
Controversial Issues in Climacteric Medicine II: Hormone Replacement Therapy and Cancer

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Hormone replacement therapy (HRT) offers well-established clinical benefits for the relief of menopausal symptoms, improving quality of life, and may reduce the likelihood of osteoporosis and cardiovascular disease. However, some physicians are still hesitant in prescribing HRT, fearful that this hormone treatment may increase the risk of developing certain malignancies, and, in particular, breast and gynecologic cancers. The understanding of the biological events involved in carcinogenesis is essential to investigate the mechanisms by which sex steroid hormones may influence the risk of developing a malignancy. Estrogens may be involved in tumor development and progression by enhancing mitosis, inducing the expression of estrogen receptors (ER) as well as progesterone receptors (PgR), and promoting vascularization. However, estrogens do not cause DNA mutations directly, but stimulate cell proliferation and thus increase the likelihood that a DNA replication error will escape repair.

Carcinogenesis

This section refers to the main biological mechanisms of carcinogenesis and underlines the possible role of sex steroid hor-

mones in this process. The human body contains a large number of regulatory molecules that are involved in the control of proliferation and differentiation processes. The control of normal cell proliferation is mediated by the interaction of activatory and inhibitory proteins. Oncogene-encoded proteins, including growth factors, growth factor receptors, G proteins, cytoplasm kinases, and DNA-binding proteins, regulate the cascade of events that maintain the ordered progression through the cell cycle, whereas tumor suppressor gene-encoded proteins are involved either in the control of genetic stability or in the negative regulation of cell growth. The most widely investigated tumor suppressor gene is p53 that encodes a DNA-binding phosphoprotein, which acts as a guardian of the genome integrity. After DNA damage, the increased levels of the protein may trigger a complex series of reactions leading to the arrest of the cell growth in the G1 phase or, alternatively, to the programmed cell death termed apoptosis. Activation of different oncogenes and inactivation of several tumor suppressor genes are required for the development of a complete neoplastic phenotype. Deranged oncogene activation can be triggered by several events, including deletions in coding sequence, point mutations, gene amplifications, and chromosome rearrangements, which result either in poorly regulated or overexpressed proteins. Tumor suppressor gene can be inactivated by gene deletions, point mutations or gene losses. Mutations of some oncogenes or tumor suppressor genes in germ cells can be responsible for inherited cancers. The lifespan of a cell is under the control of the progressive shortening of DNA sequences located at the ends of the chromosomes, called telomeres. During cell life a progressive shortening of telomeres occurs. This process leads to chromosome instability and eventually cell death or growth arrest. Immortalized cancer cells are characterized by the lack of progressive telomere loss, which is mainly due to activation of telomerase, an enzyme that elongates telomeres. Ectopic

expression of human telomerase reverse transcriptase (hTERT), encoding for the telomerase catalytic subunit, has been found to arrest telomere shortening and to immortalize human cells, whereas hTERT inhibition can cause tumor regression in xenograft models. The modulation of telomerase activity could therefore be a target for future molecular therapeutic interventions. In breast and endometrial cancer cell lines, progesterone has been shown to significantly induce the hTERT mRNA expression after a short exposure, and to inhibit the estrogen-induced activation of hTERT expression following a long-term exposure. The biological significance of these observations remains to be elucidated. Growth factors bind to specific cell membrane, tyrosine-kinase receptors. The intracellular pathways recruited by growth factor receptor activation lead to enhanced nuclear transcription of target genes, thus enhancing cell proliferation. Excessive amounts of growth factors and their receptors may influence the biological behavior of cancer cells and could explain the organ-specific metastatic process of different malignancies. Tyrosine-kinase receptors for growth factors provide novel targets for therapeutic intervention. Monoclonal antibodies against epidermal growth factor receptor (EGF-R) and small molecular weight tyrosine-kinase inhibitors are currently under evaluation as new pharmacological tools able to block cancer cell proliferation.

