLD), and PCOS, underscoring their cumulative burden on health. Therapeutic approaches, including estrogen replacement therapy (ERT), are evaluated in the context of managing insulin resistance and its associated risks, particularly concerning cancer progression. Despite advances, significant gaps remain in understanding the dual role of estrogen in metabolic dysfunction and carcinogenesis. This review highlights the need for further research into the estrogen-insulin resistance axis and its implications for personalized therapeutic strategies in cancer and metabolic disorders.

Keywords: Estrogen; Insulin Resistance; Carcinogenesis; Tumor Growth; Hormone Therapy; Metabolic Syndrome; Estrogen Receptor Signaling; Hyperinsulinemia; Breast Cancer; Polycystic Ovary Syndrome (PCOS); Non-Alcoholic Fatty Liver Disease (NAFLD); cardiovascular disease; Estrogen Replacement Therapy (ERT); Insulin-like Growth Factors (IGFs); Menopause

INTRODUCTION

Estrogen is a critical hormone with multiple physiological roles in regulating reproductive functions, bone density, cardiovascular health, and metabolic processes. Its influence extends beyond the reproductive system, impacting glucose and lipid metabolism.[1] Estrogen's effects are mediated primarily through estrogen receptors (ERα and ERβ), which are distributed in tissues such as adipose, skeletal muscle, and the liver, all of which are central to insulin action.[2] By modulating insulin sensitivity, estrogen plays a key role in maintaining metabolic homeostasis, particularly in premenopausal women, who

are more protected against metabolic diseases compared to men and postmenopausal women.[3]

Insulin resistance, characterized by the inability of peripheral tissues to effectively respond to insulin, leads to impaired glucose uptake and increased hepatic glucose production.[4] It is a central feature of metabolic syndrome and a significant risk factor for type 2 diabetes mellitus (T2DM), cardiovascular diseases, and certain cancers.[1] The interplay between estrogen and insulin resistance becomes particularly relevant in postmenopausal women, where the decline in estrogen levels is associated with increased susceptibility to insulin resistance and related metabolic complications.[3]

In view of the roles of estrogen and insulin resistance, a clear elucidation of the two terms is essential in enhancing information dissemination in metabolic disorders and their pathophysiological aspects. Estrogen's decline during menopause is a significant contributor to increased insulin resistance and metabolic dysfunction, which raises the risk of developing chronic diseases such as metabolic syndrome, cardiovascular diseases, and cancer.[4] Given the prevalence of obesity, T2DM, and metabolic dysfunction–associated fatty liver disease (MAFLD), it is essential to explore how hormonal imbalances exacerbate these conditions and the potential for hormone replacement therapy (HRT) to mitigate these risks.[1]

In addition, the interactions between hormones serve significant objectives in tumorigenesis. Insulin resistance is associated with hyperinsulinaemia and insulin-like growth factors both of which exert mitogenic stimuli which foster carcinogenesis and tumor progression.[3] The present review also sought to establish how estrogen affects the development of insulin resistance and its consequences on cancer and different diseases.

The major aim of this review is to assess the association between estrogen and insulin resistance, and to identify the molecular effects and pathological consequences of the interaction. In particular, the discussion will focus on how estrogen deficiency and insulin resistance contribute to metabolic disorder; including MAFLD, T2DM, and CV diseases.[3] Furthermore, it will briefly describe the molecular mechanisms that underlie estrogen-mediated regulation of insulin signalling and the effects of that regulation on carcinogenesis and tumor growth. For these reasons, the present review will summarize the state of affairs regarding the existing literature so as to guide the future research and potential therapy for insulin resistance and the associated diseases.

ESTROGEN AND INSULIN RESISTANCE

The prime importance of estrogen for maintaining glucose homeostasis is achieved through its influence on insulin sensitivity. Several investigators have shown that estrogen acts selectively in peripheral tissues, including adipose tissue, liver, and skeletal muscle through improving the insulin sensitivity and uptake of glucose by increasing the tissues' sensitivity to insulin.[1]. This effect is mainly exerted through ER dependent pathways, which encompass ERα and ERβ. Stimulation of these receptors improves the insulin signaling cascade and therefore increases insulin sensitivity.

Furthermore, estrogen can stimulate other molecular signaling related to glucose homeostasis including peroxisome proliferator-activated receptor-gamma (PPAR-γ), which was known as a key factor in adipogenesis and insulin sensitivity.[2] Estrogen through regulating of PPAR-γ can afford a positive impact in decreasing adipose tissue inflammation which is considered to cause insulin resistance. Also the estrogenergic action on inflammation mediators: TNF-α and IL-1β that interferes with insulin signaling play a part on the end result.[4] These molecular processes explain why estrogen is critical to make sense of the

regulation of glucose and insulin in the body, especially in premenopausal women.

