Hormones and Cancer

The recent concepts of cause and effect **interplay**

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ENDOCRINE OUR LIFE LINE

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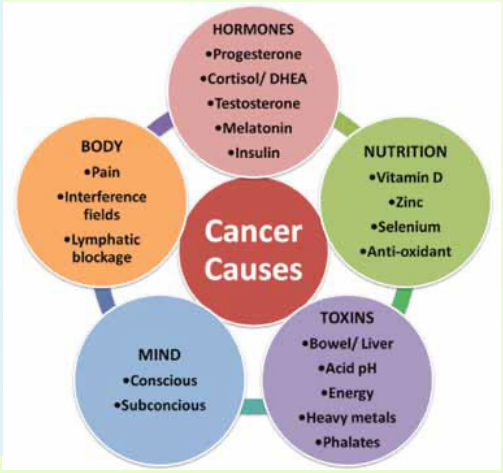


INTRODUCTION:

Endocrine oncology is a new concept with emerging multiple dimensions. Over the years, we have come to acknowledge that hormones do have a role in etiopathogenesis of some endocrine related cancers, may affect clinical course and prognosis of malignancy and may be used as endocrine therapy in management of some hormone dependent malignancies. The other side of the coin incorporates effect of various cancers on hormonal milieu of body, effect of cancer treatment on hormones and long term sequelae related to the hormonal derangements.

Role of Hormones in aetio-pathogenesis of cancer:

Excessive hormonal stimulation of proliferative cells increases the risk of their mutation and then multiplication of these mutant clones. Hormones are powerful and '' complete carcinogens'' as they are able to initiate and propagate cancer. These involve various types of cancers:

1) Endocrine related cancers: These are cancers which originate from endocrine organs as Thyroid, Pituitary, Hypothalamus, Adrenal Cortex, Pancreas, primary and secondary sex organs and Breast.
2) Hormone dependent cancers: These types of cancers show response to sex steroids and are cancer breast and cancer endometrium in females and prostate and testicular cancer in males.
3) Hormone responsive or endocrine sensitive cancers: This group involves cancers which show response to pituitary hormones e.g., ovarian and thyroid cancers.

Understanding of hormones as one of the causative factors of malignancy is important as it helps us in developing treatment for various sex-steroid dependent tumors, in form of anti-estrogenic or anti-androgenic treatment.[1] Various life-time variables which affect the exposure of human body to available sex-steroids thereby gain relevance. These include age of menarche and menopause, age at first pregnancy and parity, duration of breast feeding and presence of obesity. Exposure to endocrine disruptors, exogenous hormonal therapy and menopausal hormonal therapy may be other related contributing factors. Another emerging concept is chemoprevention of cancers which are endocrine related e.g. use of Tamoxifen in patients predisposed to Breast cancer. The role of genetic predisposition and epigenetics in causation of hormone related cancers due to 'germ-line polymorphisms' are being addressed.