Matrix metalloproteases (MMPs) are a family of endopeptidases able to degrade components of the extracellular matrix. MMPs are regulated at the transcriptional level by a variety of growth factors, cytokines, and adhesion molecules, as well as at the post-transcriptional level, since all the soluble MMPs are secreted as inactive zymogens requiring activation by cleavage of the N-terminal domain. The proteolytic activity of MMPs is also specifically inhibited by the tissue inhibitors of metalloproteases (TIMP) produced by several cell types (fibroblasts, keratinocytes, endothelial

cells, and osteoblasts). Tumors have been shown to overexpress MMPs, which seem to be involved in tumor invasion and metastasization, and, more recently, also in early tumorigenesis. MMPs appear to contribute to the initiation of tumor growth, both at primary and secondary sites, by regulating access to growth factors from the extracellular matrix surrounding the tumor and by enhancing neoangiogenesis. Although there is little evidence that MMP genes contain hormone-responsive elements, estrogens and progesterone have been shown to regulate MMP expression in several experimental systems.

The growth of solid malignancies requires the development of a new vascular bed from the pre-existing host vasculature. Substantial experimental and clinical evidence links tumor progression and metastatic potential with neoangiogenesis. Angiogenesis is modulated by several growth factors, produced by either tumor cells or host cells, such as basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF). Tumor vascularization is highly disorganized, with dilated, tortuous, fenestrated vessels, and with excessive branching and uneven diameters, which could be due to the imbalance of angiogenic factors. Estrogens stimulate the expression of different VEGF subtypes, and progestins suppress this expression in endometrial cancer cells.

Breast Cancer

The age-standardized incidence rate of breast cancer world-wide is 35.6 per 100,000 females, but rates vary substantially across countries and even among racial-ethnic groups within a country. A large amount of experimental and epidemiological data supports a correlation between ovarian sex steroid hormones and mammary carcinogenesis. The age-related increase in breast cancer incidence decreases substantially after menopause. There is a clear association between the serum levels of estrogen and progesterone and breast cell proliferation in normally

menstruating women. Serum levels of these hormones are higher in women at elevated risk of breast cancer (i.e., native U.S. white women) than in those at low risk of this malignancy (i.e., native Japanese women). Besides familial history and alcohol consumption, some of the strongest risk factors for breast cancer are linked

to sex steroid exposure, including early age at menarche, delayed menopause, nulliparity, late age at first term pregnancy, and high body weight after menopause. The high risk in the latter group is likely due to estrogen production by adipose tissue aromatization of androgens. The ER is expressed in approximately

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60% of breast cancers, and the ER+ phenotype correlates with improved survival. ER status is both prognostic for survival and predictive for sensitivity to endocrine treatment. The current standard of care in adjuvant hormonal therapy for women with ER+ breast cancer includes the selective estrogen receptor modulator (SERM) tamoxifen, which improves 10-year disease-free survival by 27% in node-positive disease and by 42% in node-negative disease, and improves 10-year overall survival by 22% regardless of nodal status. However, tamoxifen displays some estrogenic activity on endometrial cell proliferation and the coagulation system. Treating 1000 patients with adjuvant tamoxifen for 5 years prevents 80 deaths from breast cancer, at the expense of two excess deaths from endometrial cancer and one excess death from pulmonary embolism. Ovarian ablation (bilateral ovariectomy or gonadotropin-releasing hormone [GnRH] analogues) remains experimental as an adjuvant therapy but should be strongly considered for premenopausal women with high-risk ER+ tumors who continue to menstruate following chemotherapy.

Ovarian ablation, tamoxifen, aromatase inhibitors and progestins have been widely employed in the management of metastatic breast cancer. Hormonal therapy, and particularly new aromatase inhibitors, can be considered as the treatment of choice for patients with metastatic ER+ breast cancer, with the exception of those with rapidly progressive or life-threatening visceral disease for whom chemotherapy is usually indicated, or with HER-2/+ disease, for whom the standard of care includes trastuzumab.

Estrogen concentrations in breast tissue are higher than in plasma, due to local production via different enzymatic pathways. The principal enzymes involved in this local production are sulfatases and aromatases; the former group represents the main group of enzymes expressed in breast tissue. The aromatase inhibitors act in part by inhibiting intratumoral estrogen synthesis. The control and regulation of tissue estrogen production could

have a role in therapeutic strategies for breast cancer. Sulfatase activity in breast tissue is reduced by antiestrogens, certain progestins and tibolone, a synthetic molecule with mixed estrogenic and progestogenic/androgenic activity, although the clinical significance of this is unclear.

