Review

Hormone Replacement Therapy and Malignancies

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Media reports engendered by the premature closure of the two Women's Health Initiative (WHI) trials have created distorted perceptions of the risks of hormone replacement therapy (HRT) and reluctance to use it, even in the face of distressing menopausal symptoms.[1] Yet HRT remains the most efficacious and well-researched therapy available for the treatment of menopausal symptoms.[2] Following is a critical appraisal of the literature on the association between HRT and the common cancers in the general population, as well as in women with specific malignancies. This should help physicians and symptomatic women make informed decisions about using HRT. The term estrogen replacement therapy (ERT) is used to denote the use of unopposed estrogen and the term HRT is used for combined estrogen and progestin.

Endometrial cancer

The association between unopposed estrogen use, endometrial hyperplasia and cancer is unequivocal. The risk is dose- and time-dependent and does not return to baseline even after cessation of treatment. Unopposed estrogen replacement therapy produces hyperplastic lesions within a few months of use.[2,3] At three, five and ten years of use, the odds ratio (OR) of endometrial cancer in women using unopposed estrogen is reported as 3.44, 6.25 and 10, respectively. Addition of a progestin drastically lowers this risk; the protective effect is positively correlated with the number of days of progestin use during the cycle. Cyclical use, which is traditionally for two weeks every cycle, is not adequate to eliminate the risk of endometrial cancer (relative risk [RR] of 1.5), but continuous combined HRT reduces the risk to below that of the general population (figures varying from RR=0.716,[4] OR=0.84[5] and OR=0.25[6]).

Can ERT be prescribed for symptomatic women, following hysterectomy and bilateral salpingo-oophorectomy for endometrial cancer?

Although estrogen plays an important role in endometrial carcinogenesis, several observational studies, and one randomized trial from the Gynecologic Oncology Group reported a low recurrence rate (2.1%) in endometrial cancer patients on ERT.[7-9] Despite these reassuring findings, physicians are reluctant to prescribe estrogen to endometrial cancer patients.[10]

Table 1:
Risk of Cancer Stratified by Type and HRT Combination

Type of Cancer	Risk				Reference
	Estrogen Only		Continuous Combined Estrogen and Progestogen		
Endometrial	OR = 6.6		OR = 0.2		[5]
	OR = 3.4		OR = 0.2		[4]
	RR = 1.45		RR = 0.71		[6]
	—		HR = 0.81		[1]
Ovarian	RR = 1.34		RR = 1.14		[11]
	RR = 1.50		RR = 1.40		[12]
	RR = 1.6		RR = 1.1		[13]
Breast	RR = 1.30		RR = 2.00		[17]
	Ductal	Lobular	Ductal	Lobular	[15]
	RR = 0.99	RR = 1.23	RR = 1.23	RR = 2.29	
	—		HR = 1.26		[17]
CNS	RR = 1.42		RR = 0.97		[26]
CRC	OR = 0.42		OR = 0.60		[20]
Lung	HR = 1.14		HR = 1.27		[24]
Non-HRT Cancers	1.0				

*RR = Relative Risk; OR = Odds Ratio; HR = Hazard Risk

Ovarian Cancer

Several observational studies suggest that long term use of ERT and HRT appears to be associated with an increased risk of ovarian cancer, with RR ranging from 1.23 to 1.38 in current users of HRT, up to 3.2 for those with 20 years of use or more.[11-13] However, given the small absolute increase of one extra ovarian cancer per 2500 to 8300 users of HRT, and the fact that the associated risk diminishes after HRT is stopped, the use of HRT for symptom relief is worthwhile.[11-12]

Can HRT be prescribed for symptomatic women, following hysterectomy and bilateral salpingo-oophorectomy for ovarian cancer?

