PREVENTION OF BREAST & ENDOMETRIAL CARCINOMA IN POSTMENOPAUSAL WOMEN THROUGH AYURVEDA

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Abstract

Cancer is a major health problem all over the world. The Postmenopausal period is vulnerable for women as she is subjected to a state of estrogen deficiency leading to various grave disorders like Osteoporosis, heart diseases, Alzheimer's disease and others. The treatment and prevention of these diseases through Hormone replacement therapy leads to major side effects like Venous thromboembolism, breast carcinoma and endometrial carcinoma. Other alternatives like SERMS have shown encouraging results in treatment of cancer but with major side effects. The incidence of breast cancer and endometrial cancer is rising in India.

The present paper deals with prevention of breast and endometrial carcinoma through phytoestrogens and scope of Ayurveda in managing postmenopausal disorders and preventing carcinoma.

Key words: Cancer, SERMS, Phytoestrogens.

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Full paper

PREVENTION OF BREAST & ENDOMETRIAL CARCINOMA IN POSTMENOPAUSAL WOMEN THROUGH AYURVEDA

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Postmenopausal period is vulnerable for women as the aftermath of ageing strikes women twice. Along with ageing she has to face the inevitable scars of menopause. Estrogen is the primary female sex hormone which maintains the reproductive functions and homeostasis by its important functions on cardiovascular system, bone metabolism, brain, skin and others. Hormonal changes proceed gradually in men but women encounter fast hormonal change. Menopause, the permanent loss of menstruation after amenorrhea lasting more than 1 yr due to the loss of estrogen production by the ovaries, is a major aging process of women and most women encounter this hormonal change between 40 and 55 yr of age.[1] Therefore, many women spend almost 1/3 of their lives in menopause.

After menopause, there are many effects of female sex hormones on other body functions. Changes that occur in pituitary, adrenal gland physiology, and thyroid function are subtle, but alterations in glucose homeostasis, reproductive function, and calcium metabolism are more apparent.[2,3] There are significant alterations in metabolism of skin and hair, body composition, and subcutaneous fat distribution throughout life.[4] Therefore, women have many diseases and disabilities requiring intervention and treatment after menopause.[5] Significant diseases in older women that are hormone-dependent include osteoporosis, Alzheimer's disease, urinary incontinence, and coronary atherosclerosis.

Hormone Replacement Therapy (HRT) was considered as standard therapy for treatment of menopausal syndrome and postmenopausal diseases. But recent data suggests that it has more risks than benefits. The HERS (Heart Estrogen/Progestin Replacement Study) data showed that long term HRT increases the risk of cardio vascular diseases. In addition to this, latest research data indicates an excess risk from HRT regarding the incidence of **breast and endometrial cancer** as well as increased incidence of stroke, coronary artery disease and other thrombotic diseases.[6] The risk of cardiovascular event rather increased in women treated with HRT for many years after menopause.[7]

Breast cancer

The incidence of breast cancer in India is on the rise and is rapidly becoming the number one cancer in females pushing the cervical cancer to the second spot. The seriousness of the situation is apparent after going through recent data from Indian Council of Medical Research (ICMR). One fourth (or even approaching one thirds) of all female cancer cases are breast cancers. Breast cancer is the leading cause of cancer death, and is a major health concern for menopausal women, Any therapies that reduce or increase the risk will have a major impact on woman's health. Risk factors for breast cancer like late menopause, early menarche and others are consistent with the hypothesis that prolonged estrogen exposure increases the risk of breast cancer. Long term Hormonal therapy is also associated with increased risk of breast cancer. It has now been conclusively proved that a breast-cancer patient not only requires operation but also has to be treated with the multimodality treatment, which includes chemotherapy, radiotherapy, hormone therapy and immunotherapy.