In vitro studies indicate that insulin-like growth factor (IGF)-1 is a potent mitogen for many breast cancer cell lines, particularly for those that are estrogen responsive. Estrogens and IGF-1 have mutual favoring actions on breast cancer cell proliferation. Breast cancer cells secrete a variety of binding proteins for IGF (IGF-BPs), which can modulate the bioavailability of IGFs by competing with the IGF receptor (IGF-R). Estrogens can increase the number of IGF-Rs in mammary tissue, and decrease the expression of IGF-BP. Moreover, IGF-1 is necessary for maximal ER activation. High levels of IGF-1 in premenopausal (estrogenized) women represent a recognized risk factor for breast cancer. HRT can modulate the IGF system, depending on the type and route of administration (oral, transdermal and intranasal). However, the clinical relevance of these observations is currently unclear.

Progesterone seems to exert several antiestrogenic effects. In fact, it can downregulate ER, increase the expression of both 17 β -hydroxysteroid dehydrogenase (HSD) (the enzyme that converts estradiol to the biologically weaker estrogen, estrone), and sulfotransferase (the enzyme which converts estrone into estrone sulfate) and, finally, induces breast cell apoptosis.

Women with mutations in the breast cancer susceptibility genes, BRCA1 and BRCA2, have an increased risk of developing breast cancer. Both BRCA1 and BRCA2 are tumor suppressor genes: The wild-type alleles of these genes are lost in tumors from heterozygous carriers. These genes have been implicated in DNA repair and regulation of centrosome number. The loss of BRCA1 has thus been associated with high mitotic grade, lack of ER and PgR expression, and chromo-

somal instability. Hereditary tumors, which represent 5–10% of all breast cancers, are characterized by a strong family history of breast and/or ovarian cancer, onset at early age, multifocality, bilateral localization, and a lower expression of ER and PgR.

The presence of a BRCA1 or BRCA2 mutation is associated with a breast cancer risk of 40% and 20%, at the age of 40 years, respectively, and 60–70% and 80% at the age of 80 years, respectively. The clinical utility of BRCA gene mutation identification in an individual woman is currently under evaluation, and in particular the value in BRCA mutation carriers of a surgical or medical primary prevention of breast cancer is still widely debated. Risks and benefits of HRT use in BRCA mutation carriers are also still widely debated, and further studies are needed to address this issue.

Strategies for preventing breast cancer through hormonal intervention have been proposed. In particular, tamoxifen has been widely investigated in the chemoprevention of this malignancy in high-risk patients. A large American prevention trial on more than 13,000 high-risk women (National Surgical Breast and Bowel Project, NSABP P1) has shown a remarkable 50% reduction in the risk of both invasive and non-invasive breast cancer and a 69% reduction of the occurrence of ER+ tumors in tamoxifen-treated women. Importantly, this trial has shown that tamoxifen can induce endometrial hyperstimulation and an excess of thromboembolic events predominantly in postmenopausal subjects, while no significant difference has been noted in premenopause. Two smaller ongoing European studies (one in the UK and one in Italy) have not shown similar results so far. However, the more recent data from the Italian study after 8 years of follow-up show a late benefit from tamoxifen as compared to placebo and especially confirm this benefit when tamoxifen is combined with the use of HRT (data in press). Moreover, the recent data on the preventive use of low doses of tamoxifen, show-

ing the same efficacy of 5 mg/day or even less on a large number of biomarkers, encourage the study of the combination of HRT and low-dose tamoxifen for the prevention of breast cancer. In fact, a large International phase III trial in HRT users called the HOT Study (HOrmone replacement therapy and Tamoxifen Study) is to begin. However, it can induce an excess of thromboembolic events, diabetes and influenza-like symptoms. Conversely, the new SERM raloxifene does not appear to induce any endometrial stimulation. In a trial designed to evaluate osteoporotic fracture rates, raloxifene was associated with a 76% reduction in the incidence of breast tumors, and with a 90% reduction in the incidence of ER+ breast cancers. As expected, no effect was shown on ER- tumors. This encouraging trend towards breast cancer prevention with raloxifene has to be confirmed by a specifically designed study, currently ongoing.

In fertile women, the mammographic density is closely correlated with the cycle phases and the peripheral levels of endogenous ovarian steroids, being higher during the luteal phase. Similarly, HRT may exert a comparable effect on breast tissue, resulting in an increase in mammographic density in comparison to that in untreated postmenopausal women. Progestogens induce a higher mammographic density in estrogen-treated women, especially when given in continuous combined regimens. However, there exist no data that pharmacologically induced changes in breast density can be correlated to an elevated breast cancer risk.