There is no conclusive evidence that HRT increases the risk of recurrence of ovarian cancer after treatment. Retrospective studies have not shown detrimental effects on prognosis or survival. Mascharenas, *et al*. found no difference in five-year survival between patients with epithelial ovarian cancer on HRT before diagnosis (hazard ratio [HR] of 0.83) and those who did not use

Frequently Asked Questions

Are bio-identical hormones less detrimental than the synthetic hormones commonly used in HRT preparations?

The term 'bio-identical' has been hijacked and used to market poorly researched creams and concoctions. However, micronized progesterone available on prescription is bio-identical to endogenous progesterone and appears to have a better safety profile than the synthetic progestins used in North America.[28] Therefore, it is the progesterone of choice for HRT.

Transdermal estrogens available on prescription are also bio-identical, in that they are identical to endogenous estradiol, and they too appear to have a better safety profile.

These are not to be mistaken for the creams and potions marketed as 'natural/bio-identical' hormones, even if they are prepared by pharmacies. Such preparations are to be avoided because of a lack of safety and efficacy data.[28]

HRT. For patients beginning HRT after diagnosis, a better survival rate was reported (HR=0.57), as compared to patients who did not use HRT after diagnosis.[14]

Breast Cancer

There is an undeniable association between breast cancer risk and HRT with increasing duration of use. However, the evidence from randomized controlled trials (RCTs), as well as large cohort studies suggests that the risk associated with estrogen alone is very small; the significant factor appears to be combined estrogen and progesterone use.[15-17] In the WHI RCTs, while combined HRT for five years was associated with a 23% increase, ERT for eight years was associated with a 30% decrease in risk.[18]

Can HRT be prescribed for symptomatic survivors of breast cancer?

In the "Hormone replacement therapy after breast cancer - is it safe?" (HABITS) RCT of HRT use in breast cancer survivors, HR was 2.4 in patients assigned to the HRT group. The use of tamoxifen with HRT, rather than conferring protection, increased the risk of recurrence (HR=4.7). In addition, the cumulative incidences of new breast cancer events after two years were 9.5% for the HRT arm, as compared to 3.8% in the non-HRT arm.[19] HRT is therefore best avoided in breast cancer survivors.

Colorectal Cancer

HRT reduces the risk of colon cancer, due to the protective effects of estrogen: inhibition of bile synthesis, methylation of estrogen receptor genes responsible for colorectal carcinogenesis and an increase in the expression of vitamin D receptors, which have anti-neoplastic properties.[2] Both ERT and HRT confer a reduction in risk of colorectal cancer, but the reduction is lower with ERT (OR=0.42) than with HRT (OR= 0.60).[20]

Can HRT be prescribed for symptomatic survivors of colorectal cancer?

There is a 40% reduced risk of disease-specific mortality in colorectal cancer survivors who use HRT. Women on HRT for more than four years have the lowest risk of dying of colon cancer (HR=0.5).[21]

Lung Cancer

Although several small case-controlled studies report lower lung cancer incidence and mortality in HRT users, larger, rigorous cohort studies and post hoc analysis of the WHI I RCT indicate that the use of combined HRT increases the risk of dying from lung cancer.[22-24]

Other cancers

Neither ERT nor HRT increases the risk of cervical cancer; rather, young women being treated for cervical cancer would greatly benefit from use of either therapy.[25] There is a slightly increased relative risk of CNS tumours, particularly meningiomas in patients on ERT; therefore, it is best avoided in women treated for meningiomas.[26] HRT does not affect carcinogenesis of the thyroid or the skin. Caution should be exerted in prescribing hormones in patients with gastric cancer.[27]

Take-home Message

The absolute risk of cancer associated with ERT is minimal. As its use has been well researched, it is the treatment of choice for severe menopausal symptoms in the general population, as well as in the survivors of most cancers, except meningiomas and breast cancer. The addition of a progestin, which is necessary in women who have not had a hysterectomy, increases the risk of breast and lung cancer in the general population. However, as the risk is duration-dependent, the key is to prescribe HRT for short periods, as the absolute risks are minimal for periods of use of less than five years. Dx

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