

Alcohol-containing mouthwash and oral cancer – can epidemiology prove the absence of risk?

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Re: Gandini S, Negri E, Boffetta P, La Vecchia C, Boyle P, 'Mouthwash and Oral Cancer Risk - Quantitative Meta-analysis of Epidemiologic Studies', in: *Ann Agric Environ Med* 2012; 19(2): 173-80.

Gandini et al. [1] are to be commended for providing the most detailed meta-analysis of epidemiological studies about the connection between mouthwash use and oral cancer risk.

The result (i.e. the absence of an association between use of alcohol-containing mouthwash and risk) was not completely unexpected, based on previous meta analyses financed by manufacturers of this type of mouthwash [2, 3, 4, 5], which were critically scrutinized in the past as the outcomes were often more favourable than in independently financed studies [6]. Nevertheless, no obvious industry bias was recognizable in the current piece and, especially, the authors have clearly separated alcohol-containing from alcohol-free mouthwashes in their analysis.

Based on mechanistical studies conducted by my group, the question arises, nevertheless, whether the effort was not doomed to failure from the beginning, and if the conclusion of the authors to undertake further epidemiological studies can be maintained, considering available data from quantitative risk assessment using toxicological methods.

One of the major mechanisms leading to the carcinogenicity of alcohol (ethanol) is the formation of acetaldehyde as first metabolite [7, 8, 9]. Indeed, my group has shown that the use of an alcohol-containing mouthwash leads to short-term formation of acetaldehyde in the oral cavity, which is detectable in the saliva for up to 10 min [10]. This finding was independently confirmed by two other research groups [11, 12]. Based on the acetaldehyde exposure in saliva and using a methodology of the EU's scientific committee on cosmetic products and non-food products intended for consumers (SCCNFP), we had estimated the lifetime cancer risk for twice-daily alcohol-containing mouthwash use (and including additional acetaldehyde exposure from other cosmetics) as being 3-4 cases per 1,000,000 [10] [10]. If looking at the case numbers of the meta analysis (Table 1 in Gandini et al. [1]), the largest study investigated 918 cases vs. 2,752 controls [13].

If we are correct with our risk estimation, it is obvious that even the combination of all studies in the meta-analysis (4,484 cases vs. 8,781 controls) would not be sensitive enough to detect such a small risk. In my opinion – independent of the availability of funding for the required large-scale studies

– it will probably never be possible to epidemiologically detect the low risk of alcohol-containing mouthwash, even with the most advanced statistical methodology in light of confounders such as drinking and smoking that may contribute to the same mechanism of carcinogenicity (acetaldehyde exposure).

In conclusion, the main question centres around what would be an acceptable risk for genotoxic carcinogens, such as acetaldehyde? Is the safety margin of some cases per million acceptable or not in light of the many million mouthwash users worldwide? Some authors have suggested that at least high risk populations (children, alcohol dependent persons, and persons with genetic deficiencies in acetaldehyde metabolism) should use alcohol-free mouthwashes for the maintenance of oral health [14], while others felt it completely inadvisable for oral healthcare professionals to recommend the long-term use of alcohol-containing mouthwashes [15]. Apart from these considerations for the individual, the risk of alcohol-containing mouthwash for public health appears very low compared to other routes of exposure to alcohol and acetaldehyde, so that priority for risk management actions should be placed rather on reducing alcohol consumption and smoking.

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