Health consequences of short- and long-term postmenopausal hormone therapy

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Some women take an estrogen preparation for as long as several years to ease symptoms of the menopause. Such women appear to have little or no alteration in their risk of endometrial cancer, especially if they are also taking a progestogen, and no alteration in their risk of breast cancer. Similarly, the incidence of fractures is unaffected by relatively short-term hormone use. The risk of ischemic heart disease also is reduced among women who currently take estrogens (with or without a progestogen), but the influence of duration of use on this association is uncertain. Postmenopausal women who take estrogens for an extended period of time (e.g., a decade or more) incur a sharply increased risk of cancer of the endometrium. This is largely abated by use of a progestogen for at least 10 days per month. Such long-term estrogen use, whether accompanied by a progestogen or not, may increase the risk of breast cancer slightly, but this is an area of great controversy, at present unresolved. The incidence of both myocardial infarction and fracture is substantially reduced in long-term users of menopausal hormones.

INDEXING TERMS: estrogen • progestogen • endometrial cancer • breast cancer • myocardial infarction • bone fracture

Some women take an estrogen preparation for as long as several years as a means of easing symptoms of the menopause, especially hot flashes. Others take estrogens for an extended period of time—a decade or more—for a variety of reasons, including prevention of some chronic diseases. The goal of this paper is to indicate the consequences of these two approaches to hormonal therapy with respect to the incidence of two forms of cancer (endometrial and breast cancer) and also the incidence of myocardial infarction and fracture, two other major health concerns of older women. Although other serious conditions exist whose occurrence is suspected of being influenced by postmenopausal hormone use (e.g., colon cancer and gall bladder disease), more data on these possible associations need to be obtained before any firm conclusions can be reached.

My approach will be to show data from representative studies, rather than from the results of an exhaustive metaanalysis of data pertaining to each of the four diseases. None of the studies to be described had randomized women to receive or not to receive hormones. Some studies of exogenous estrogens have been designed in that way, but they included too few subjects to reliably evaluate specific disease outcomes. Instead, I will focus on the results of cohort and case-control studies. Cohort studies are those that identify women who have taken hormones, along with others who have not, and compare the two groups for their subsequent occurrence of one or more illnesses. Case-control studies, in contrast, compare the prior use of hormones in women who developed a particular condition with their use in women who did not. Data from a case-control study generally allow close estimation of the relative incidence of a disease in hormone users and nonusers (by means of the odds ratio), even though the actual incidence is not known in either group.

Short-Term Estrogen Use

Endometrial cancer. Estrogen use for just a few months produces, at most, a very small increase in the incidence of endometrial cancer. Methodological difficulties prohibit us from concluding whether or not the small excess risk seen in most studies is genuine. Use of unopposed estrogens over a period of several years probably increases the risk of endometrial cancer, perhaps by 50% or so [1]. However, even this increase in risk is of relatively small clinical concern, because (a) endometrial cancer is relatively uncommon around the time of menopause, the time when estrogen use is usually initiated; (b) the increase in risk almost certainly does not linger to an appreciable degree once treatment has been stopped [1]; and (c) endometrial cancer is curable in the very large majority of hormone users who develop it [2].

Breast cancer. Although the many studies of breast cancer occurrence in relation to hormone use have not produced consistent results, apparently no increased risk is associated with estrogen use that lasts for no more than several years [3]. None of the three most recent large studies of this question found any increase in risk in women who used estrogens for <5 years [4-6].

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Mycocardial infarction. Among the many investigations of hormone use in relation to the incidence of myocardial infarction in postmenopausal women, little attention has been paid to the possible importance of duration of hormone use. In a report from the Nurses Health Study, Stampfer et al. [7] observed a reduced risk of heart attack associated with current estrogen use, but "no notable trends with regard to duration of use." In contrast, the case-control study of Rosenberg et al. [8] noted that the risk of a heart attack diminished with increasing duration of hormone use. Clearly, this important issue needs to be addressed in additional studies.