The link between sex steroid administration and increased breast cancer risk is biologically plausible, but there is at most only a modest association between ERT use and breast cancer risk. The experimental data are conflicting, and the magnitude of the increased risk is not constant for all the studies and nevertheless appears small, so the clinical relevance is uncertain. Today, evidence is insufficient to determine whether different preparations, routes of delivery, doses, or differ-

ent progestins have a more favorable or adverse effect on breast. Breast cancer risk increases from the basal individual risk by 2.3% for each year of ERT use. Similar risk applies for delayed menopause, which is estimated to increase risk by 2.8% per year. In North America and Europe, the cumulative incidence of breast cancer between the ages of 50 and 70 years in never-users of HRT is about 45 per 1000 women. The cumulative excess numbers of breast cancers diagnosed between these ages per 1000 women who began use of HRT at age 50 and used it for 5, 10, and 15 years, respectively, are estimated to be 2 (95% CI 1–3), 6 (95% CI 3–9), and 12 (95% CI 5–20). The increase in breast cancer risk seems to be almost entirely limited to lean women. Overweight postmenopausal women already have achieved the maximum hormone-related risk due to their endogenous production of estrogens.

The breast cancers diagnosed during HRT use are more likely to contain ER and are less aggressive. Most reports indicate no increase in breast cancer mortality in HRT users. Any increased risk associated with HRT is reduced after HRT is discontinued.

Particular importance may be attributed to the specific composition of HRT. There is recent evidence that combined estrogen–progestin therapy is associated with higher breast cancer incidence rates than estrogen alone. In addition, the use of sequential or continuous combined estrogen–progestin may also have different effects, but this notion remains controversial.

Following the diagnosis and treatment of breast cancer, women enter a menopausal state often suffering from severe, sometimes debilitating symptoms of hormone deficiency, which adversely affects their quality of life. On occasion, these symptoms are refractory to non-hormonal therapies. For this reason, a small number of women who have experienced breast cancer could elect to take HRT. There are observational studies reporting that HRT use after breast cancer does not

seem to have an adverse impact on recurrence or mortality. However, for the time being, estrogen replacement therapy (ERT)/HRT is generally considered to be contraindicated in breast cancer patients, as no firm safety data are yet available from randomized clinical trials. Despite the potential risks, ERT/HRT could be considered but limited only to patients suffering from menopausal symptoms resistant to alternative treatments, after completely informed consent is given, particularly in women with ER-negative cancers. Specifically designed studies are currently ongoing.

Endometrial Cancer

The age-standardized incidence rate of endometrial cancer worldwide is 6.4 per 100,000 females. Two major types of endometrial cancer have been classically identified. Both types of endometrial cancers are characterized by different genetic alterations, type I being more frequently associated with microsatellite instability, PTEN, K-ras or β -catenin mutations, whereas amplification or over-expression of erbB-2, mutation of p53 and loss of heterozygosity at chromosome 14 are features of some type II cancers.

Type I endometrioid adenocarcinoma, representing about 80% of all endometrial malignancies, occurs mostly in perimenopausal and early postmenopausal women. It is related to estrogen exposure and is frequently associated with endometrial hyperplasia. In most cases, it presents as a low histological grade lesion, with minimal myometrial invasion at the time of diagnosis, and generally has a good prognosis. Type I adenocarcinoma is associated with several risk factors, such as unopposed exogenous estrogen exposure, polycystic ovary disease, obesity, and nulliparity.

Type II non-endometrioid endometrial cancers (serous or clear cell carcinomas) more often develop after menopause. They are not evidently correlated with estrogens or endometrial hyperplasia, and tend to be more aggressive than type I adenocarcinoma, being character-

ized by high histological grade and deep myometrial invasion at the time of diagnosis.

The two types of endometrial cancers are characterized by different genetic alterations: type I cancers are more frequently associated with microsatellite instability, PTEN, K-ras, or β -catenin mutations, whereas type II carcinomas are more often positive for p53 mutations or with loss of heterozygosity. Estrogens and progesterone are the primary endocrine regulators of endometrial growth and function. In addition, there exists a great number of locally produced growth factors, such as IGFs, which are also at least in part controlled by ovarian sex steroid hormones, either enhancing or inhibiting endometrial cell growth. IGF-R is expressed both in epithelial as well as in stromal endometrial cells. IGF-1 synthesis in stromal cells is stimulated by estrogens, and is more abundant in the proliferative and early secretory endometrium. IGF-2 is synthesized in stromal cells, with amounts increasing during the middle and late secretory phase. IGF-BP-1 is the major IGF-BP in the endometrium, expressed in late secretory to decidual endometrium only. IGF-BP-1 synthesis is induced by progesterone, glucocorticoids and hypoxia, and reduced by insulin.