Insulin resistance has been linked to estrogen deficiency especially after a woman has ceased to be of childbearing age. This is due to the androgen effect brought about by low levels of estrogen thus reducing insulin sensitivity markedly and causing onset of metabolism syndromes like the type 2 diabetes and the metabolic syndrome.[1] The postmenopausal female undergoes central obesity, viscerally distributed fat, and impairment of glucose homeostasis, all of which aggravate insulin resistance.[3]

As a method of avoiding the effects outlined above, estrogen replacement therapy (ERT) has been used. Research has also shown that ERT can help to recover insulin sensitivity by awakening estrogen receptor signaling and lessening inflammation.[2] In animal models, its application increased insulin sensitivity of female rats of older age by means of regulating IRS-1 and Akt phosphorylation, which are involved in insulin signaling.[4] In addition, a recent research has highlighted the anti-inflammatory effect of ERT that enhances the output of FDA-approved 'anti-inflammatory cytokine ' IL-10 and reduces the level of 'pro-inflammatory cytokine 'TNF-α that leads to insulin resistance.[4] ERT indicates great potential concerning post-menopausal changes in Insulin sensitivity, yet, more sizable clinical trials are required to determine the prospective complication and benefit risks.

CARCINOGENESIS AND TUMOR GROWTH

Oestrogen has a central part in the growth and spread of different cancers including oestrogen receptor positive or oestrogen dependent kind of cancer-like breast and endometrial cancers. The activation of the estrogen and its receptors include ERα and ERβ results in a variety of cellular activities affecting tumor characteristics. ERα primarily gives signals to oncogenic activities of the cell linking to cell growth and anti-apoptosis signaling in most estrogen receptor-positive carcinomas.[5] On the other hand, the Studies have shown that ERβ has the tumor repressor property and activates tumor suppressor genes and inhibits cell cycle progression.[6] In breast cancer, it has been observed that, ERβ has better survival outcomes; this shows that balance between proliferation signals offered by ERA and the suppressive effects of ERβ is equally important.[7] This kind of bid option in estrogen signaling makes it easier to target estrogen dependent tumor growth since selective modulation of these receptors may provide a way of regulating estrogen's mitogenic activity.

Tumourigenesis has been found to be associated with the insulin resistance, a feature of metabolic syndrome. Pathophysiological of hyperinsulinaemia, is also associated with hyperglycaemia this promotes the secretion of insulin like growth factors (IGFs) that stimulate on cellular pathways of cell proliferation and survival.[8] Insulin resistance also stimulates tumorigenesis, and in combination with estrogen, significantly increases cancer development. As was stated above, the increased levels of Insulin encourage estrogen stimulated proliferation of cancer cells and decreased sensitivity to treatment in estrogen-dependent cancers.[9] Further, on metabolic front, insulin resistance has also influenced an increased endometrial and breast carcinogenesis risk by influencing oncogenic signaling in tissues which are estrogen sensitive.[10] These relationships should be well understood to demonstrate the need to incorporate metabolic disorders to cancer management approaches.

Thus, the synergistic action between estrogen and insulin resistance supports the development of a favourable tumourigenic situation mainly due to the effects of IGFs. High levels of IGFs that are a feature of insulin resistance increase the levels of signaling through the estrogen receptor, thereby helping estrogen to promote cancer growth.[11] Selective estrogen receptor modulators specifically augment cell

cycling and tumor progression when teamed up with IGF in hormone receptive tissues including the breasts and uterus. Furthermore, metabolic disease including insulin resistance, obesity and dyslipidemia affect the tumour micro-environment to promote estrogen-driven tumourigenesis.[8] Within this regard, integrating metabolic and hormonal signaling pathways as a cross talk greatly contributes in promoting the proliferative character of estrogen dependent tumours, which makes metabolic/hormonal synergy involving the two approaches as a novel direction in cancer treatment.

ESTROGEN AND PATHOLOGICAL ASPECTS RELATED TO INSULIN RESISTANCE

Role of Estrogen on Cardiovascular Complications

Estrogen is indisputably a cardio-protective hormone, especially to pre-menopausal women and, from data collection, it was evident that the rate of CVD among women of this bracket is lower than that of male counterpart of the same age bracket.[12] This protection is mostly exerted through the binding of estrogen to estrogen receptors including ERα, ERβ and GPER, which are expressed widely in the cardiovascular system. These receptors are useful moderating oxidative stress a condition that plays a major role in crafting atherosclerosis, myocardial dysfunction, and heart failure.[13] Furthermore, estrogen helps to restore responsiveness of cardiovascular tissue; it means that estrogen has the ability to modulate the function of vascular endothelium and myocardial tissue.[14] A dramatic increase in cardiovascular risk among postmenopausal women also supports the importance of estrogen in cardiovascular function. Gender specific changes at the time of menopause are that there are changes in hormonal concentrations, pro-oxidant/antioxidant changes, and the subsequent alterations to have increased incidences of cardiovascular diseases such as hypertension, atherosclerosis and myocardial ischemia.[13]