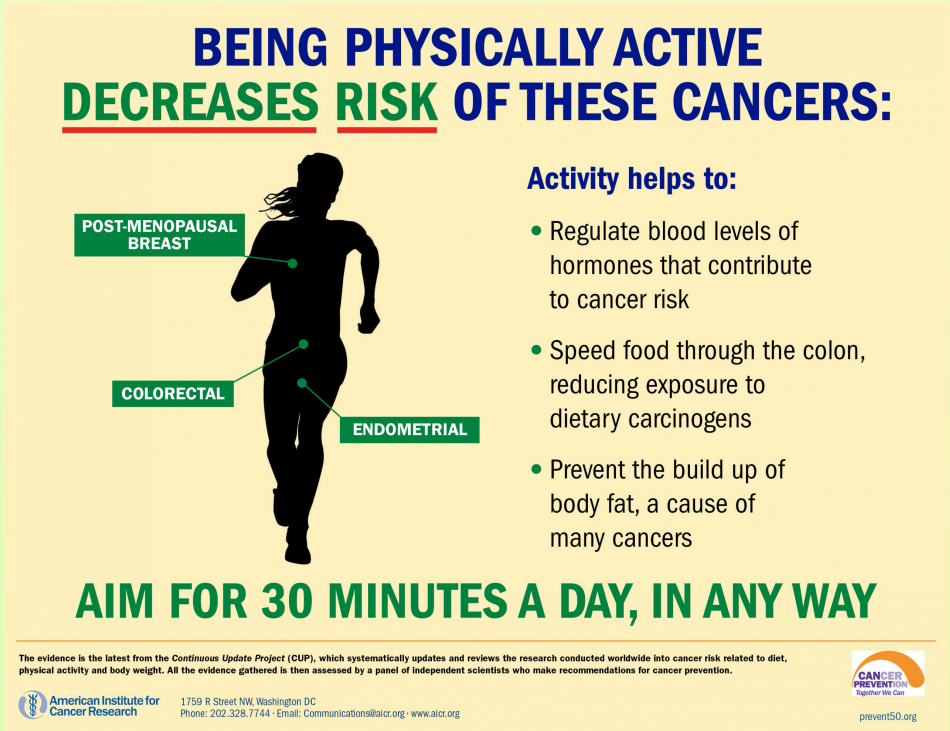
At molecular level, up-regulation of Membrane-initiated steroid signaling (MISS) due to cellular stimulation by estrogens or androgens has been shown in cancer cells, the description of which is beyond the scope. G-protein coupled receptor family (GPER) is also known to expedite transcriptional events in cancer cells when stimulated by estrogen. GPER expression happens both in ER positive and ER negative Breast cancer cells, Endometrial carcinoma, Ovarian malignancy and Thyroid cancer. GPER

expression leads to malignancy and is a basis of anti-estrogen treatment. Tamoxifen which is a partial ER antagonist and act as a GPER agonist.

Role of Metabolic Hormones in cancer causation:

Diabetes and obesity are important cause of increased risk of cancer and are major preventable and modifiable factor. Main determinants of diabetics increasing cancer risk are Insulin resistance and hyperinsulinemia. This also contributes to poor prognosis in cancer. Epigenetic's plays a role and life style modifications by diet and exercise can modulate the genetic predisposition to insulin resistance. Drugs which cause weight gain and insulin resistance e.g. Tri-cylic antidepressants, anti-epileptics, Cisplatin based chemo-therapy ,may worsen its effect in cancer patients. Aromatase inhibitors and anti-androgens also contribute to insulin resistance. Development of insulin resistance may interfere with effectiveness of cancer treatment.

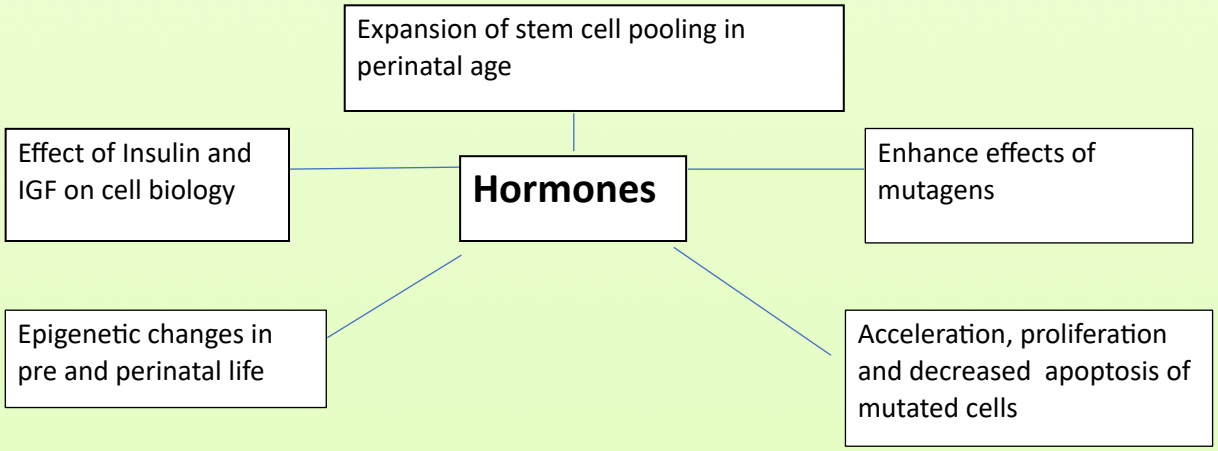
Other metabolic hormones which are associated with obesity are ‘increased leptin levels’ and ‘reduced adiponectin levels’. Leptin may induce carcinogenesis directly or by enhanced Aromatase expression and more estrogen production. Reduced Adiponectin levels increase cancer risk. ‘Vitamin D deficiency’ is known to worsen insulin resistance and increase aromatase activity.