Endometrial adenocarcinomas express IGF-R, but are usually lacking IGF-BP-1. All the clinical conditions known to be associated with increased risk for endometrial cancer (anovulatory cycles, unopposed estrogen exposure or insulin resistance) are also characterized by low levels or absence of IGF-BP-1. These data suggest that enhanced or unopposed IGF-1 action may have a role in the development of endometrial cancer.

Hormonal agents (progestins, combined oral contraceptives) may be useful tools for chemoprevention in women at high risk of endometrial cancer. Conversely, adjuvant progestin therapy offers no clinical benefit to patients with early-stage endometrial cancer. Among patients with advanced or recurrent disease,

progestins achieve an objective response in approximately 15–20% of cases, whereas chemotherapy regimens obtain response rates ranging from 35% to 60%. However, both hormonal therapy and chemotherapy provide an unsatisfactory survival benefit, less than 12 months. Treatment with progestins is a rational therapeutic approach for patients with a long disease-free interval, well-differentiated tumors or positive steroid receptor status. Chemotherapy should be reserved for patients with rapidly progressive disease, poorly differentiated tumor, or unfavorable histologic type. Progestins combined with chemotherapy offer no clear survival advantage with respect to chemotherapy alone. New therapeutic tools are under evaluation (wild-type p53 gene, transfected by viral vectors, monoclonal antibodies against growth factor receptors, and small molecule tyrosine kinase inhibitors).

Unopposed estrogen administration (ERT) is associated with an increased risk of endometrial cancer. The risk is proportional to the duration of therapy, but is not clearly correlated with the dose. Endometrial cancer risk is elevated when using either interrupted or continuous estrogen administration. Risk decreases after cessation of ERT in a time-dependent manner, but risk is still elevated after more than 10 years. The excess risk in morbidity is not associated with a comparable risk in mortality. Current estrogen use increases the relative risk by 1.0 each year of use. After 10 years of ERT the risk is elevated about 10-fold compared to a lifetime non-user.

Adding a progestogen to ERT is therefore mandatory to avoid endometrial hyperstimulation in women with an intact uterus. The addition of an adequate dose of a progestin for an adequate time significantly reduces the incidence of endometrial cancer associated with ERT. With sequential progestogen administration, the duration of progestogen use is at least as important as the dose, depending on the type of progestogen. In a 28-day estrogen regimen, long-term HRT

with a progestogen supplementation for less than 10 days/month is still related to an elevated risk of about 2–3-fold, compared to a non-user, while the use of a progestin, depending on both the potency and half-life of a given progestogen, for 10–12 days or more per month decreases the excess risk. As expected, continuous combined HRT has been demonstrated to decrease the relative risk of endometrial cancer with respect to both ERT and sequential HRT, probably due to the antimetabolic effect of prolonged progestogen administration. This effect is similar to that exerted by combined oral contraceptives, the use of which reduces the risk of endometrial cancer. This protective effect is proportional to the duration of oral contraceptive use and persists after cessation of pill use. Different SERMs have different actions on the endometrium: Tamoxifen is associated with an increased risk of endometrial hyperplasia and cancer, while the long-term administration of raloxifene induces no endometrial stimulation. The synthetic steroid tibolone has not been reported to cause endometrial proliferation, although long-term safety data are still pending.

HRT is generally considered to be contraindicated in endometrial cancer patients. Nonetheless, as with breast cancer, non-randomized, uncontrolled studies have shown a decreased risk of recurrence in low-risk endometrial cancer survivors treated with HRT. However, randomized clinical trials are still ongoing. Despite the potential risks, HRT could be considered for patients suffering from menopausal symptoms resistant to alternative treatments, after completely informed consent is given.

