EDITORIAL

Tamoxifen as a Potential Preventive Agent in Healthy Postmenopausal Women

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Much of the recent interest in the biological effects of long-term tamoxifen treatment stems from its potential application as an agent for the prevention of breast cancer and other diseases in postmenopausal women. The report by Love and colleagues at the University of Wisconsin (*1*), which appears in this issue of the Journal, adds considerable force to this primary prevention premise. These investigators demonstrate substantial effects of tamoxifen (10 mg twice a day) on blood lipids and lipoproteins, in a carefully controlled toxicity trial in 140 postmenopausal women with axillary node-negative breast cancer. This editorial offers some perspectives on the next steps in evaluating the prevention potential of tamoxifen and on the role that a full-scale tamoxifen prevention trial could play in an overall research program for the primary prevention of disease in postmenopausal women.

Stimulated by a National Cancer Institute Clinical Alert in 1988, adjuvant therapy with tamoxifen is now being widely used in the United States and elsewhere in women with estrogen receptor-positive breast cancers, regardless of nodal or menopausal status. A comprehensive overview (*2*) of trials of early breast cancer demonstrated a highly significant reduction (approximately 20%) in mortality rate associated with tamoxifen therapy among breast cancer patients who were 50 years of age or older. Knowledge that tamoxifen appears to retard the growth of breast tumor cells, rather than killing such cells, argues for longer periods of tamoxifen therapy or, perhaps, indefinite maintenance therapy with tamoxifen. Hence, since approximately half of the 150,000 new breast cancers diagnosed in the United States are estrogen receptor positive, there may, within a decade or so, be several hundred thousand breast cancer patients receiving tamoxifen in this country alone (*3*).

Love and associates demonstrated that a standard regimen of tamoxifen reduces total blood cholesterol by approximately 12% on average and low-density lipoprotein (LDL) cholesterol by 20% on average, with a presumed corresponding reduction in risk of coronary heart disease. This finding is very welcome information in the therapeutic context. Their related finding that tamoxifen leads to an estimated 15% increase, on average, in total serum estrogens adds to the list of estrogen-agonistic effects of this agent. Like tamoxifen, menopausal estrogens reduce LDL cholesterol but tend to have little effect on total cholesterol, since the LDL reduction is mostly compensated by an increment in high-density lipoprotein (HDL) cholesterol (*4*).

The effects of tamoxifen on blood lipids and blood hormones assume a central role if tamoxifen is contemplated as an agent for the primary prevention of disease. For example, among US women in the age range 55–69 years, the incidence of breast cancer is about 0.3% per year, depending somewhat on age, whereas the incidence of coronary heart disease is about 1% per year, depending strongly on age. If the results linking cholesterol lowering to the reduction of risk of coronary heart disease in men (e.g., *5*) apply to women in this age range, then one would project that the lipid and lipoprotein changes observed by Love and co-workers would confer a substantial reduction, perhaps in the vicinity of 40%, in the risk of coronary heart disease. Thus, the projected benefit of the decrease in incidence of heart disease would substantially overshadow the projected benefit in breast cancer incidence, even if tamoxifen were able to reduce breast cancer risk by 50% or more. In fact, the potential reduction in the risk of coronary heart disease may well exceed that for the risk of breast cancer, even among women with a family history of breast cancer or with other standard breast cancer risk factors. This illustration reinforces the importance of examining the entire range of potential health risks and benefits, with emphasis on total mortality rate, when a disease-prevention maneuver in the general population is being considered. A concentration on overall health promotion and disease prevention, however, does not integrate easily with our disease-oriented approach to health research in this country.

It is unfortunate that the research base is so sparse concerning the relationship between blood lipids and lipoproteins and heart disease risk among women. HDL cholesterol may be a particularly strong protective factor in women (*4*); if this is so, even the modest (approximately 5%) reduction in HDL cholesterol concentration among women taking tamoxifen, which was observed by Love et al. (*1*), could largely offset the benefits of the much larger LDL cholesterol reduction. Also, the observed 20% rise in triglycerides in women taking tamoxifen (*1*) is presumably not a major factor in the risk of coronary heart disease, but it has been suggested that HDL cholesterol may appear to be a strong protective factor partly because of its negative correlation with triglycerides, coupled with measurement difficulties in assessment of triglyceride concentrations (*6*). Further information on the relationship between blood lipids and lipoproteins and coronary heart disease risk among women appears to be extremely important to the potential application of tamoxifen as a preventive agent in healthy women.