Thyroid hormone implications in oncogenesis:

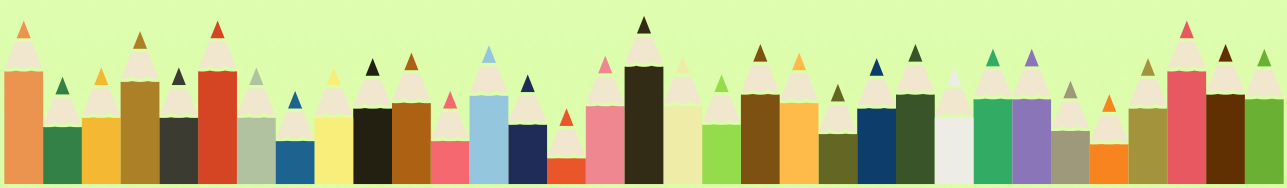
TSH is known to cause metastasis in differentiated Thyroid cancer. This is the basis of TSH suppressive therapy with Levo-Thyroxine in post-operative patients of differentiated thyroid cancer. Iodine deficiency leading to endemic goiter makes an individual more responsive to mitogenic effects of TSH. TSH receptor stimulating antibodies (TSHR-Abs) in Graves' disease are known to increase thyroid cancer risk and aggressiveness of cancer. Thyroid follicular cancer cells have ER -alpha, ER -beta and non-classical GPER Estrogen receptors , making females more prone to thyroid cancers. Over expression of IR and IGF-IR by thyroid cells increases the cancer risk in obesity and insulin resistance.

Various ways of Endocrinal Carcinogenesis



Hormones in pathogenesis of Gynae cancers:

Estrogens are known human carcinogens. Historically Di-ethyl-stilbestrol (DES) given to pregnant mothers in USA between 1940 and 1971 to prevent miscarriage and premature labor had increased risk of breast cancer, their daughters had increased risk of Clear-cell Adenocarcinoma of vagina, cervix and Breast cancer especially after 40 years and even grand-daughters were found to be at risk.[2] DES is now considered an 'Endocrine-disrupting chemical' which interferes with endocrine system causing cancer ,besides being a cause of birth defects and developmental abnormalities and is the basis of 'Hormonal transplacental carcinogenesis' studies. Other endocrine disruptors e.g, Bisphenol-A used in plastic may also be carcinogenic.



Relationship between Oral contraceptive use and cancer:

Breast cancer: A large prospective Danish study in 2017 reported a modest (about 20%) increase in the relative risk of breast cancer in women who were using or had recently stopped using OCPs , in comparison to women who had never used OCPs. The diagnosis maybe related to increased surveillance of these patients. The risk varied according to various types of OCPs used and increased with longer use.

Cervical cancer: OCPs used for 5 years or more, increase cervical cancer risk than in non-users which is proportional to duration of use. The risk declines over the time after usage is stopped. This increase of cervical cancer risk maybe due to increased susceptibility of cervical cells following OCP use, to persistent high risk HPV infection which leads to cervical cancer.

Endometrial cancer: OCPs have protective effect in users, reducing the risk by 30% proportionate to duration of use. The risk reduction was more obvious in obese, sedentary women and smokers. The protective effect persists for many years after stoppage of OCPs.

Ovarian cancer: OCPs users have 30% to 50% lower risk than non-users and protection is proportional to duration of use and effects of risk reduction continues up to 30 years of stoppage. Some protective effects of OCPs use has been observed in carriers of BRCA 1 and BRCA 2 gene mutation. The protective effect is due to suppression of ovulation like protection rendered by parity and lactation.