In addition, estrogen has anti-inflammatory effects and affect lipid metabolism in that it enhances the ratio of HDL / LDL cholesterol thus decreasing risks of formation of unhealthy blood plaques in arteries.[14] Altogether these mechanisms justify why oestrogen replacement therapy, especially in the early postmenopausal period, is linked to improved CVD morbidity and mortality tantamount to that of HRT.[15] Nevertheless, there remain increasingly concerns on side effects like venous thromboembolic events in HRT, which need to be weighed before starting of the therapy.

Estrogen and Insulin resistance are two factors that are involved in the regulation of Cardiovascular disorders mostly in postmenopausal women. Whereas insulin sensitivity decreases, accompanied by the increasing risk factors for cardiovascular disease due to dysregulated glucose metabolism, increases in visceral fat content, and atherogenic lipoprotein.[15] T2DM causes changes that contribute to oxidative stress and inflammation which in turn exacerbate endothelial dysfunction and arterial stiffness that are major predictors of myocardial infarction and stroke.[16]

In postmenopausal women, with higher adiposity the risk of CVD is further increased by high levels of circulating estradiol which induces insulin resistance and metabolic syndrome.[16] Estrogen is otherwise considered cardioprotective but this benefit may be abrogated or transformed with insulin resistance and obesity. It is evident that the findings are useful for understanding that controlling both estrogen concentrations and metabolic factors are crucial in postmenopausal women for decreasing cardiovascular risks. Thus, insulin sensitizing interventions may confer additional cardiovascular disease risk reduction in this population especially among those with histories of estrogen mediated metabolic dysfunctions.

Role of Estrogen on Non-Alcoholic Fatty Liver Disease (NAFLD)

Estrogen is as an important factor in the metabolism of the liver and NAFLD, and is a major concern for NAFLD patients. This complicated disease involves the deposit of fat within the liver cells and is not demanding alcohol drinking or other liver diseases. Recently, it has been evidenced that estrogen, especially oestradiol (E2) can be beneficial for individuals with NAFLD, particularly in males. Tian et al.[17] performed a study that corresponds to the present analysis showing that lower E2 levels increase the probability of NAFLD, and hepatic fat infiltration in men.[17] The authors also pointed out that it is possible to reduce the risk of NAFLD if women had appropriate levels of estrogen, which supported the importance of estrogen for the liver.

Deficiency of estrogen and insulin resistance both collectively play a vital role in the NAFLD as hormonal changes can reflect the metabolic alterations independently. For example, Zhang et al.[18] also showed that estradiol significantly derivative fatty acid synthesis and ameliorated hepatic I lipid metabolism in an experimental model pointing to one of the possible ways through which estrogen may assist in preventing NAFLD.[18] According to their observations, the protective roles come from estrogen regulation of some metabolic processes which are important for suppression of lipogenesis and promotion of fatty acid oxidation to lessen accumulation of liver fat.

Further, in a cross-sectional study by Yoshioka et al.[19], the authors analyzed effects of changes in life style and weight on NAFLD and its steatosis, as well as its active phase. In their longitudinal study they noted that weight loss played a pivotal role in achieving NAFLD remission and emphasized the importance of hormonal control, reduction of body weight, and metabolic profiles.[19] Moreover, the research revealed that hormonal mediators, specifically estrogen, might have roles in the metabolic alterations in weight changes influencing NAFLD.

The hormonal shift involving estrogen, insulin resistance and NAFLD demonstrates that hormones do play a role in the welfare of the liver. Ovarian hypofunction and estrogen deficiency have been observed to increase insulin resistance and promote the transition of NAFLD. These results support the importance of studying estrogen and its analogues and their administration as a therapeutic option for NAFLD, a common metabolic disease.