Love and colleagues have in mind a formal feasibility study of tamoxifen use in healthy postmenopausal women, and they are eminently qualified to conduct such a trial. There are compelling reasons why some form of feasibility trial should precede any full-scale, disease-prevention trial with tamoxifen. There is the need to establish suitable recruitment sources and procedures. A full-scale trial may, for example, require as many as 20,000 study

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subjects for adequate power with respect to important outcomes. Recruitment of this number of volunteers, satisfying a range of eligibility criteria, may require a variety of recruitment strategies, possibly including the establishment of a national network of female relatives of women with breast cancer.

A feasibility study would also provide valuable compliance information. While compliance appears to be excellent in the Wisconsin Tamoxifen Study (*1*), the willingness of women without a disease diagnosis to take a powerful hormonal agent for a sustained period, solely for disease prevention, has yet to be established. For example, certain known side effects of tamoxifen, including hot flashes and vaginitis (*7*), may be more readily accepted by breast cancer patients than by women without such a diagnosis. Lack of compliance could noticeably affect the design of a full-scale trial.

One need only look as far as the experience with oral contraceptives and menopausal steroids to realize that many profound health consequences may follow from hormonal manipulation and that such consequences may not become apparent for several years after the beginning of exposure to hormonal agents. For example, the original sequential oral contraceptives, which involved a period of unopposed estrogen, appeared to approximately double endometrial cancer risk (*8*), while the early menopausal estrogens evidently increased endometrial cancer risk by a factor of about five (*9*). In comparison, the older oral contraceptive combinations reduced the risk of endometrial cancer and ovarian cancer about twofold and appeared to slightly increase the risk of liver and cervical cancer and possibly to increase breast cancer risk among certain subgroups of women. Likewise, there is inconsistent evidence that menopausal estrogens increase breast cancer risk, perhaps by about 40%.

Despite this impressive list of cancer rates that may be affected by hormonal manipulation, the cardiovascular implications of the use of these exogenous hormones appear to dominate the risk–benefit profile (e.g., *8*). The early high-dose oral contraceptives were found to increase the risk of thromboembolic events, including pulmonary embolism, while their most important effects in terms of disease incidence and mortality involved enhancement of the risks of hemorrhagic and thrombotic stroke and particularly coronary heart disease (*8*). These latter effects appear to be attributable to the progestin component of the oral contraceptives, while menopausal estrogens appear to have important beneficial implications for coronary heart disease, quite possibly mediated through the favorable lipid and lipoprotein effects mentioned above.

To the extent that tamoxifen acts as an estrogen agonist, related long-term effects on these disease processes would be anticipated. Indeed, in one Swedish adjuvant study (*10*), investigators reported a significant elevation of endometrial cancer incidence among tamoxifen-treated women. This report, however, has not been confirmed by other trials. A formal feasibility study would allow additional valuable study of the effects of tamoxifen on pertinent biomarkers of the diseases mentioned above, particularly cardiovascular diseases.

Assuming successful results in feasibility studies, there would appear to be strong motivation for a full-scale primary prevention trial using tamoxifen. A preventive maneuver that could lead to noteworthy risk reductions for both coronary heart disease and breast cancer would be of considerable public health importance. An adequate disease-prevention research strategy, in my opinion, would necessarily involve simultaneous concentration on lifestyle and behavioral approaches that have potential to reduce the risk of these and other diseases without requiring ostensibly healthy persons to take pharmacologic agents for sustained periods. For example, dietary maneuvers involving fat reduction and the supplementation of vitamins and fiber also appear to have potential for important reductions in disease risk. Analogous to current approaches to the prevention and control of hypertension and hyperlipidemia, such a pure dietary change may be a sensible general population goal, while tamoxifen treatment could prove to have a valuable additional role among women at considerably elevated risk of breast cancer or heart disease. A well-rounded research program, including emphasis of both of these intervention strategies, could lead to a greatly strengthened health-promotion and disease-prevention arsenal within a few years of the turn of the century.

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