Colorectal cancer: 20% lower risk of development of colo-rectal cancers is observed in OCPs users. This is related to bile acid metabolism and presence of estrogen receptors in colon epithelial cells which inhibit cell proliferation. OCPs also reduce risk of development of adenomatous polyp - a premalignant lesion.[3]

Fertility treatment with hormones and risk of cancers:

Infertility itself is related to increased risk of Breast, Ovarian and Endometrial cancers. Assisted reproductive technologies involve use of multiple hormones for down-regulation, then ‘Controlled Ovarian Hyperstimulation’, ovulation trigger and then progesterone support in luteal phase and early pregnancy. This had raised concerns regarding cancers linked to super-physiological levels of these hormones.[4] However, no increased risk of Breast cancer, Ovarian cancer or Endometrial cancer was found in women treated with fertility drugs.

Menopausal Hormonal Therapy and Cancer:

MHT/HRT usually involves treatment with Estrogen alone or Estrogen with Progestins, which may be synthetic. Some ‘bio-identical hormones’ are being sold through internet

which are not FDA approved. The concerns of MHT use in various cancers are as follows.

Ovarian cancer:

HRT to be given with caution as they may have Estrogen and Progesterone receptors.

Breast cancer-Recent studies have concluded that, women who took Estrogen plus Progestins were more likely to be diagnosed with breast cancer in comparison to placebo. The breast cancers in these women were larger and much more spread to lymph nodes was found at the time of diagnosis. The risk increased with duration of use but fell remarkably after stopping MHT. Tibolone and Raloxifene are good alternatives as MHT in them. It was also noted that use of MHT made mammography less effective for early detection of breast cancer and required more biopsies due to increased density of breast tissue.[5] Higher breast cancer mortality rates were observed in women who took Estrogen and Progesterone than Estrogen alone in comparison to placebo. Breast cancer detected within 5 years of HRT are amenable to treatment as they are usually ER and PR positive.

Endometrial cancer- Risk of recurrence is there with MHT. Low grade malignancy may be given HRT in required cases if disease free interval is more than 2 years.

Lung cancer – The risk was comparable with non-users but some increased mortality was seen in patients diagnosed with lung cancer who took Estrogen and Progestins as HRT.

Colorectal cancers- No strong evidence of increased risk was found with Estrogen alone or Estrogen and Progestin combination for the risk of developing colorectal cancer, tumor stage at diagnosis or death.

Findings from WHI observation study concluded that among women with an intact uterus, similar risk of invasive breast cancer, colorectal cancer and endometrial cancer was found in patients using vaginal estrogen versus non-users.

FDA currently advises women to use MHT for shortest time and lowest dose possible to control the menopausal symptoms or alternative medications are advised depending on main menopausal symptoms.

Hormones in management of cancers:

Hormone therapy or Endocrine therapy involves treating cancer with hormones. It envisages treatment that block or alter hormones to prevent proliferation of hormone sensitive cancers. The ‘systemic’ hormone therapy works by 1) preventing synthesis of hormones 2) blocks or prevents attachment of hormone to cancer cell. 3) alters the hormone to render it ineffective. Hormonal treatment has a role in recurrent or

metastatic gynae cancers including Ovarian cancer, Endometrial carcinoma and Granulosa cell tumor.[6]

Types of hormonal therapy used in various cancers may be having different response depending on tumor type, disease grade, stage and type of drug used. Patients with granulosa cell tumors and endometrial stromal sarcomas have good response. Patients who are hormone receptor positive and are having well-differentiated cancers show better response. Some examples of hormonal treatment of cancers are given below:

a) Breast cancer- Aromatase inhibitors, SERMs, Estrogen receptor antagonists (Fulvestrant, Toremifene), LHRH agonists or oophorectomy.

b) Endometrial cancer- Progestins (MPA, Megestrol Acetate, LNG IUD), SERMS, LHRH agonists, Aromatase inhibitors (Letrozole, Anastrozole, Exemestane)

c) Prostate cancers- Anti-androgens, CYP 17 inhibitors, LHRH agonists and antagonists, orchidectomy

d) Adrenal cancer- Adrenolytic, Estrogen receptor antagonists, SERMs

Side effects of hormonal treatment-

In females- hot flushes, vaginal dryness/irritation, decreased libido, fatigue, nausea, myalgia, arthralgia, osteoporosis, fracture risk, secondary cancers, stroke, thrombo-embolism, cataract, and CVS complications.

