

## Summary

Interindividual variations in radiotoxicity responses exist despite uniform treatment protocols. It is speculated that normal genetic variants, particularly single nucleotide polymorphisms (SNPs) may influence normal head and neck (HN) tissue radiotoxicity. This first-ever systematic review was undertaken to evaluate the association of SNPs with normal HN tissues radiotoxicity. Multiple databases (1950–February 2012) were reviewed using a combination of related keywords and MeSH terms. All published HN radiotoxicity studies with sufficient relevant data for extraction were included. The outcomes evaluated were acute and late radiotoxicity endpoints. Methodological quality assessment based on the STrengthening the REporting of Genetic Association (STREGA) statement was performed. Seven articles from 692 articles searched fulfilled the eligibility criteria. Recruited sample sizes were small (range, 32–140). There were 5/7 case-control studies. All studies used multimodality treatment with heterogeneous radiation parameters. Candidate gene approach was used in all studies. Fourteen SNPs from 9 genes were evaluated from the following pathways: DNA damage response, radiation fibrogenesis and oxidative/xenobiotic metabolism. Acute radiotoxicity events were associated with SNPs of DNA repair genes (OR, 3.01–4.08). SNPs of TGF $\beta$ 1 were associated with osteoradionecrosis (OR, 4.2) and subcutaneous fibrosis. Genetic association studies in HN radiotoxicity currently provide hypothesis-generating findings that require validation in larger studies. Future studies must incorporate critical methodological issues and technological improvements, including using a genome-wide approach. Headway is possible through case-pooling of existing clinical trial data which could create a larger sample size of well-characterized treatment and endpoints. Also, on-going HN cancer clinical trials should consider extending their toxicity evaluation to include genetic association studies.