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LETTER TO THE EDITOR

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Risk of malignant brain tumor as a second primary is significantly reduced after treatment of breast cancer

To the Editor:

Treatment of glioblastoma, which represents 60%-75% of primary malignant brain tumors, remains unsatisfactory, and overall mortality is high. Standard treatment includes maximal surgical resection, radiation therapy, and chemotherapy with temozolomide. A recent study showed that the addition of bevacizumab (Avastin) to radiotherapy and temozolomide did not improve survival, but did improve progression-free survival, maintenance of baseline quality of life, and performance status. However, the rate of adverse events was higher with bevacizumab than with placebo.[1]

Glioblastoma and breast cancer share pathophysiologic characteristics:

- PTEN, a protein tyrosine phosphatase gene, is mutated in human brain and breast cancer.[2]
- Programmed cell death 4 is an important functional target of the microRNA miR-21 in breast cancer cells. miR-21 stands out as the miRNA most often found overexpressed in solid tumors, and increased levels of miR-21 have been found in very diverse cancer types including glioblastoma and breast cancer.[3]
- An epidermal growth factor receptor-targeted synthetic double-stranded RNA eliminated glioblastoma, breast cancer, and adenocarcinomas in mice.[4]

We now report that the risk of malignant brain tumor as a second primary is reduced after treatment of breast cancer. Our finding suggests that aromatase inhibitor therapy for breast cancer might be helpful to patients with glioblastoma, even though results of treatment with the selective estrogen receptor modulator tamoxifen have been disappointing.[5]

The study population was assembled using records from the surveillance, epidemiology, and end results (SEER) program of the National Cancer Institute. We used SEER program data-base records from patients starting in 1984. A 98% case ascertainment is mandated from 14 population-based registries and three supplemental registries representing approximately 26% of the U.S. population. The SEER registries contain information on patient demographics, tumor site, histology, date and source of diagnosis, date of death, and treatment. Each year quality and completeness studies are conducted in SEER areas to ensure high-quality data.

The SEER program statistical analysis software package (SEER*-Stat, version 8.2.1) was used to identify patients diagnosed with a primary breast cancer from 1973 to 2002 (the histologic subtypes included in analysis were ICD codes 174.0-174.9). Patients with other cancer histologies or whose breast malignancy was not their first primary cancer were excluded from analysis. Second primary cancers diagnosed within 2 months of the breast cancer diagnosis were also excluded. The time to development of second primary malignancies was calculated from the date of diagnosis of breast cancer.

The SEER*Stat Multiple Primary-Standardized Incidence Ratio (MP-SIR) tool was used to calculate SIRs and excess risk for second primary malignancies by comparing these patients' subsequent cancer profile to the number of cancers that would be expected based on incidence rates for the general U.S. population.

Seventy-one cases of ER-positive postmenopausal breast cancer received beam radiation but no surgery, and later developed a malignant brain tumor (Figure 1).

There was a significantly ($P<.05$) reduced observed to expected ratio (O/E) of malignant brain tumors in these time intervals:

- 2-11 months (2 brain tumors, O/E=0.22)
- 60-119 months (20 brain tumors, O/E=0.63)
- 71 total brain tumors all months (O/E=0.72)

There was no significant effect of beam radiation without surgery on the development of a second primary malignant brain tumor

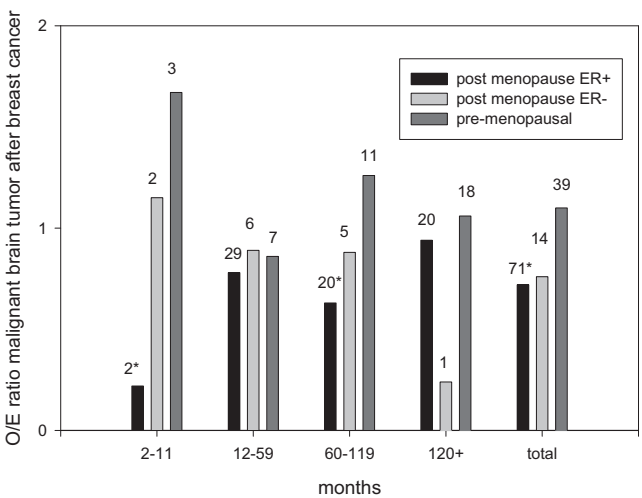

FIGURE 1 Second primary malignant brain tumor in the months following breast cancer treated with beam radiation but no surgery. There was a significantly (*$P<.05$) reduced observed to expected ratio (O/E) of malignant brain tumors only in postmenopausal ER-positive women. ER-negative postmenopausal women were also trending in this direction. Number of cases in each group is above corresponding bar

in postmenopausal women with ER-negative breast cancer, although these women did have a reduced O/E. There was no effect at all on premenopausal women.

Because ER-positive postmenopausal women are routinely given anti-estrogen therapy, our analysis suggests that an aromatase inhibitor can inhibit the development of malignant brain tumor, even though radiotherapy for breast cancer is significantly associated with increased risk of second nonbreast cancer, overall and in organs adjacent to the previous treatment fields.[6] ER-negative postmenopausal breast cancer patients often receive anti-estrogen therapy as well, no doubt responsible for the trend toward reduced second primary malignant brain tumor in this group (Figure 1).

Brain tumors contain estrogen receptors and some of these tumors may respond to estrogen through the cellular estrogen receptor. Aromatase, the enzyme responsible for estrogen biosynthesis, is expressed by human and rat glioblastomas.[7] Estrogen receptors have been identified in the glioblastoma cell line UI38MG. The selective estrogen receptor modulator (SERM) tamoxifen inhibits glioma cell proliferation and induces apoptosis in vitro. Both tamoxifen and a benzopyranone with SERM activity, CC-8490, have been reported to induce apoptosis in vitro and in vivo in ER-negative glioma cells.[8] Tamoxifen also markedly inhibits tyrosine phosphorylation of the neu/c-erbB receptor as well as DNA synthesis and cell proliferation in the malignant glioma cell lines U251-MG and T98G.[9]

Tamoxifen is used to treat both pre- and postmenopausal breast cancer. The aromatase inhibitors anastrozole, letrozole, and exemestane are usually used to treat only postmenopausal women. Postmenopausal women with hormone receptor-positive breast cancer may start hormone therapy with an aromatase inhibitor or tamoxifen; those on tamoxifen may switch after a few years to an aromatase inhibitor.

Tamoxifen has been tested as a treatment for glioblastoma, but the results have not been impressive, probably because tamoxifen is an estrogen receptor agonist and antagonist, as well as a weak carcinogen that increases the risk of endometrial cancer. Pre-clinical studies of letrozole have shown more promise.[10] No investigations of anastrozole or exemestane have been reported.

Besides aromatase inhibitors and tamoxifen, early and locally advanced breast cancers treated with beam radiation are also treated with chemotherapeutic agents, among them cyclophosphamide, docetaxel, doxorubicin, epirubicin, methotrexate and paclitaxel. We hypothesize that the combination of these chemotherapeutic agents and aromatase inhibitors could be beneficial for glioblastoma patients. Further studies would be worthwhile.

CONFLICTS OF INTEREST

No conflicts of interest.

Steven Lehrer MD
Sheryl Green MBBCh
Kenneth E. Rosenzweig MD
Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Correspondence
Dr. Steven Lehrer, Mount Sinai Medical Center, New York, NY, USA.
Email: steven.lehrer@mssm.edu

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