

headandneck 5000

Vitamin D and head and neck cancer risk and progression: An examination of causality and mechanisms.

Principle applicant: Tom Dudding

Co-applicants: Steve Thomas, Richard Martin, Nic Timpson, Paul Brennan

Scientific outline

Summary: Head and neck cancer (HNC) is the world's sixth most common cancer and is rising in incidence, more than 600,000 new patients are diagnosed and approximately 350,000 die from this disease annually. Survival rates for HNC are low (<50% 5-year survival) and progression factors for this disease are not well characterised.

Recent epidemiological studies and several basic science studies have reported strong associations between vitamin D and HNC risk and progression, although no causal link has been established.

Vitamin D is a pro-hormone with a role in calcium and phosphate balance. However in vitro and in vivo studies have also shown anticarcinogenic effects. Vitamin D is thought to affect multiple biological pathways via intermediates. Some of these, including insulin-like growth-factor-binding-protein-3, are potentially important intermediates in HNC risk and progression.

This study will investigate the intermediates that are altered by vitamin D and therefore have the potential to explain its association with HNC. Mendelian randomization will be utilised to quantify the causal association between vitamin D and HNC progression. Factors that either mediate a causal effect or explain a non-causal association between vitamin D and HNC progression will be identified.

1) Investigating the causal effect of vitamin D on HNC progression. 2-sample MR will be conducted in all suitable HNC patients in HN5000 to investigate the casual effect of vitamin D on 3-year cancer recurrence or survival. This endpoint is selected as the majority of HNC recurrence and death occurs within the first 3 years. Results will be replicated in UK Biobank. Further work will stratify results by cancer site to assess site-specific associations.

2) Investigating factors identified as being associated with vitamin D either mediate a causal effect or explain a non-causal association between vitamin D and HNC progression.

In the presence of a causal effect of vitamin D on HNC progression: Intermediates identified as causally affected by vitamin D will be investigated using 2-step MR to identify whether they are on the causal pathway between vitamin D and HNC progression.

If the relationship between vitamin D and HNC progression is found to be non-causal: Intermediates identified as causally affecting vitamin D will be investigated using MR to see if they are causally related

to HNC and therefore explain the non-causal association between vitamin D and HNC (i.e. confound this association).

