AbstractID: 14515 Title: Genetic Susceptibility, Radiation Exposure and Risk of Second Primary Breast Cancer

Background: Deficiencies in cellular responses to DNA damage can predispose to cancer. Ionizing radiation induces double strand breaks (DSB). Upon activation by DSB-inducing agents, *ATM* (for ataxia-telangiectasia (A-T) mutated) phosphorylates a large number of downstream targets, including the products of several known breast cancer susceptibility genes (e.g., *BRCA1, BRCA2, Chek2, p53).* In this study, we examine whether defects in these breast cancer susceptibility factors are associated with radiation-induced breast cancers. **Methods:** The WECARE Study is a case-control study, nested within 5 population-based cancer registries in the US and in Denmark. The 708 cases were women with asynchronous bilateral breast cancer (CBC) and the 1399 controls were women with unilateral breast cancer (UBC) individually matched to cases on year of birth, race, geographic region, and date of diagnosis (interval). All participants were interviewed, medical records were comprehensively reviewed, and full genetic screening was conducted. For women who received radiation therapy (RT), absorbed radiation doses to quadrants of the (CB) were estimated using dosimetry reconstruction. Rate ratios (RR) and 95% confidence intervals were calculated using multivariable-adjusted conditional logistic regression models. **Results:** The mean dose to the specific quadrant of the CB tumor was 1.1 Gy. Women <40 years of age who received >1.0Gy and with >5 year follow-up had a 3-fold increased risk of CBC (95% CI-1.1-1.8). The RR of CBC associated with carrying a *BRCA1/2* mutation was 4.2 (95% CI=2.8-6.1); however among carriers, radiation was not associated with risk. Among women carrying rare *ATM* missense mutations, the risk of developing CBC was slightly increased, but was significantly elevated among women treated with RT, and strongest for mutations selected on their likelihood to disrupt structure. **Conclusions:** Risk of radiation-associated CBC was inversely related to age at exposure and dose dependent. A subgroup of rare mutations may increase risk of CBC among women with early onset breast cancer treated with RT. However, the fraction of CBC attributed to this is quite small suggesting that radiation contributes little to the already high risk of CBC associated with carrying these breast cancer susceptibility factors.

Learning Objectives:

1. Understand the role of DSB in CBC
2. Understand the basic study design of the WECARE Study
3. Understand the issues relating to genetic susceptibility and CBC risk