**ABSTRACT**
Current evidence supports the hypothesis that chronic inflammation promotes neoplastic transformation of healthy tissue to malignant disease. Papillary Thyroid Carcinoma (PTC) is the most common form of thyroid cancer and up to 30% of cases demonstrate a mutation in the RET receptor kinase (RK) gene. Mutations of the RET-RK produce inflammation, and thus may be the underlying cause of subsequent PTC development. In this study, we performed ELISA to determine serum levels of inflammatory cytokines: IFN-γ, IL-6, IL-10, IL-12, and TNF-α in patients with PTC, benign goiters, and no known thyroid disorder. Analysis of serum levels demonstrated significantly increased levels of IFN-γ, IL-6, and IL-10 in cancer patients when compared to control, as well as a trend of increased levels of TNF-α and decreased IL-12/IL-10 ratio between the same groups. This cytokine profile is reflective of an inflammatory immune response. Additionally, IFN-γ normally induces anti-tumor effects on tumors via the STAT1 pathway. However, in the absence of STAT1 IFN-γ promotes tumor proliferation and survival via the STAT3 pathway.

**BACKGROUND**
Previous studies have demonstrated a strong relationship between chronic inflammation and the subsequent development of cancer. In thyroid cancer, patients previously diagnosed with benign thyroid disorders such as goiter or nodules have been found to have an increased risk of developing malignant disease. Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy in humans. Rearrangements of the RET-RK gene occurs in up to 30% of all PTC cases. Previous studies have demonstrated that normal thyrocytes expressing a mutation in the RET receptor kinase exhibit a transcriptional program related to inflammation.

In this study, we performed ELISAs to determine the level of cytokines associated with inflammation. IFN-γ, IL-6, IL-10, IL-12 and TNF-α in patients with PTC, benign goiters, or no known thyroid disorder. Elevated levels of TNF-α, IL-6, and IL-10 are classically associated with inflammatory responses and IL-12 levels are normally decreased. IFN-γ has been demonstrated to have both pro-inflammatory and anti-inflammatory effects, depending on the availability of the STAT3 and STAT1 pathways.

**METHOD**
Blood samples were obtained from PTC, benign goiter, and healthy control patients. Controls were serum specimens from patients who attended the ENT clinic, but had no known condition that would alter serum cytokine levels. Plasma was immediately separated from the blood after collection by centrifugation at room temperature. All samples remained frozen at -80°C until cytokine levels were quantified by ELISA. Cytokine levels for IFN-γ, IL-6, IL-10, IL-12 and TNF-α were measured in duplicate for each patient. Statistical analyses were conducted by an unpaired t-test and post-hoc comparisons conducted with Bonferroni’s correction as appropriate to determine significance.

**CONCLUSIONS**
- Serum levels of IL-6, IL-10, and IFN-γ are significantly elevated in PTC patients as compared to controls.
- Serum levels of TNF-α demonstrate an elevated trend in PTC patients as compared to controls.
- Serum IL-12/IL-10 ratios demonstrate a decreased trend in PTC patients as compared to controls.
- PTC patients, as compared to controls, demonstrate cytokine levels reflective of an inflammatory immune response.
- Although not significantly different than controls, benign goiter patients also appear to demonstrate cytokine levels reflective of an inflammatory immune response.

**FUTURE STUDIES**
- To analyze serum cytokine levels between PTC patients with compromised integrity of the RET receptor kinase gene and PTC patients with no mutation.
- To determine whether a M1 or M2 macrophage response is occurring in PTC by immunohistochemistry
- To determine if IFN-γ is signaling similar to IL-6 via STAT3 during the inflammatory process in PTC.