Other compounds used in management of postmenopausal conditions and cancer are SERM's. Selective Estrogen Receptor Modulators act by inhibiting the binding of estrogen to estrogen receptors. The SERM – estrogen receptor complex is a unique structure which in the presence of several co-regulatory proteins, exhibits estrogenic and anti estrogenic activities in different target organs. They act as anti estrogenic in breast and uterine tissue, but estrogenic in bone, brain and lipid metabolism.[8]

Tamoxifen and Raloxifen are SERM which are used in the treatment of breast cancer has shown to increase risk of venous thromboembolism. Hot flushes are increased with raloxifene and tamoxifen whereas raloxifene alone is associated with leg cramps. It is observed and concluded through various studies that Tamoxifen should not be used in patients with DVT, VTE and other thromboembolic diseases. [9,10]

Endometrial carcinoma

Endometrial carcinoma is the most common malignancy of female genital tract. Endometrial carcinoma is the fourth most common cancer, ranking behind breast, lung, and bowel cancers, and the eighth leading cause of death from malignancy in women. Overall about 2 to 3% of women develop endometrial cancer during their lifetime. It is a disease the most primarily occurs in postmenopausal women and is increasingly virulent with advancing age. The role of estrogen in

the development of endometrial cancers has clearly been established. Any factor that increases exposure to unopposed estrogen increases the risk of endometrial cancer.[11]

Estrogen therapy is an established risk factor for endometrial cancer. The risk for endometrial cancer is 4 to 8 times greater in postmenopausal women receiving unopposed estrogen therapy, and the risk increases with time and higher estrogen doses. Tamoxifen has been evaluated for treatment of endometrial carcinoma.

About one fourth of patients treated for early endometrial cancer develop recurrent disease. More than one half of the recurrences develop within 2 years and about three fourths occur within 3 years of initial treatment. Many women who have been successfully treated for endometrial cancer suffer side effects of estrogen deficiency such as vasomotor instability, vaginal dryness, dyspareunia as well as long term risk of osteoporosis. [11]

Increased incidence of postmenopausal diseases like osteoporosis, cardiovascular diseases and cancer along with their mortality rate and burden of their management and side effects have turned attention of all medical sciences to a safe, cheap and effective alternative. This has led to tremendous interest in ***Phytoestrogens.***

PHYTOESTROGENS

The word phytoestrogens comes from "phyto" which means plant and "estrogen" due to their ability to affect estrogenic activity in the body. Ample research data on Soy, which is rich in Isoflavone (one of the group of phytoestrogens) have attracted attention of health professionals as an alternative method of treatment. Phytoestrogens bind to estrogen receptors just as estrogen, but they have more affinity for estrogen receptor β found in brain, bone, bladder and vascular epithelia. In breast and endometrial tissue, phytoestrogens acts as anti estrogenic.

Phytoestrogens also stimulate the production of sex hormone–binding globulin (SHBG) by the liver. Higher SHBG levels result in more bound and thus less free estradiol, reducing the amount of estrogens available for binding with estrogen receptors [12,13]. Phytoestrogens also bind competitively to estrogen receptors, thereby blocking binding by estradiol and other estrogens [14-19]. Because of their weak estrogenic potential (0.1% that of estradiol), phytoestrogens do not elicit a strong estrogenic response and thus have an antiestrogenic effect that inhibits the growth and proliferation of estrogen- dependent cancer cells [20]. Isoflavones resemble estrogen structurally, are able to bind to the estrogen receptor (ER), and have ER-mediated estrogenic properties

(transcriptional activity). They also act as antiestrogens by competing with the more potent endogenous estrogen for the ERs. Additionally, phytoestrogens have antioxidative, antiproliferative, and antiangiogenic activities, which are hormonally independent. The plant lignans show hardly any binding affinity to ERs. However, in animal and in vitro studies, lignans were reported to have antioxidative activity and to reduce tumor progression and metastasis. [21,22]

Phytoestrogens found in many foods including soya, orange juice have shown to reduce the production of estrogen in the body.

PHYTOESTROGENS AND BREAST CANCER

Interest in phytoestrogens as a natural anti cancer agent has grown from various case control and epidemiological studies. High rates of cancer are observed in populations who consume a western diet that typically contains less than 5 mg of isoflavones daily. Lower cancer rates are seen in Asian populations with plant based diets rich in soy protein and phytoestrogens. [23-24]

Various animal studies have also been undertaken to study the effects of phytoestrogens on hormone dependent cancers; these studies have given an insight into the various possible mechanisms by which phytoestrogens may influence cancer.