Low-Grade Endometrial Stromal Sarcoma

The annual incidence of endometrial stromal sarcoma is very low, affecting fewer than 0.2 per 100,000 women, and more than 50% of patients are premenopausal. Low-grade endometrial stromal sarcomas are hormonally sensitive. These tumors have been reported to occur in women

with exogenous or endogenous hyperestrogenism. Among women with stage I low-grade endometrial stromal sarcomas, a higher recurrence rate is found in patients with ovarian residual tissue when compared to those treated by bilateral ovariectomy. Metastatic tumors can regress and even completely disappear following progestin therapy, and, moreover, progestins and GnRH analogues have also been successfully used as neoadjuvant hormone therapy in patients with locally advanced disease. Low-grade endometrial stromal sarcoma should be considered to be a contraindication to HRT.

Colon Cancer

In countries with a western lifestyle, colon cancer is the third leading cause of cancer death in men and women. The age-standardized incidence rate of colon cancer worldwide in females is 14.4/100,000. Colon cancer risk is increased by sedentary lifestyle and reduced by occupational or recreational physical activity. High saturated fat intake, alcohol consumption and cigarette smoking are positively associated with this malignancy. In addition, the assumption that dietary fiber intake and high consumption of fruit and vegetables can offer protection has not been confirmed. Some studies have reported a potential protective role for calcium, vitamin E, and selenium. Colon cancers, as well as other epithelial tumors, over-express the cyclo-oxygenase (COX) type-2 (COX-2) gene, and have elevated PGE₂ and PGF_{2 α} . COX-2 over-expression is associated with inhibition of apoptosis, inhibition of terminal differentiation of cells, and enhancement of angiogenesis. Non-steroidal anti-inflammatory drugs appear to have a protective role in colon cancer development. COX-2 inactivation by genetic targeting or by selective COX-2 inhibitors is able to prevent colon cancer in a mouse model with genetic predisposition to this malignancy, which resembles human hereditary polyposis syndrome.

The protective role of estrogens in colon carcinogenesis is still under study. ER- α and ER- β have been identified in

normal colon in both sexes. ER- β is the predominant ER subtype in the human colon, and decreased levels of ER- β -1 and ER- β -2 mRNA are associated with colonic tumorigenesis in females. It has been demonstrated that the ER gene is methylated in 90% of colon cancer tissues. Methylation of DNA is equivalent to gene silencing, with inactivation of a number of genes downstream. Methylation-associated inactivation of the ER gene in aging colorectal mucosa could be one of the earliest events in colorectal carcinogenesis. *In vitro* estrogens reduce the ER-gene methylation and inhibit cell proliferation. Estrogens may influence microsatellite instability, which occurs in approximately 10–15% of colon tumors. Moreover, estrogens have been shown to increase the expression of vitamin D receptors (VD-R) in a variety of tissues; 1,25-dihydroxyvitamin D and several of its analogues are known to be potent antineoplastic and prodifferentiative agents in several cell types, including colon-derived cells. The protective effect of estrogens against dimethylhydrazine-induced colon carcinogenesis in mice is associated with reduced methylation of the VD-R gene and with up-regulation of both VD-R gene transcription and protein expression. Therefore, increased VD-R activity may be one of the mechanisms by which estrogens protect against colon carcinogenesis. Moreover, exogenous estrogens and progestins decrease bile acid production, thus reducing chronic irritation on the colonic mucosa.

Gender differences in the incidence and biological history of colon cancer have been observed since 1950. In particular, more favorable colon cancer incidence and mortality trends have been reported in females compared to males. However, observational studies have documented no clear association between age at menarche, parity, age at menopause, or type of menopause and colon cancer risk. However, pooled analysis of HRT studies performed on Caucasian women suggests a 30% reduction in colon carcinoma risk among current HRT

users, with less protection seen after HRT cessation. A statistically significant reduction of colorectal polyps has also been detected in HRT users. Colon cancer protection by HRT is linked to duration of use, with greater protection in women receiving longer duration HRT. Although preliminary data suggest a possible additional benefit with concurrent progestin administration, data on regimen/formulation of menopausal hormones are very sparse. No conclusive evidence has been reached regarding the dose or the route of administration of HRT or on a possible difference in the protection versus right or left colon cancers. Some potential confounders may influence the relationship between HRT and colon cancer risk, so additional well-designed studies are still needed before we can conclude that HRT truly reduces colon cancer risk. Nonetheless available data suggest a reduced risk of colorectal adenoma and colon cancer in HRT current users. There is no contraindication to HRT prescription in colon cancer survivors.