Role of Estrogen on Polycystic Ovary Syndrome (PCOS)

Hormonal dysharmony is the major trigger of PCOS and, in particular, the connection of the disease with insulin resistance. Recently, the pathophysiology of PCOS has also been linked to endocrine disorder and described by hormonal imbalance where aberrant ERα/ERβ signaling plays a major role for the development of metabolic complications.[20] It has been found that in women with PCOS, the estrogen metabolism is abnormal and that the levels of estrogen, and estrogen metabolites themselves also have an influence on the insulin level of the body. This hormonal disruptions can worsen the insulin resistance, which is a hallmark of PCOS through direct as well as indirect ways on the insulin signaling pathways.[21] In the man, hyperandrogenism as implicated in PCOS, the involvement of estrogen in the option of insulin resistance brings into focus that therapeutic manipulation of estrogen pathways might provide fresh approaches in handling more metabolic-in pornost for these patients.[22]

PCOS also has critical pathophysiologic connection between estrogen and cancer risk in women. Polymorphic factors, particularly those of the estrogen receptor, ESR1 and ESR 2 have been studied to try and find links between PCOS and its evolution.[23] For the association between ER gene polymorphisms and genetic susceptibility to PCOS, some clinical

investigations have documented that risks may be mediated by estrogen receptor gene variants, although such findings appear to variably resound in different populations as well as in relation to different genetic models of estimation. Nonetheless, deregulated estrogen signaling in PCOS is said to be directly linked to the risk of developing endometrial hyperplasia and endometrial cancer mainly to chronic anovulation, and unameliorated estrogen activity. Also, a reduction in follicular angiogenesis including changes in 2-hydroxyestradiol (2-OHE2) and vascular endothelial growth factor (VEGF) levels have been attributed to follicular arrest in PCOS to further underscore the relationship between estrogen disorders and reproductive disorders coupled with; cancer risks (24). Clarifying the relationship between estrogen dysregulation, insulin resistance in PCOS, and risk factors we can work on being closer to effective treatment.

THERAPEUTIC IMPLICATIONS

Estrogen Replacement Therapy (ERT) has been discussed in the amelioration of insulin resistance especially among post-menopausal women. This is because, during the menopausal process, estrogen levels are low and these conditions such as insulin resistance and type 2 diabetes are likely to occur.[24] Fluctuating levels of estradiol (E2) used in ERT affect glucose homeostasis through modulation of adipose tissue function. Experimental observation has demonstrated that in post-menopausal females, E2 affects the glucose transporters in adipocytes, further impaired in the late post-menopausal age enhancing insulin resistances.[25] These data indicate that ERT may have favorable effects on metabolism such as the change in fat distribution but the effect on insulin resistance is more complex and may be related to stage of menopause and the density of estrogen receptors in adipose tissue.[26] Therefore, special attention should be paid to the timing of the treatment with ERT to correct insulin resistance in postmenopausal women as well as individual hormonal characteristics.

This is in addition to the metabolic side effects of ERT which include cancer risk. If insulin resistance is involved then knowing how ERT affects the risk for cancer becomes essential. Generic estrogen HRT was found to increase the risk of recurrence of breast cancer and patients with hormone receptor-positive breast cancer are more vulnerable.[27] One meta-analysis showed that there is a significantly increased risk of recurrence among BC survivors taking ERT, with the risk higher in HR-positive BC.[27] ERT, as an intervention may potentially have benefits as observed through decreased menopause related effects, and, the potential to better metabolic profiles, ERT administration we agreed should be approached cautiously in patients with history of hormone associated cancers. Similarly, when ERT was investigated in cervical cancer survivors, there was no adverse effect on the oncological parameters while the metabolic risk may be decreased.[28] Nevertheless, these results provide rationale for patient-tailored strategies in ERT use for patients with cancer risk factors, particularly with reference to insulin resistances.

New developments in cancer therapy have provided evidence regarding the expansion of new therapies for the estrogen-insulin resistance signaling pathway. The chief malignancy related to estrogen is that of hormone-dependent malignancies, particularly breast cancer where ER+ carcinomas are most common. Such research has emerged from the interaction between estrogen signaling and insulin resistance, major features that manifest in type 2 diabetes and obesity. Some papers showed that insulin resistance can enhance cancer risk, especially in ER+ breast cancer, by increasing the serum insulin level, which may enhance the estrogen availability and tumor proliferation.[29] Therefore, er beta and insulin pathways should be targeted as a strategy of treating patients with cancer and metabolic diseases.