Genistein inhibits the enzyme tyrosine kinase that is involved in the regulation of cell growth. [25] It also augments transforming growth factor B which inhibits the cell cycle and cell growth.. It influences transcription factors that are involved in programmed cell death. Isoflavones also have antioxidant activity, anti proliferative effects and anti angiogenic effects. [26, 27]

Phytoestrogens may exert a protective effect on breast cancer, which may be partly explained by reduction in endogenous sex steroid levels and reduction in luteal phase. The highest level of mammary cell proliferation occurs during the luteal phase of menstrual cycle, therefore prolongation of the follicular phase of the cycle would reduce the number of total cycles a woman would have in her lifetime and thereby reduce the risk of getting breast cancer. Further, epidemiological studies suggest that soy containing diet in adult women is protective with regard to breast cancer and it may be beneficial if consumed in early life before puberty or during adolescence. [26]

PHYTOESTROGENS AND ENDOMETRIAL CANCER

In a case control study it was found that high consumption of soy products and other legumes was associated with decreased risk of endometrial cancer.[28]. In Hawaii's multiethnic population, greater consumption of tofu alone or in combination with other soy products was associated with a 50%reduction in endometrial cancer risk.

In addition to lowering endogenous estrogen levels and binding competitively to estrogen receptors, phytoestrogens may also affect endometrial cancer risk through the inhibition of aromatase, the enzyme responsible for the conversion of androstenedione to estrone .

PHYTOESTROGENS IN AYURVEDA

Elaborated research studies conducted in the recent past has shown medicinal values of many herbs containing phytoestrogens and or possessing estrogenic activity. In a study of 64 plant species commonly found in India, many plants were pointed out showing estrogenic activity including Carrot and Asafoetida. The experimental study estrogenic activity of palasha seeds in rats was revealed.. Chemical analysis of fenugreek seeds identified steroidal estrogen like saponine trigoneosides, which have therapeutic potential in the treatment of diabetes, menopausal syndrome and hypercholestremia. [29]

In a case control study, it was found that 144 women who had recently diagnosed with breast cancer excreted less amount of phytoestrogens in urine when compared to equal number of women matched for age and area of residence. They concluded as diets high in plant estrogens may be protective against breast cancer. [30]

Ayurveda, the oldest system of medicine, has provided many herbs which can be used in prevention of geriatric problems in women. About 300 herbs containing phytoestrogens and possessing estrogenic property have been studied; following is the list of some identified herbs containing phytoestrogens.

Common phytoestrogenic food/herbs containing: Coumestrol

• Brassica spp. (Brussels Sprouts, Cabbage) • Pisum sativum (Pea)• Vigna radiata (Mungbean)

Common phytoestrogenic food/herbs containing: Biochanin A:

• Baptisia tinctoria (Wild Indigo) • Vigna radiata (Mungbean)

Common phytoestrogenic food/herbs containing: Daidzein:

• Phaseolus coccineus (Scarlet Runner Bean) • Pueraria spp. (Kudzu; Pueraria) • Vigna radiata

Common phytoestrogenic food/herbs containing: Formononetin:

• Pueraria spp. (Kudzu; Pueraria) • Vigna radiata (Mungbean)

Common phytoestrogenic food/herbs containing: Genistein:

• Baptisia tinctoria (Wild Indigo) • **Glycyrrhiza glabra (Licorice root)** • Pueraria spp. (Kudzu; Pueraria)

• Vigna radiata (Mungbean)

Common phytoestrogenic food/herbs containing: Beta-Sitosterol:

• Allium cepa (Onion) • **Allium sativum (Garlic)** • Aloe vera (Aloe) • Anethum graveolens (Dill)

• Angelica archangelica (Angelica) • Angelica sinensis (Dong Quai) • Artemisia annua (Sweet Annie)

• Artemisia dracunculus (Tarragon) • Artemisia vulgaris (Mugwort) • Asarum canadense (Wild Ginger)

• Asclepias syriaca (Milkweed) • Calendula officinalis (Marigold) • **Capsicum** annuum **(Chili Pepper)**

• Centella asiatica (Gotu Kola) • Commiphora myrrha (Myrrh) • Cucurbita pepo (Pumpkin)

• Daucus carota (Wild Carrot) • **Echinacea spp. (Echinacea)** • Elettaria cardamomum (Cardamom) • **Eleutherococcus senticosus (Siberian Ginseng)**) • Foeniculum vulgare (Fennel) • **Glycyrrhiza glabra (Licorice root)** • Gossypium spp. (Cotton) • Hordeum vulgare (Barley) • Inula helenium (Elecampane) • Liquidambar orientalis (Oriental Styrax)