Melanoma

The annual incidence of cutaneous malignant melanoma ranges from 2 per 100,000 in Spain and in South America to more than 20 per 100,000 in Australia. Melanoma incidence and mortality rates are increasing in most countries. Genetic predisposition and increased exposure to ultraviolet radiation play a major role in melanoma development. Contrasting data exist about hormonal and reproductive factors and risk of this malignancy in women. Immuno-cytochemical or immuno-histochemical assays do not detect ER in melanoma, and several studies have failed to demonstrate a stimulating effect of estrogens on proliferation or invasiveness of melanoma cell lines *in vitro*. Pregnancy before, during, or after the diagnosis of early-stage melanoma does not influence 5-year survival. Oral contraceptives do not increase the risk of melanoma, and they are no longer contraindicated for patients who have been treated for this malignancy. In advanced

melanoma, no response has been obtained with antiandrogens, progestins, and aromatase inhibitors. Tamoxifen has no significant activity as a single agent (response rates less than 10%), and clinical investigations on the role of tamoxifen in combination therapy of advanced disease have produced inconclusive results. HRT in menopause does not increase the risk of melanoma, and it can be given to patients previously treated for this malignancy.

Epithelial Ovarian Cancer

The age-standardized incidence of ovarian cancer world-wide is 6.5 per 100,000 females. Epithelial ovarian cancer, which accounts for more than 90% of ovarian malignancies, is the gynecological tumor with the worst prognosis, in part because more than 70% of cases are diagnosed at an advanced stage of disease. Risk factors for this malignancy include nulliparity and a possible family history. An increased crude risk of ovarian cancer has been reported in infertile women who have used fertility drugs. However, epidemiological studies on this issue are hampered by several methodological problems, including small sample sizes, short follow-up, and low prevalence of fertility drug use. Studies have consistently demonstrated that oral contraceptive use significantly reduces ovarian cancer risk.

Familial/hereditary ovarian cancer, which accounts for approximately 5% of all ovarian carcinomas, can be associated with three distinct clinical entities: the breast/ovarian cancer syndrome, the site-specific ovarian cancer syndrome, and the hereditary non-polyposis colon cancer syndrome, called Lynch II syndrome. While the first two conditions are linked with BRCA1 and BRCA2 germ line mutation, Lynch II syndrome is related to mutated mismatched repair genes. A difficult goal for clinicians is to select the population of women who are at high risk for a BRCA1 or BRCA2 mutation. A careful family history of breast/ovarian cancer is essential, and the pedigree criteria for including women in the BRCA genetic tests have been discussed by dif-

ferent scientific societies. Women who carry a BRCA1 mutation have approximately a 60% lifetime risk of developing ovarian cancer, and women who carry a BRCA2 mutation have approximately a 30% lifetime risk of developing this malignancy. There is no clear evidence for a peculiar clinical profile of familial/hereditary ovarian cancer. As for BRCA1 mutation carriers, the U.S. Cancer General Studies Consortium suggests a surveillance program consisting of monthly breast self-examination from age 18–20 years, annual/semi-annual breast clinical examination from age 25–30 years, annual mammography from age 30–35 years, and annual/semi-annual CA125 and transvaginal sonography with or without color Doppler from age 25–30 years. Contraceptive use seems to be protective also in the familial/hereditary ovarian cancer setting. Prophylactic bilateral oophorectomy can be considered in BRCA1–2 mutation carriers over 35 years after an extensive discussion in a multidisciplinary setting, including psychological consultation with accurate information about incomplete protection from subsequent primary peritoneal papillary serous carcinomas.

Several oncogenes, such as *fms*, *HER-2/neu*, *myc*, and *ras*, and tumor suppressor genes, such as *p53*, *ARHI*, *SPARC* and *DOC-2*, are involved in the regulation of normal and malignant ovarian surface epithelial cell growth. As for growth factors, ovarian epithelial cells express EGF and TGF- α , which stimulate cell proliferation by binding to EGF-R. Patients whose ovarian cancer is EGF-R positive have a worse prognosis than those whose tumor does not express these receptors. TGF- β inhibits the growth of normal ovarian epithelial cells and induces apoptosis in ovarian cancer cells. Progestins seem to be able to induce up-regulation of TGF- β and to enhance apoptosis in ovarian epithelium.

