EDITORIAL

Wanted: More Evidence on Whether Estrogen Replacement Causes Cancer

The opportunity to furnish an editorial for the Journal focuses attention on a wish list of what one would like to find in these pages over the coming year. Clear, experimental evidence regarding the possible role of estrogen in the development of cancer among hormone replacement therapy patients is high on that list. It has been nearly a quarter century since the original epidemiologic studies indicated a higher incidence of the diagnosis of endometrial cancer among climacteric women who historically took estrogen replacement. The response to these data and subsequent similar data was dramatic: women stopped taking estrogen. Ultimately, the putative relationship of estrogen to endometrial cancer was institutionalized by the Food and Drug Administration's requirement of a statement indicating that estrogen treatment may cause endometrial cancer on the package information sheet, even though there is no direct, experimental evidence to support this conclusion. To be sure, some voices of dissent were cast regarding the general acceptance of the epidemiologic findings as indicating a causal link to endometrial cancer. As well, data continues to accumulate indicating that the increased diagnosis of endometrial cancer is not a factor in the life expectancy of climacteric women receiving estrogen. However, despite the indications that the increased diagnoses of cancer were not ominous, it was the downscaling of estrogen dosages and the development of estrogen-progestin regimens that allowed women to return to hormone replacement therapy. In fact, concerns over estrogen-induced cancer remain, and have been expanded to include breast cancer, on the basis of even less convincing evidence than for endometrial cancer.

With the passage of time it has become clear that many estrogen-deficient women, regardless of their age, are at risk of osteoporosis, hypothalamic dysfunction, cognitive disorders and cardiovascular disease at greater attack rates than if they were not estrogen-deficient. Furthermore, evidence is accumulating that estrogen replacement treatment forestalls these complications. It has also become clear that the addition of progestins to avoid endometrial cancer has a generally antagonistic effect on the estrogen treatment and may have its own negative effect on brain function and cardiovascular parameters.

Lately, attention has focused on the role of estrogen in possibly forestalling dystrophic brain disease, particularly Alzheimer's disease, and the possibility that estrogen may treat the established syndrome. Moreover, evidence is accumulating of late life-positive effects of estrogen treatment on bone loss and cardiovascular risk. Finally, the first studies demonstrating effects of estrogen on the immune system and the possible salutary effects of estrogen treatment on immune competence have begun to appear and it seems that the first decade of the twenty-first century will be the decade of the immune system.

The progress listed above has been made without resolution of the question of estrogen's effect on the rate of endometrial cancer in women who take estrogen. However, important progress has been made regarding the disease, itself. It appears that there are two forms of endometrial cancer: a histologic low nuclear grade cancer, the endometrioid type, and a high histologic grade cancer, usually termed serous or clear-cell. The former appears to be an extension of complex atypical hyperplasia, expresses steroid hormone receptors and is more common among hormone replacement therapy users. Endometrioid cancer has an extremely positive outcome since it metastasizes late and responds to hormone/antihormone treatment. On the other hand, serous/clear-cell endometrial cancers generally metastasize early, do not express estrogen receptors, and may not respond well to hormone therapy.

In light of the lack of an effect of the diagnosis of endometrial cancer on mortality in cases from the epidemiologic studies, and a lack of studies showing estrogen to be a carcinogen, the question of whether endometrial cancer is caused by estrogen replacement therapy, especially at contemporary doses, is due for reconsideration. Since the diagnosis of early endometrioid endometrial cancer is subjective, because it depends solely upon the histologic picture, it seems that this question cannot be answered through the use of traditional morphologic methods. Rather, a marker of the change from complex atypia to endometrial cancer is required. Such a marker is not yet available, although there have been many attempts to find it. In the meantime, hundreds of thousands of women around the globe avoid hormone replacement therapy under the concern that estrogen treatment causes cancer, though this has never been proven in appropriate experimental studies. Women are also being exposed to progestin regimens that, on balance, have significant anti-estrogenic, negative effects on estrogen-sensitive systems.

Objective indicators of the presence of cancer versus hyperplasia are certainly at the top of our scientific wish list, to help resolve the controversy over whether contemporary hormone treatment in fact causes endometrial or breast cancer and to settle the concerns of the women we have the privilege of serving.

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