**Risk of Secondary Malignancies after Radiation Therapy for Breast Cancer: Comprehensive Results**

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**Purpose/Objective(s):** To comprehensively assess risks of secondary malignancies (SMs) in breast cancer (BC) patients with and without radiation therapy (RT) with attention to age at diagnosis and latency.

**Materials/Methods:** Using the NCI’s Surveillance, Epidemiology, and End Results (SEER) database, females with a diagnosis of BC as their first malignancy were identified from 1973-2008. Subjects with metastatic disease, age <18 years, no surgical intervention of BC or those who developed a SM within 1 year of BC diagnosis, were excluded from the analysis. Standardized incidence ratios (SIRs) and absolute excess risk (AERs) were calculated using statistical software and cumulative incidence was estimated using survival analysis software.

**Results:** There were 374,504 BC subjects identified in the SEER database meeting the inclusion criteria, and 153,676 subjects received RT. There was an excess risk of SMs in subjects not receiving RT of 9.44 per 10,000 patient-year compared to 34.13 per 10,000 patient-year for subjects receiving RT (P < .01). The majority of SM were breast SMs, with an excess risk of 15.74 per 10,000 patient-year without RT and 29.72 per 10,000 patient-year with RT (P < .01). With a median follow-up of 8.9 years, 51,307 (13.7%) subjects developed a non-breast SM, of which 20,219 (39.4%) subjects received RT and 31,088 (60.6%) did not receive RT; overall, there was a significant increase in risk in SMs in both subjects treated without RT (O/E 1.07, 95% CI = 1.06 - 1.08) and with RT (O/E 1.29, 95% CI = 1.27 - 1.3) compared to the endemic rate. Cumulative incidence of non-breast SMs at 10 years for the subjects not receiving RT compared to RT was 11.4% ± 0.1% and 11.9% ± 0.1% (P < .001) and at 20 years was 23.1% ± 0.1% and 26.4% ± 0.2% (P < .001), respectively. Median age at BC and SM diagnosis was 60 and 71 years, respectively. In subjects without RT there was a significant excess risk of breast, cervix, ovary and endocrine malignancies, and in subjects treated with RT, there was a significant excess risk of esophageal, pleural, soft tissue, bones and joints, melanoma, breast, cervix, ovary and leukemia. Younger age lead to greater risks of SMs in both the RT and no RT cohort (P < .0001). Additionally, longer latency periods led to a more pronounced increased risk of all SMs in BC subjects treated with RT compared to those without RT (P < .0001).

**Conclusion:** There was an overall increased risk of SMs for BC subjects with and without RT compared to the general population. There was a small but significant increased risk in specific sites in patients treated with RT. As expected, this risk was most evident in young pa- tients with increasing length of follow-up. These data quantitate the small yet significant risk of SMs, and largely demonstrate the safety of radiation therapy in this important and common oncologic procedure.