Anti estrogens are still considered standard initial cancer treatment especially in treating; breast cancer through the use of select estrogen receptor modulators and aromatase inhibitors.[30] They decrease estrogen-stimulated cancer development and are most suitable for female clients who are past their childbearing years. However, in cases of I.R., utility of anti-estrogenic agents might be further strengthened by combating insulin resistance. Newer treatments meant for use alongside antiestrogen agents utilizing insulin sensitizers for instance, metformin, look rather promising in tackling the risk of cancer and bettering the take of insulin resistant patients. This organization approach of cancer treatment does not only focus on destruction of cancer cells but also addresses the issue of metabolic disorder which remain one of the major causes of cancer progression.[31]

Another area of potential future work in targeting the estrogen-insulin resistance link is the application of SERDs, which is based on the functional antagonistic properties of SERD. Promising direction in the targeting of the estrogen–insulin resistance axis is the usage of selective estrogen receptor degraders. These compounds present a new mode of endocrine resistance by degrading the estrogen receptor thus down regulating estrogen signaling which is critical in tumor progression. New generation SERDs including giredestrant and elacestrant have been investigated previously and they are more potent in terms of performance and clinical efficacy then first-generation SERDs and particularly beneficial in cases, when patient developed resistance to first line endocrine therapies.[32] Withholding these drugs for estrogen receptor positive and patients with insulin resistance cancers may could prove better disease control with hormone and metabolic changes.

Moreover, a consideration of the place of estrogen deprivation therapy in cancer therapy in relation to insulin resistance should transpire. Estrogen suppression in the postmarketing treatment however improves cancer recurrence but has significant side effects such as cardiovascular disease, osteoporosis and metabolic syndrome especially in young women.[33] Considering these side effects, one may look at emerging therapies that try to reduce metabolic disturbances arising from estrogen deprivation, for example by adding insulin sensitizing drugs, or administering estrogen blockers in cycles to allow the body to recover from estrogen depletion. Further research into these combinations is required, especially in patients with other metabolic pathologies.

CHALLENGES AND LIMITATIONS

A considerable problem in cancer research, especially in breast cancer, is that the molecular mechanisms of endestrogen and insulin resistance interplay remain rather ill-defined. Whereas, it is well documented that both estrogen and insulin are involved in metabolic regulation and cancer development, still the metabolic impact of estrogen is not globally described. Estrogen has been shown to regulate glucose metabolism and insulin sensitivity, which may influence cancer risk, especially in populations with insulin resistance, such as those with obesity or type 2 diabetes.[29] There are, however, no extensive clinical investigations carried out on the manner in which estrogen metabolism relates with cancer progression. A vast majority of previous investigations is directly related to cancer or the metabolic activity of estrogen as two different pathways that have not been reconciled for clinical application. This gap in knowledge hinders the development of targeted therapies that could address both estrogen-driven cancer proliferation and the metabolic dysregulation seen in insulin-resistant patients.[31]

Further, the cellular processes through which estrogen favorably influences metabolic functions are still not well understood, particularly with reference to effects on insulin responsiveness and glucose homeostasis. Further investigations must be done to examine how estrogen

affects the insulin signaling pathways and the differences of this impact depending on the type of the tissue, adipose and muscle which are mainly involved in metabolic function. The absence of such studies is a factor to the present day poor maximal optimization of estrogen-modulating therapies for both cancer and metabolic benefits. Future research should aim to bridge this gap by conducting comprehensive, large-scale clinical trials that investigate the interplay between estrogen and insulin resistance in cancer patients.[33]

Another major problum associated with the treatments in estrogen related cancers is the factors that determine the variation in the response of different patients to the treatment. Estrogen therapy, particularly in breast cancer, is highly effective for many patients, but outcomes can vary significantly depending on numerous factors, including genetic variations, tumor heterogeneity, and metabolic status.[30] For example, individuals with specific gene changes in ESR1 gene can become resistant to simple endocrine treatments including SERMs, and AIs. Additionally, factors such as age, menopausal status, and the presence of metabolic disorders like insulin resistance can further complicate treatment outcomes, leading to a heterogeneous response to estrogen-targeting therapies.[32]

These variations in individual response raise both ethical and methodological questions in clinical research. That is why a diagnosis of ethical issues arising from randomised clinical trials for patients; treatment is a difficult balancing act, in the light of subjects of treatment, starting with inter-individual variability. Another disadvantage is that the variety of responses can hardly allow the formulation of general recommendations on further treatment, as these recommendations often do not take into consideration cases or certain populations that may exhibit different reactivity to the references applied. From a methodological point of view, this variability makes clinical trials unrefutable because the results obtained cannot be extrapolated for all patient populations. Even worse, there are no definite biomarkers that could help estimate in advance which patient would react well to estrogen therapy. Personalized medicine approaches, which consider individual genetic, metabolic, and hormonal profiles, are needed to address these limitations and improve the efficacy of estrogen therapies.[34] Furthermore, the hazards of estrogen therapy are always attributed to ethical issues of follow-up examinations and side effects. Estrogen suppression therapies, for example, can lead to significant side effects such as bone density loss, cardiovascular disease, and cognitive decline, particularly in premenopausal women.[33] Picking between proper cancer care and potential for harm in the long term is again an ethical dilemma when it comes to trials as well as application. Further studies should be aimed at understanding how to better target estrogen and prevent undesired side effects, as well as discuss the methodological and the ethical issues connected with the further research of such multifaceted hormone.