Fracture. Use of menopausal estrogens for a period not exceeding several years has little or no effect of the incidence of fracture, either while the hormone is being taken or later after it has been discontinued [9, 10].

Long-Term Estrogen Use

Endometrial cancer. Long-term unopposed estrogen use markedly increases the incidence of endometrial cancer [11]. Use beyond a decade is associated with at least a 10-fold increase in risk. Conjugated estrogens have been the most widely used and the most widely studied form of estrogen therapy, and an increased risk appears to present for long-term use of any type of estrogen preparation. Each of the more commonly used doses of conjugated estrogens—0.625 and 1.25 mg per day—are related to an increase in risk; data on the lowest available dose of these hormones, 0.3 mg per day, are not adequate at present to support any conclusions regarding its safety. Among women who have used estrogens for a long time and then stopped taking them, the risk of endometrial cancer does fall. Whether it declines to the risk level of a woman who has never taken hormones is uncertain [11]. Estrogen use could well increase risk by stimulating growth of endometrial cells, thereby increasing the likelihood of a mutation that eventually leads to the development of a cancer. If this is true, one would expect that the incidence of endometrial cancer would remain increased even when a woman stops taking estrogens, at least for some period of time.

Breast cancer. Metaanalyses of studies of breast cancer in relation to use of unopposed estrogens suggest that 1–2 decades of use is associated with an increase of ~30% in risk of this disease [12]. However, results are considerably inconsistent from study to study [4–6]. Furthermore, epidemiological studies have difficulty in distinguishing true increases in risk of this magnitude from spurious increases. So, although a true 30% increase in the risk of breast cancer associated with long-term use of menopausal hormones would be quite worrisome (given the frequency and severity of this disease), it is not possible to conclude from currently available data that such an increase in risk is indeed a consequence of hormone use.

Mycocardial infarction. There is no dispute among the available studies that long-term estrogen therapy reduces the incidence of myocardial infarction—perhaps by as much as 50%—at least as long as the therapy continues. There is less consensus, however, regarding the presence or size of a lingering benefit of hormone therapy once that therapy has been discontinued. The magnitude of the reduced risk among current hormone users appears to be greater than what would be predicted on the basis of the changes in serum lipid concentrations that accompany estrogen therapy. Other mechanisms might be responsible for the beneficial effect on the occurrence of heart disease [13], including enhanced endothelium-dependent vasodilation, vessel wall stability, and formation of collaterals.

Fractures. Both cohort and case-control studies have consistently found that long-term use of estrogens by postmenopausal women is associated with a reduced risk of fracture of the hip, forearm, and other parts of the skeleton [9, 10]. This reduction in risk is substantial (two- to threefold) while a woman continues to take these hormones, but the beneficial effect wanes quickly once the hormone has been stopped. The reduced risk of fracture in current hormone users almost certainly results from the effect of estrogens in maintaining, or even increasing, the bone density of postmenopausal women [14].

Addition of a Progesterone to Long-Term Menopausal Estrogen Therapy

In an effort to achieve the benefits of long-term estrogen therapy for the cardiovascular and skeletal systems, while minimizing the extra risk of cancer of the endometrium (and possibly breast), many physicians now prescribe a progesterone as well as estrogen for their postmenopausal patients. The progesterone is given either on an intermittent basis, typically 10–14 days per month, or every day. The former approach appears to largely or completely offset the increased risk of endometrial cancer that is present when estrogens are used alone, as long as the progesterone is taken for at least 10 days per month [13]. Intermittent progesterone therapy has been less extensively studied with respect to breast cancer, and with no clear results: Some studies suggest a small increase in risk [4], others suggest no increase at all [5, 6]. Intermittent progesterone therapy does not appear to attenuate the beneficial effect of estrogens alone on the incidence of either myocardial infarction [15, 17] or fracture [10]. In the past several years, it has become popular to prescribe a relatively lower dose of a progestogen to be taken daily, along with estrogen. We do not yet know the influence of this regimen on the occurrence of cancer, heart disease, or fracture.

References