In males- erectile dysfunction and systemic side effects as in females.

Long term sequelae and endocrine disorders following cancer treatment:

Therapy related late effects of cancer treatment are recognized and endocrine disorders are the most common of these long-term effects , which may present decades after treatment. Children cancer survivors develop endocrinal problems depending on age and sex.[7]

Radiotherapy effects endocrine organs like Thyroid and Pituitary gland by damaging DNA and cells especially total body irradiation.

Chemotherapy leads to oxidative stress and tissue damage along with vascular toxicity may cause secondary malignancies in Thyroid and other endocrine disorders. Alkylating agents cause most damage.

Surgery and immunotherapy may also contribute to these sequelae.

These patients thereby need ‘structured lifelong surveillance’ as there is now paradigm shift from ‘surviving cancers’ to ‘living with and beyond cancers’.

The cancer survivors may present to ‘onco-endocrinology multi-disciplinary team’ with following problems:

1) Growth hormone deficiency- somatotrophic axis is vulnerable to radiotherapy and its consequences.
2) Functional alterations in Hypothalamo-pituitary axis
3) Abnormal thyroid function tests
4) Abnormal Parathyroid function
5) Hyperprolactinemia
6) Risk reduction of Adrenal insufficiency and dose weaning of glucocorticoids may be required. The cortisol needs to be started before thyroxine to avoid Adrenal crisis in hypo-pituitarism.
7) Adrenal/Pituitary/Thyroid nodules
8) Biochemical derangements e.g., hypercalcemia, hypocalcemia, hyper-phosphatemia or hypo-phosphatemia
9) Menstrual abnormalities- delayed or early puberty, primary or secondary amenorrhea, premature ovarian insufficiency, short reproductive phase, infertility, early menopause or sometimes ‘acute ovarian failure’ following Procarbazine and Cyclophosphamide use.
10) High risk pregnancy- increased abortions, preterm labor, low birth weight babies and neonatal death
11) In males they may present with delayed puberty, hypogonadism, impotence, infertility and decreased testosterone levels
12) Bone metabolism complications – low bone mineral density, halting of bone accrual and absence or delay of attainment of peak bone mass, bone pain, increased fracture risk
13) cognitive and psychosocial issues
14) metabolic syndrome
14) hypothalamic obesity
15) deprivation symptoms- hot flushes etc.

A structured screening and regular 6 to 12 monthly follow up and surveillance by a multi-disciplinary team is required along with requisite infrastructure development to provide continuum of care. Pediatric cancer survivors may need HRT for bone health.[8] Before starting cancer treatment of young girls and boys they need age appropriate counselling or their parents need to take a decision about 'onco-fertility concerns' and 'fertility preservation'.

Recent advances and future challenges:

Initially hormone sensitive tumors responding to endocrine therapy may later transform into 'hormone-independent phenotype' leading to resistance. These refractory tumors evolve into aggressive cancers posing a clinical challenge. This endocrine therapy resistance is due to de-novo mutations in hormone receptor ESR genes, differential activation of signaling pathways, alteration in cell cycle regulators and enhanced autophagy.

1) Development of radiation oncology e.g., 3 dimensional conformal radiotherapy (3DCRT) and Intensity modulated radiotherapy (IMRT) for head and neck cancer
2) Identification of dose volume constraints of organs like thyroid
3) Omics analysis e.g., metabolomic, proteomic and transcriptomics may be the future strategy to identify cancer risk and cancer resistance to therapy
4) Genetic testing to identify patients at risk for treatment related complications, so that their therapy protocol may be changed, follow up intensified and necessary recommendations made for life-style changes like smoking cessation and weight management.

CONCLUSION

Hormonal carcinogenesis of endocrine related cancers is a widely accepted concept. Most cancers are hormone sensitive at some stage of their development or progression. Endocrine therapy is important in hormone sensitive cancer management. Long term structured surveillance is required for survivors of cancers for early detection and timely treatment of resultant endocrinopathies

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