• Mentha spicata (Spearmint) • Ocimum basilicum (Basil) • • Pisum sativum (Pea) • Plantago psyllium **(Psyllium seed)** • Punica granatum (Pomegranate) • Rosmarinus officinalis (Rosemary)

• Smilax spp. (Sarsaparilla) • Solanum dulcamara (Bitter Nightshade) • Taraxacum officinale (Dandelion) • Theobroma cacao (Cacao) • Tribulus terrestris (Puncture-vine) • Trigonella foenum-graecum (Fenugreek) • Urginea maritima (Squill) • **Valeriana officinalis (Valerian)** • Viburnum opulus (Crampbark) • Vinca minor (Periwinkle) • Vitis vinifera (Wine Grape)• Withania somnifera (Ashwagandha) • Zea mays (Corn silk) • **Zingiber officinale (Ginger)**

Common phytoestrogenic food/herbs containing: Diosgenin:

• Asparagus officinalis (Asparagus) • Balanites aegyptiaca (Desert Date)• Daucus carota (Wild Carrot) • Dioscorea bulbifera (Potato Yam)• Dioscorea villosa (Mexican Wild Yam) • Jateorhiza

palmata (Calumba Root)• Momordica charantia (Bitter Melon) • Smilax spp. (Sarasaparilla) • Solanum dulcamara (Bittersweet) • Solanum nigrum (Black Nightshade)• Tribulus terrestris (Puncture-vine) • Trigonella foenum-graecum (Fenugreek)

Out of these Shatavari- Asparagus racemosus contains active compounds Steroidal saponins, Shatavarin I – IV, Isoflavones including 8-methoxy-5,6,4'- trihydroxyisoflavone 7-O-beta-D-glucopyranoside which shows estrogenic activity. Shatavari is a well known female rejuvenative and is widely used by women for overall health and vitality, for conception and to promote lactation. Clinical Studies on Shatavari prove the efficacy of this drug in relieving menopausal symptoms. The specific effect of Shatavari on women in balancing homeostasis can be attributed to presence of phytoestrogens.

Pharmacological action of Shatavari shows Antioxidant, Immunomodulatory, Antimicrobial, Cardiotonic, Digestive, Antiallergic, Anti-oxytocic and Estrogenic properties.

Shatavari has also shown the reduction in bone loss and hence minimizing the risk of postmenopausal osteoporosis without any other effects. [32-35]

Of particular interest for cancer prevention is the role of turmeric (curcumin), an ingredient in common Indian curry spice. Researchers also have investigated cumin, chilies, kalakhar, Amrita Bindu, and various plant seeds for their apparent cancer preventive properties.[36]

The Singapore scientists learned that the best effect could be achieved by another source of phytoestrogens, from Vigna radiata -- mung bean. The bean extract compliments the formulation with mild alpha estrogen receptor activity, effectively suppressing hot flashes and mood swings, but doing so with out over stimulation of the alpha receptor which is linked to health risks such as DVT (deep venous thrombosis), breast cancer and more. [37-39]

Conclusion

The mortality rate of breast cancer in younger women has been reduced substantively because of early diagnosis and surgery. Although in the postmenopausal women because of other complications, and side effects of hormonal treatment, the management of breast and endometrial carcinoma becomes difficult and less effective. It must be pointed out that the heightened search for preventive measures against cancer is owing to the dismal failure of modern medicine in the treatment of most of the forms of cancer. Here the proverb ‘prevention is better than cure’ is

hardly applicable because the cure is not available. Hence the ultimate goal is the prevention of the very inception of cancer.

Cancer in Ayurveda literature is mentioned under '*Arbuda*'. Various stages along with malignancy, prognosis and management of *Arbuda* is available in classics. Breast cancer and Endometrial carcinoma is postmenopausal women has different pathogenesis. As the management of cancer in postmenopausal women is difficult, its preventive aspect will have more significance. There is no reference available in Ayurveda literature for preventing '*Arbud*a'. For achieving this aim, herbs containing phytoestrogens especially like Shatavari should be consumed by female throughout the life time. Such herbs will maintain the reproductive homeostasis and prevent her from postmenopausal and menopausal disorders by maintaining the hormone levels. Many epidemiological studies have shown that phytoestrogens found in soy are protective against breast and endometrial carcinoma. It will be worth to include in further studies, in line with the role of phytoestrogens available in herbs such as Shatavari, Yashtimadhu, Gokshur, Methi and others as preventive measure in different types of cancers.

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