Future Directions

As the link between estrogen signaling and insulin resistance becomes more realized, further studies are only looking at the use of hormonal agents in cancer types that are related to metabolic diseases. The preceding consequences of insulin resistance, which is characteristic of type 2 diabetes and obesity, plays a role in cancer development and progression of at least breast, endometrial and colorectal. Since estrogen has a central role in regulating metabolic pathways, and new compounds are being examined as selective estrogen and insulin pathway modulators. These agents have the potential to interrupt the processes through which insulin resistance has a means of fuelling cancer, and this could be a welcome advance for patients presented with both of these diseases.

One direction for bringing about a selective shift in estrogen’s effects on cancer and

metabolism is through the use of selective estrogen receptor modulators (SERMs) together with estrogen receptor degraders (SERDs). The initial investigations indicate that these new compounds may hinder cancer cell growth and at the same time enhance insulin signaling and glucose homeostasis. Furthermore, because insulin sensitizing drugs like metformin are used together with the estrogen modulators, which are a type of estrogen antagonist, various trials are currently underway to explore the possibility of reducing cancer risk in insulin-resistant patients. I believe that such approaches are capable of changing the face of cancer care a lot by targeting the metabolomics that sustain cancer.

Besides, pharmacologic intervention should complement the qualitative and evolving understanding of how diet, exercise and weight intervention affects estrogen-insulin axis. Early studies show that these strategies could help in increasing the effectiveness of hormonal therapies and lower the instances of cancer relapse especially in cases of those with metabolic syndrome. There is a need for other studies, especially large, controlled clinical trials in which both intervention and pharmacological treatments for insulin resistance are combined and tested for efficacy in treating insulin resistance related cancers.

With the development of the oncology and endocrinology practices, there is an increasing demand for pathophysiological information derived from estrogen and insulin resistance studies to become more incorporate into the concept of precision medicine. The variability of the reaction to estrogen therapies, especially in insulin-resistant patients, indicates further that the treatment should be more flexible depending on the metabolic-gene hormonal characteristics of a patient. The system of precise medicine can significantly enhance the efficacy of treatment for patient with metabolic disease and estrogen dependent cancer using its biomarkers and risk factors.

Specifically, for breast cancer and other estrogen-sensitive cancers, properly individualized hormone therapy could solve the problem of both cancer growth and metabolic disorders. Clinicians can create individual treatment plans based on estrogen receptors, insulin resistance, and heredity to bring better effectiveness to the treatment. For instance, patient diagnosed with both insulin resistance and estrogen receptor positive breast cancer might find useful a combination of such estrogen modulating and insulin sensitizing medications. Consequently, creating individual patient-centered strategies can help decrease both cancer risk and metabolic related burdens providing a more comprehensive method of treatment.

Molecular diagnostic technologies and increased understanding of human variation through genomics are also stimulating the search for biomarkers that will help to estimate an individual's response to estrogen therapies. These biomarkers could be used to sort patients according to their likelihood of getting insulin resistance or cancer and thereby receiving the right treatment at the right time. Likewise, future studies are needed to compare potential risk factors for the administration of hormone therapies and resulting adverse outcomes such as heart disease or osteoporosis in order to tailor the therapy even more precisely.

The combinations of estrogen and insulin resistance in precision medicine have a potential of enhancing the performance of cancer patients with metabolic complications. Therefore, as research advances, the emphasis should be on how this data can be implemented in actual clinical practice for hormone based targeted cancer and treatment of metabolic hazards associated with cancer syndromes.

CONCLUSION

Estrogen and insulin resistance are inversely related with different complicated and intricate correlations that play a crucial role in distorting several pathological processes,

including carcinogenesis. The fact that estrogen has a bimodal effect on metabolism and cancer makes it central to endocrinology as well as oncology. Metabolic disorders are like insulin resistance are not only seen to be potentially making the metabolic condition worse but also in promoting tumor growth, especially cancers that is sensitive to estrogen such as the breast and endometrial cancers. It thus is imperative to gain insight into these interactions so that targeted treatments that may help manage the metabolic as well as the oncogenic components of the diseases can be formulated.

Although there is increased knowledge on the way that estrogen and insulin resistance affect one another, there are still lose ends that have not been closed. More research work is direly required to deconvolute these issues especially through well controlled clinical trials that will help dissect out the various qualitative aspects of responses to estrogen therapy in relation to metabolic derangements. Such investigations will contribute not only to the understanding of the molecular basis of estrogen-mediated metabolic and cancer activities, but also to the development of better targeted therapies.