The evidence concerning a possible positive relationship between HRT use and ovarian cancer risk is less consistent than that for endometrial and breast can-

cer. Most data exclude any strong association between HRT use and ovarian cancer risk, even if published studies analyzing such a relationship have shown controversial results. A relative risk of ovarian cancer for ever-use of HRT is reported as 0.9 in hospital-based and 1.1 in population-based studies, with no consistent duration–risk relation. A collaborative re-analysis of four European studies, based on 1470 cases of ovarian cancer, found a relative risk of 1.71 (95% CI 1.30–2.25) for ever-use of HRT, a weak positive association with duration of use, and some indication that the excess risk for ovarian cancer declined with time since last use. A large U.S. study of 211,581 postmenopausal women treated for more than 10 years with estrogen alone, concluded that postmenopausal estrogen use was associated with increased risk of ovarian cancer mortality ranging from 1.59 (95% CI 1.13–2.25, for the former users) to 2.2 (95% CI 1.53–3.17) for baseline users. However, little information is available on the addition of progestins to estrogen preparations. In fact, no association has been described between the use of estrogen-progestins and ovarian cancer risk in a cohort study conducted in Britain, and similar results have been obtained in various areas in the United States. Furthermore, a retrospective British study and a South African prospective, randomized trial did not detect an adverse influence of HRT on the clinical outcome of patients previously treated for ovarian cancer. Thus, there are no data contraindicating HRT use in epithelial ovarian cancer survivors. However, it is well known that tamoxifen can stabilize advanced ovarian cancer in 30% of patients and produce objective regression in 10%. Studies of HRT in ovarian cancer patients performed to date cannot exclude the possibility that HRT might stimulate growth of metastatic disease in a subset of ER+ patients. Additional critical studies are needed with particular attention to hormone receptor status and function.

Summary

Sex steroids are not known to damage DNA directly. They can stimulate or inhibit cell proliferation, and thus can modulate tumor developmental progression. Sex steroid-related tumors in women are represented by breast cancer and endometrial cancer, and a possible relationship exists between sex steroids and both ovarian and colon cancer.

Among current ERT users or those who stopped use 1-4 years previously, the relative risk of having breast cancer diagnosed increases by a factor of 1.023 for each year of hormone use. This increase is comparable with the effect on breast cancer of delaying menopause, and seems to be largely limited to lean women. The breast cancers diagnosed during ERT are more likely to contain ER and are less aggressive. Some reports indicate no increase in breast cancer mortality in HRT users. Recent data suggest that an estrogen-progestin regimen may increase breast cancer risk beyond that associated with estrogen alone. However, the effect of progestogens on the breast awaits further clarification. ERT/HRT is generally considered to be contraindicated in breast cancer patients, as no firm data are yet available from randomized clinical trials. Despite the potential risks, ERT/HRT could be considered for breast cancer patients suffering from menopausal symptoms resistant to alternative treatments, after completely informed consent is given, particularly in women with ER-negative cancers.

Unopposed estrogen therapy is known to increase endometrial cancer risk, and is appropriate only for hysterectomized women. To negate the excess risk of endometrial hyperstimulation, an adequate progestin dose must be given in a continuous combined regimen or for an appropriate number of days in sequential regimens (10 days or more for some progestogens or 12 days or more for other progestogens).

An appropriate combination of estrogen and progestin does not appear to increase, and may even decrease, the risk

of endometrial cancer. HRT is generally considered to be contraindicated in endometrial cancer patients. Despite the potential risks, HRT could be considered for patients suffering from menopausal symptoms resistant to alternative treatments, after completely informed consent is given.

Available data suggest a reduced risk of colorectal adenoma and colon cancer in current users of HRT, but definitive studies are still needed. There is no contraindication to HRT prescription in colon cancer survivors. Consistent epidemiological data describe a decreased incidence of ovarian cancer with oral contraceptive use during the reproductive years. Studies on HRT and risk of epithelial ovarian cancer have produced conflicting results, but most data seem to exclude a strong association. While no data contraindicate HRT use in epithelial ovarian cancer survivors, current studies do not allow us to exclude the possibility that estrogens alone could stimulate ovarian cancer growth in a small fraction of patients. Additional studies are required.

It is important to consider that not all estrogens and progestins are used with the same dosage, route of administration (oral, transdermal and, for estradiol, intranasal) and, mostly, different estrogens do not show the same bioavailability and tissue effects. The available data do not allow us to discriminate for all these variables and, therefore, it is inappropriate to consider jointly all forms of hormonal therapy. This issue is considered as an important area for future evaluation and research. The International Menopause Society is in the process of drawing up specific recommendations for further research in the field of HRT and cancer. ■

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