Tamoxifen Use and Risk of Endometrial Cancer

Bergman L, Beelen ML, Gallee MP, et al. Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Lancet 2000;356:881–7.

Study Overview

Objective. To assess the risk of developing endometrial cancer and the cancer-specific mortality of women who received tamoxifen for the treatment of breast cancer.

Design. Case-control study.

Setting and participants. Cases were identified through the Netherlands Cancer Registry (and its predecessors) and 2 national tumor registries. Case patients developed histologically proven endometrial cancer at least 3 months after being diagnosed with breast cancer. Potential cases were excluded if the patients had other neoplastic diseases (except for carcinoma in situ of the cervix, basal cell carcinoma of the skin, or contralateral breast cancer) occurring between the diagnoses of breast and endometrial cancer. For all but 10 cases, 1 or more controls were enrolled who did not have endometrial cancer and whose dates of breast cancer diagnosis and birth dates corresponded to within 3 years of those of their matching case. Controls were identified through the national cancer registry and tumor registries and the Dutch National Database for Pathology. There were 309 cases and 860 controls.

Main exposures. Exposure to tamoxifen in terms of daily dose, cumulative dose, and duration of therapy.

Main outcome measures. Total cases of endometrial cancer as well as type, stage, and grade, and cancer-related and overall survival. Potential confounders included age, weight, body mass index (BMI), breast cancer stage, menopausal status, parity, exposure to hormone replacement therapy, other hormonal therapy for breast cancer, and pelvic irradiation; these were measured and included in analyses.

Main results. Case patients received their diagnosis of endometrial cancer at a median interval of 40 months (range, 4 to 235 months) after their breast cancer diagnosis. Most women were older than 55 years and postmenopausal at the time they were diagnosed with breast cancer.

The adjusted relative risk for developing endometrial cancer after receiving tamoxifen for more than 2 years compared with never receiving tamoxifen was 2.3 (95% confidence interval [CI], 1.4 to 3.9); for more than 5 years, it was 6.6 (95% CI, 2.2 to 19.7). Detailed analyses support a link between more than 2 years of tamoxifen use and increased risk of endometrial cancer. There did not seem to be a link between dosage and endometrial cancer. When the interval between cancer diagnoses was analyzed, a significant association was seen between 2 to 5 years of tamoxifen use and the development of endometrial cancer 5 years after breast cancer.

Of case patients, 21 died from endometrial cancer, with a 3-year endometrial cancer–specific survival of 76% for 5 years or more of tamoxifen use, 85% for 2 to 5 years of tamoxifen use, and 94% for nonusers ($P = 0.02$). Patients who used tamoxifen for more than 2 years were more likely to have FIGO (International Federation of Gynecology and Obstetrics) grade III or IV tumors (IV being the worst) than nonusers (17.4% versus 5.4%, $P = 0.006$) and more likely to have malignant mixed mesodermal tumors or endometrial sarcomas (15.4% versus 2.9%, $P = 0.02$). These differences seemed to explain most of the increased cancer-specific mortality.

Conclusion

Tamoxifen not only increases the risk of endometrial cancer but also may predispose women to develop tumors with a worse prognosis.

Commentary

Although this study was not very large (309 cases and 21 deaths), it provides the largest analysis of the effects of tamoxifen on the uterus to date. There were no major flaws in the design or the execution of the study; however, the relatively small numbers, particularly in the subgroups of case patients who took tamoxifen for 2 to 5 years ($n = 39$) and for 5 years or more ($n = 15$), make the relatively weak evidence (because of the type of study) weaker. Nonetheless, this evidence is important in light of the conflicting results of 3 large studies assessing tamoxifen use for breast cancer prevention among high-risk women [1–3].

Applications for Clinical Practice

There is no argument over the role of tamoxifen in the treatment of breast cancer. However, the decision of whether to use tamoxifen as primary prevention in high-risk women with

intact uteri should be handled carefully. Bergman and colleagues found a number needed to harm of 500 for excess endometrial cancer and 2000 to 3333 for FIGO stage III/IV tumors. By comparison, the number needed to treat with tamoxifen to prevent a case of breast cancer ranges from 115 to 333 among subgroups who benefited [4]. It should be noted that not all women benefited, even in the positive trial. Given the increased risk of thromboembolic events, tamoxifen use for primary prevention should be decided on a case-by-case basis. Gail and colleagues [5] developed a risk-estimate table that helps to quantify the benefit-to-risk ratio. Forthcoming data should elucidate how best to use tamoxifen for primary prevention.

References

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