Histologic Changes in the Ovaries of Cancer-Prone Women: an Indication of Premalignant Change?

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Ovarian cancer will be diagnosed in an estimated 26,700 women in the United States in 1996 and approximately 14,800 women will die of the disease (1). Of the 26,700 new cases, roughly 6,000 will be diagnosed while cancer is confined to the ovaries and 4,000 will be confined to the pelvis. Thus, more than 16,000 women will have advanced stage disease (International Federation of Gynecology and Obstetrics III and IV) at the time of diagnosis. The 5-year survival rate for patients with ovarian cancer confined to the ovaries is reported to be 91% by the Surveillance, Epidemiology, and End Results (1) Program of the National Cancer Institute (1). In contrast, the survival rate is only 23% for patients with stage III or IV disease. Overall 5-year survival rates for patients with ovarian cancer has improved from 32% in the early 1960s to 42% in the late 1980s (2). Most of this improvement can be attributed to improvements in surgery and chemotherapy. There has been little change in the rate of early diagnosis.

While it is quite likely that continued improvements in chemotherapy and more accessibility to proper surgical treatment will be able to improve survival slightly over the next few decades, significant improvements in survival rates for women with epithelial ovarian cancer will depend on improved understanding of the biology of these cancers so that methods of early detection and prevention can be developed. The analysis of the microscopic characteristics of the ovaries of women from familial and hereditary breast and ovarian cancer families reported in this issue of the Journal by Salazar et al. (3) is a valuable contribution to our knowledge about the biology of ovarian tissue in women at increased risk of developing ovarian cancer.

These authors have studied the histologic features of ovarian tissue removed from women undergoing prophylactic oophorectomy because of familial or hereditary ovarian cancer and have compared these histologic features to ovarian tissue from 20 women undergoing oophorectomy for a variety of benign gynecologic disorders. Although evaluation of the study cases reveals that only nine of the 20 patients are known to be BRCA positive, the family histories indicate that most of the patients are at significant risk of belonging to a hereditary breast-ovary cancer family, and a large percentage of the remaining 10 patients are probably BRCA1 positive on the basis of their family history. In a similar fashion, the control population is not a pure low-risk population, since neither extensive family histories nor BRCA1 testing was available for the control subjects. Despite the above deficiencies, the populations chosen are reasonably likely to represent cancer-prone versus non-cancer-prone individuals.

The authors found two occult epithelial ovarian cancers that are 500 times the expected incidence for women in that age group, since, based on epidemiologic data, the incidence of ovarian cancer in women aged 35-44 years is 10 per 100,000 (4). In addition, they found a statistically significant increase in incidence of papillomatosis, inclusion cysts, epithelial invagination, epithelial pseudostratification, and increased stromal activity. All of these characteristics have been postulated by various investigators to be potentially premalignant histologic features (5). The investigators could not, however, identify a transition from any of the above features to either low malignant potential or invasive epithelial cancer of the ovary.

The identification of a premalignant ovarian abnormality has eluded investigators. Bourne and Lynch (6) described a comparison between an ultrasound screening study of a random population versus an ultrasound screening study of women with an ovarian cancer family history and showed an increased incidence of primary ovarian cancer, benign epithelial tumors, bilateral masses, and mixed ovarian lesions in women with a family history of ovarian cancer. Puls et al. (7) studied ovarian cystadenocarcinomas and found what they described as transi- tion from benign cystadenomas to malignant lesions. They postulated that benign cystadenomas might be precursors of epithelial ovarian cancer in some cases. Other authorities have questioned this theory. To date, there are no proven premalignant lesions for epithelial ovarian cancer. Nor is it known whether or not tumors of low malignant potential represent an intermediate step between a benign lesion and an invasive cancer.

Although the study by Salazar et al. (3) in this issue of the Journal does not establish that the epithelial abnormalities described are premalignant changes that will develop into invasive ovarian cancer, they do add further indirect evidence that such precancerous abnormalities do exist. Identification of such abnormalities could greatly increase our knowledge about the pathogenesis of this disease. Understanding the pathogenesis is a prerequisite first step in the development of both early diagnosis and better therapies, particularly biologic therapies. Perhaps most important, these investigators have identified a

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See "Note" section following "References."
potentially valuable model to study the biologic differences within the ovaries of women at increased risk of developing ovarian cancer and the ovaries of women without increased risk. It is quite likely that the biologic mechanisms of the development of ovarian cancer in sporadic cases is similar to the mechanisms of development in women with genetic predisposition to develop the disease. The elucidation of these biologic mechanisms will allow rational approaches to the diagnosis, treatment, and, most important, prevention of this deadly disease.

References


Note

1 Editor's note: SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

Five Years of Tamoxifen—or More?

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Before 1990 there had been, for half a century, little evidence of any decrease in the U.S. age-standardized death rate from breast cancer. Chu et al. (1), however, have recently described a sudden decrease in breast cancer mortality during the 1990s, which they ascribe to the combined benefits of early detection and better treatment (particularly adjuvant chemotherapy and hormonal therapy) during the 1980s. A decrease during the 1990s relative to the previous pattern of U.S. breast cancer mortality is seen in each decade of age from 30-39 years to 70-79 years. In Britain, where there had been much less mammography during the 1980s but perhaps even more adjuvant hormonal therapy, a similarly sudden decrease in breast cancer mortality has also been seen during the 1990s, and at least some of this decrease is also attributable to better treatment of the disease, particularly with tamoxifen (2).

Although the absolute benefit produced by a few years of adjuvant tamoxifen therapy for patients with early breast cancer is not large (50% survival might, for example, be increased to 55% or 60%), the treatment is widely practicable and the disease is common. Since about one million women worldwide are now taking tamoxifen, this drug may well be preventing more cancer deaths than any other. But there is still widespread uncertainty as to how long such adjuvant therapy should usually continue. This question is being addressed directly by several trials that randomly assign women to different durations of adjuvant tamoxifen therapy (e.g., 2 versus 5 years or 5 versus 10 years). Last month and this month in the Journal, preliminary results have been reported from four of these trials (3-6). One of the reports, i.e., the one from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial (6), also includes some of the best evidence ever published on the advantages of 5 years of adjuvant tamoxifen versus no adjuvant tamoxifen, finding highly significant delays in disease recurrence both for women who were under 50 years of age when they were randomly assigned and for older women.

The original trials of adjuvant tamoxifen versus control that began in the 1970s quickly showed that both local and distant recurrences could be delayed. However, when distant recurrence occurred in those women who had not been allocated to adjuvant tamoxifen, then hormonal treatment would often be used to try to delay its progress. Since the additional recurrences in the control groups were those that could have been delayed if tamoxifen had been given initially, many of them could still respond to hormonal treatment. Thus, as far as survival is concerned, many of these studies should be thought of not as trials of tamoxifen versus no tamoxifen but rather as trials that compared two different strategies for using tamoxifen (i.e., as trials of adjuvant tamoxifen versus tamoxifen only when recurrence occurred). Hence, especially in the first few years after randomization in these studies, the effect of adjuvant tamoxifen on survival was less extreme than its effect on recurrence and was less quickly recognized. Indeed, in the early 1980s, it was widely, though mistakenly, believed that the previous trials had proved that adjuvant tamoxifen did not affect survival.

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