

## **CHEK2 mutations and the risk of papillary thyroid cancer**

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Mutations in the cell cycle checkpoint kinase 2 (CHEK2) tumor suppressor gene are associated with multi-organ cancer susceptibility including cancers of the breast and prostate. A genetic association between thyroid and breast cancer has been suggested, however little is known about the determinants of this association. To characterize the association of CHEK2 mutations with thyroid cancer, we genotyped 468 unselected patients with papillary thyroid cancer and 468 (matched) cancer-free controls for four founder mutations of CHEK2 (1100delC, IVS2 + 1G>A, del5395 and I157T). We compared the family histories reported by patients with a CHEK2 mutation to those of non-carriers. A CHEK2 mutation was seen in 73 of 468 (15.6%) unselected patients with papillary thyroid cancer, compared to 28 of 460 (6.0%) age- and sex-matched controls (OR 3.3;  $p < 0.0001$ ). A truncating mutation (IVS2 + 1G>A, 1100delC or del5395) was associated with a higher risk of thyroid cancer (OR = 5.7;  $p = 0.006$ ), than was the missense mutation I157T (OR = 2.8;  $p = 0.0001$ ). CHEK2 mutation carriers reported a family history of breast cancer 2.2 times more commonly than non-carriers (16.4% vs.8.1%;  $p = 0.05$ ). A CHEK2 mutation was found in seven of 11 women (63%) with multiple primary cancers of the breast and thyroid (OR = 10;  $p = 0.0004$ ). These results suggest that CHEK2 mutations predispose to thyroid cancer, familial aggregations of breast and thyroid cancer and to double primary cancers of the breast and thyroid.