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Interactive effects of 1, 25-dihydroxyvitamin D3 and soy protein extract (SPE) on oral cancer growth in vitro: evidence for potential functional relationships.

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ABSTRACT:

Background: Previous studies have found specific soy isoflavones (Genistein, Daidzein, Glycitein) demonstrate anti-tumor properties against several cancer types, including oral cancer. Few studies have evaluated whole soy extract, containing a combination of these isoflavones and other bioreactive compounds, which may function synergistically and more effectively against oral cancers. Preliminary work by this group has now demonstrated whole soy protein extract (SPE) inhibits oral cancer cell growth specifically and selectively, through independent cell-cycle and apoptotic pathways. However, more recent evidence now suggests that ingestion of vitamin D_3, either in dietary foods or supplements may potentiate the activity of soy components and their anti-tumor effects.

Objective: The primary goal of this study was to investigate the interactive and inter-connected effects of 1, 25-dihydroxyvitamin D_3 administration with the anti-proliferative effects of whole soy protein extract (SPE) on oral cancer and normal cell lines *in vitro*.

Methods: Three oral squamous cell carcinoma cell lines (SCC15, SCC25, and CAL27) were treated with 1, 25-dihydroxy Vitamin D_3 at physiological concentrations (10-125 nmol). Cell growth was then compared with cell treatment using soy protein extract (SPE) within the normal physiologic range (0 - 10 μM/L). Interactive effects were then evaluated using co-administration of SPE and 1, 25-dihydroxy Vitamin D_3. Quantitative RT-PCR was performed at various time points to determine any changes in mRNA expression for key cell cycle and apoptotic signaling

pathway regulators, including *p53, c-myc, ornithine decarboxylase (ODC), caspase-2, caspase-8,* and *bax.*

Results: Administration of 1, 25-dihydroxy Vitamin D_3 induced distinct dose-dependent, growth-inhibitory effects in all three oral cancer cell lines examined. These inhibitory effects were comparable to the overall range of growth inhibition induced by SPE. However, the combined effects of co-administration were far greater, suggesting the presence of synergistic relationships between these components. In addition, these results indicate that either treatment alone appeared to modulate mRNA expression of oral cancer cell-cycle promoters *c-myc* and *OD*C, as well as the *caspase*-dependent apoptosis pathway, while only 1, 25-dihydroxy Vitamin D_3 administration appeared to influence the *bax* pathway.

Conclusion: These results suggest that co-administration with 1, 25-dihydroxy Vitamin D_3 and SPE may enhance their anti-tumor effects. This study may help to explain, in part, why balanced diets rich in fruits, vegetables, and soy protein, are associated with protection against development and progression of oral cancers, although further study is needed to develop specific public health recommendations for oral cancer treatment and prevention.

Key words: vitamin D, soy extract, whole soy protein, oral cancer, growth inhibition.