Evidence for a link between \textit{TNFRSF11A} and risk of breast cancer

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Abstract Intracellular signaling mediated by the receptor activator of nuclear factor-κB [Rank, encoded by the tumor necrosis factor receptor superfamily, member 11a (Tnfrsf11a) gene] is fundamental for mammary gland development in mice, regulating the expansion of stem and progenitor cell compartments. Conversely, Rank overexpression in mice promotes abnormal proliferation and impairs differentiation, leading to an increased incidence of tumorigenesis. Here, we show that a common genetic variant near the 5' end of \textit{TNFRSF11A}, rs7226991, is associated with breast cancer risk in the general population and among carriers of mutations in the \textit{BRCA2} gene. Akin to the results of the Cancer and Genetics Markers of Susceptibility initiative, combined analysis of rs7226991 in two Spanish case-control studies (1,365 controls and 1,323 cases in total) revealed a significant association with risk: odds ratio (OR) = 0.88, 95% confidence interval (CI) 0.78–0.98, \(P_{\text{trend}} = 0.025\). Subsequent examination of \textit{BRCA1} (\(n = 1,017\)) and \textit{BRCA2} (\(n = 885\)) mutation carriers revealed a consistent association in the latter group: weighted hazard ratio (\(w\)HR) = 0.70; 95% CI 0.55–0.88; and \(P_{\text{trend}} = 0.003\); compared to \textit{BRCA1} mutation carriers, \(w\)HR = 0.91; 95% CI 0.76–1.10; and \(P_{\text{trend}} = 0.33\). The results of this study need to be replicated in other populations and with larger numbers of \textit{BRCA1/2} mutation carriers.

Keywords Breast cancer · \textit{BRCA1/2} mutation carriers · RANK · \textit{TNFRSF11A}

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