Apparently, the understanding of the relationship between estrogen, insulin resistance and such pathological outcomes should be expanded to enhance patients' management. We need to step up our efforts in researching these combined diseases and work towards finding treatment that not only manages the metabolic consequences of cancer treatment but also targating cancer and its related risks at the same time thus improving the quality of life for such patients.

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REFERENCES

1. De Paoli M, Zakharia A, Werstuck GH. The role of estrogen in insulin resistance: a review of clinical and preclinical data. *Am J Pathol.* 2021;191(9):1490-1498. https://doi.org/10.1016/j.ajpath.2021.05.011
2. Wei Y, Yuan P, Zhang Q, et al. Acacetin improves endothelial dysfunction and aortic fibrosis in insulin-resistant SHR rats by estrogen receptors. *Mol Biol Rep.* 2020;47(1):6899-6918. https://doi.org/10.1007/s11033-020-05746-3
3. Pal SC, Eslam M, Mendez-Sanchez N. Detangling the interrelations between MAFLD, insulin resistance, and key hormones. *Hormones.* 2022;21(4):573-589. https://doi.org/10.1007/s42000-022-00391-w
4. Esmailidehaj M, Kuchakzade F, Rezvani ME, Farhadi Z, Esmaeili H, Azizian H. 17β-Estradiol iproves insulin signalling and insulin resistance in the aged female hearts: Role of inflammatory and anti-inflammatory cytokines. *Life Sci.* 2020;253(1):117673. https://doi.org/10.1016/j.lfs.2020.117673
5. Chimento A, De Luca A, Avena P, et al. Estrogen receptors-mediated apoptosis in hormone-dependent cancers. *Int J Mol Sci.* 2022;23(3):1242. https://doi.org/10.3390/ijms23031242
6. Mal R, Magner A, David J, et al. Estrogen receptor beta (ERβ): a ligand activated tumor suppressor. *Front Oncol.* 2020;10(1):587386. https://doi.org/10.3389/fonc.2020.587386
7. Langdon SP, Herrington CS, Hollis RL, Gourley C. Estrogen signaling and its potential as a target for therapy in ovarian cancer. *Cancers.* 2020;12(6):1647. https://doi.org/10.3390/cancers12061647
8. Somasundaram A, Rothenberger NJ, Stabile LP. The impact of estrogen in the tumor microenvironment. *Adv Exp Med Biol.* 2020:1277(1):33-52. https://doi.org/10.1007/978-3-030-50224-9_2
9. Hickey TE, Selth LA, Chia KM, et al. The androgen receptor is a tumor suppressor in estrogen receptor–positive breast cancer. *Nat Med.* 2021;27(2):310-320. https://doi.org/10.1038/s41591-020-01168-7
10. Chakraborty B, Byemerwa J, Shepherd J, et al. Inhibition of estrogen signaling in myeloid cells increases tumor immunity in melanoma. *J Clin Invest.*

2021;131(23):e151347. https://doi.org/10.1172/JCI151347
11. Smida T, Bruno TC, Stabile LP. Influence of estrogen on the NSCLC microenvironment: a comprehensive picture and clinical implications. *Front Oncol.* 2020;10(1):137. https://doi.org/10.3389/fonc.2020.00137
12. Visniauskas B, Kilanowski-Doroh I, Ogola BO, et al. Estrogen-mediated mechanisms in hypertension and other cardiovascular diseases. *J Hum Hypertens.* 2023;37(8):609-618. https://doi.org/10.1038/s41371-022-00771-0
13. Xiang D, Liu Y, Zhou S, Zhou E, Wang Y. Protective effects of estrogen on cardiovascular disease mediated by oxidative stress. *Oxid Med Cell Longev.* 2021;2021(1):5523516. https://doi.org/10.1155/2021/5523516
14. Ueda K, Fukuma N, Adachi Y, et al. Sex differences and regulatory actions of estrogen in cardiovascular system. *Front Physiol.* 2021;12(1):738218. https://doi.org/10.3389/fphys.2021.738218
15. Anagnostis P, Lambrinoudaki I, Stevenson JC, Goulis DG. Menopause-associated risk of cardiovascular disease. *Endocr Connect.* 2022;11(4):e210537. https://doi.org/10.1530/EC-21-0537
16. Dashti SG, Simpson JA, Karahalios A, et al. Adiposity and estrogen receptor-positive, postmenopausal breast cancer risk: quantification of the mediating effects of fasting insulin and free estradiol. *Int J Cancer*. 2020;146(6):1541-1552. https://doi.org/10.1002/ijc.32504
17. Tian GX, Sun Y, Pang CJ, et al. Oestradiol is a protective factor for non-alcoholic fatty liver disease in healthy men. *Obes Rev.* 2012;13(4):381-387. https://doi.org/10.1111/j.1467-789X.2011.00978.x
18. Zhang H, Liu Y, Wang L, et al. Differential effects of estrogen/androgen on the prevention of nonalcoholic fatty liver disease in the male rat [S]. *J Lipid Res.* 2013;54(2):345–357. https://doi.org/10.1194/jlr.M028969
19. Yoshioka N, Ishigami M, Watanabe Y, et al. Effect of weight change and lifestyle modifications on the development or remission of nonalcoholic fatty liver disease: Sex-specific analysis. *Sci Rep.* 2020;10(1):481. https://doi.org/10.1038/s41598-019-57369-9
20. Xu XL, Deng SL, Lian ZX, Yu K. Estrogen receptors in polycystic ovary syndrome. *Cells.* 2021;10(2):459. https://doi.org/10.3390/cells10020459
21. Lazo M, Zeb I, Nasir K, et al. Association between endogenous sex hormones and liver fat in a multiethnic study of atherosclerosis. *Clin Gastroenterol Hepatol.* 2015;13(9):1686-1693. https://doi.org/10.1016/j.cgh.2014.12.033
22. Walters KA. Polycystic ovary syndrome: is it androgen or estrogen receptor?. *Curr Opin Endocr Metab Res.* 2020;12(1):1-7. https://doi.org/10.1016/j.coemr.2020.01.003
23. Zhou S, Wen S, Sheng Y, et al. Association of estrogen receptor genes polymorphisms with polycystic ovary syndrome: A systematic review and meta-analysis based on observational studies. *Front Endocrinol.* 2021;12(1):726184. https://doi.org/10.3389/fendo.2021.726184
24. Henríquez S, Kohen P, Xu X, et al. Significance of pro-angiogenic estrogen metabolites in normal follicular development and follicular growth arrest in polycystic ovary syndrome. *Hum Reprod.* 2020;35(7):1655–1665. https://doi.org/10.1093/humrep/deaa098
25. Spanos C, Bretherton I, Zajac JD, Cheung AS. Effects of gender-affirming hormone therapy on insulin resistance and body composition in transgender individuals: a systematic review. *World J Diabetes.* 2020; 11(3):66–77. https://doi.org/10.4239/wjd.v11.i3.66
26. Poggio F, Del Mastro L, Bruzzone M, et al. Safety of systemic hormone replacement therapy in breast cancer survivors: a systematic review and meta-analysis. *Breast Cancer Res Treat*. 2022;191(2):269-275. https://doi.org/10.1007/s10549-021-06436-9
27. Vargiu V, Amar ID, Rosati A, et al. Hormone replacement therapy and cervical cancer: a systematic review of the literature. *Climacteric*. 2021;24(2):120-127. https://doi.org/10.1080/13697137.2020.1826426
28. Almeida CF, Oliveira A, Ramos MJ, Fernandes PA, Teixeira N, Amaral C. Estrogen receptor-positive (ER+) breast cancer treatment: Are multi-target compounds the next promising approach?.

Biochem Pharmacol. 2020;177(1):113989. https://doi.org/10.1016/j.bcp.2020.113989
29. Clusan L, Ferrière F, Flouriot G, Pakdel F. A basic review on estrogen receptor signaling pathways in breast cancer. *Int J Mol Sci.* 2023;24(7):6834. https://doi.org/10.3390/ijms24076834
30. Verhoog NJ, Spies LM. The anti-aromatase and anti-estrogenic activity of plant products in the treatment of estrogen receptor-positive breast cancer. *J Steroid Biochem Mol Biol.* 2024;243(1):106581. https://doi.org/10.1016/j.jsbmb.2024.106581
31. Chen X, Chu C, Doebis C, von Baehr V, Hocher B. Sex-Dependent association of vitamin D with insulin resistance in humans. *J Clin Endocrinol Metab.* 2021;106(9):e3739-e3747. https://doi.org/10.1210/clinem/dgab213
32. Kauffman RP, Young C, Castracane VD. Perils of prolonged ovarian suppression and hypoestrogenism in the treatment of breast cancer: Is the risk of treatment worse than the risk of recurrence?. *Mol Cellular Endocrinol.* 2021;525(1):111181. https://doi.org/10.1016/j.mce.2021.111181
33. 34: Traphagen NA, Hosford SR, Jiang A, et al. High estrogen receptor alpha activation confers resistance to estrogen deprivation and is required for therapeutic response to estrogen in breast cancer. *Oncogene.* 2021;40(19):3408-3421. https://doi.org/10.1038/s41388-021-01782-w

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