



Review

Clinical application of micronucleus test in exfoliated buccal cells: A systematic review and metanalysis

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ABSTRACT

The micronucleus assay in uncultured exfoliated buccal mucosa cells, involving minimally invasive sampling, was successfully applied to evaluate inhalation and local exposure to genotoxic agents, impact of nutrition and lifestyle factors. The potential use of the assay in clinics to monitor the development of local oral lesions and as an early biomarker for tumors and different chronic disorders was also investigated. A systematic review of the literature was carried out focusing on the clinical application of the assay. The literature search updated to January 2015 allowed to retrieve 42 eligible articles. Fifty three percent of investigations are related to oral, head and neck cancer, and premalignant oral diseases. Our analysis evidences a potential usefulness of the MN assay applied in buccal exfoliated cells in the prescreening and in the follow up of precancerous oral lesions. A significant excess of MN, in patients compared with matched controls was observed for subgroups of oral and neck cancer (meta-MR of 2.40, 95% CI: 2.02–2.85) and leukoplakia (meta-MR 1.88, 95% CI: 1.51–2.35). The meta-analysis of studies available on other tumors (meta-MR 2.00; 95% CI:1.66–2.41) indicates that the MN frequency in buccal cells could reflect the chromosomal instability of other organs. Increased MN frequency was also observed in small size studies on patients with chronic diseases, with Alzheimer's disease and with Down syndrome. The application of the cytome approach providing information of genotoxic, cytotoxic and cytostatic effects is suggestive of the possibility of an improvement in the predictive value of the assay and this deserves further investigations.

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1. Introduction

The cytokinesis-block micronucleus (CBMN) assay, due to its ability to detect both structural and numerical chromosomal alterations in human peripheral lymphocytes, is the best validated method in monitoring recent exposure of individuals to chemical and physical genotoxic agents [1–3]. The CBMN assay was also proposed as a marker of risk of developing cancer and other chronic diseases. Many studies showed increased MN frequency in untreated patients with cancer [4,5], neurodegenerative diseases [6], cardiovascular disease, diabetes [7]. Moreover elevated MN frequencies in peripheral lymphocytes of healthy subjects have been shown to reflect genomic instability and a higher risk of developing cancer later in life, suggesting a predictive role of the assay [8].

The use of surrogate cells, other than lymphocytes, such as exfoliated cells from epithelial tissues is of particular interest because they can be collected with non-invasive methods and is being explored with the aim to evaluate their suitability in biomonitoring studies [9,10].

The application of the MN test in uncultured buccal exfoliated cells, started in the 1980s, to assess local exposure to genotoxic agents, impact of nutrition and lifestyle factors [11,12]. Increased MN frequency was detected in buccal cells of subjects affected by cancer-associated congenital syndromes characterized by defects in genes encoding for DNA-repair processes, such as ataxia telangiectasia [13,14] Bloom's syndrome [15], xeroderma pigmentosum [16], suggesting a role of the assay in detecting chromosomal instability. The test is nowadays widely applied in biomonitoring inhalation and local exposure to environmental and occupational genotoxic agents [9]. A growing interest in this assay in the last years was also associated with the follow up of oral cancer and premalignant lesions. MN frequency in buccal cells was shown to be a prognostic marker for mouth diseases and cancer in a number of studies [17–19] and seems to be a good candidate for oral cancer biomonitoring. The oral epithelium is the target for the development of lesions characterized by different clinical outcome and grade of malignancy due to the frequent exposure to mechanical, chemical and thermal insults [20–22]. Some of oral lesions such as leukoplakia, oral lichen planus and oral submucous fibrosis were defined as premalignant and were associated with an increased risk of developing oral squamous cell carcinoma [20–22]. The use of specific biomarkers to complement clinical analyses could be relevant to identify individuals who are at increased risk for cancer.

The MN assay in buccal cells was also applied in groups of patients with tumors in different regions of the body other than head and neck to explore the suitability of this biomarker as an index of cancer risk/susceptibility [23–31]. In addition, an increase of MN frequency was observed in a number of studies on diabetes [32–34] and different chronic diseases [35–40]. Nuclear alterations and different chromatin status have been characterized in exfoliated buccal cells as markers of cytotoxic effects, pyknosis, karyolysis and karyorrhexis representing different degenerative and/or adaptive cellular death phenomena [41,42].

The “cytome” approach involving the evaluation of different cell types and nuclear anomalies associated with cell proliferation, differentiation and cell death was applied in a number of studies, although the biological meaning of these parameters was not completely explored.

The aim of the present study was to retrieve, review and analyze the published studies on the application of the MN test in buccal cells focusing on clinical application to investigate:

- the usefulness of this assay for the identification of individuals at increased risk of developing oral cancer and head and neck cancer,
- the potential use of this test as a marker of risk/susceptibility for cancer other than oral and head and neck, and degenerative diseases.
- The advantage of using the cytome approach in clinical application of the MN test in exfoliated buccal cells.

2. Materials and methods

2.1. Search strategy, eligibility criteria and study selection

This systematic review follows the methodology described in the PRISMA statement [43]. A literature search through electronic databases MedLine/PubMed, TOXLINE was carried out up to January 2015. Key search terms included “micronucleus” and “micronuclei” in combination with “buccal” and “exfoliated”. A manual search of the reference list of studies and review articles was subsequently performed. References of retrieved articles were also analyzed to identify any publications which may have been potentially missed in the initial search. The first author (C.B.) did the initial selection based on titles and abstracts. Eligible for the inclusion in the present review were all studies which concerned clinical application of the MN test in exfoliated buccal cells in which the MN frequencies were available in untreated patients and matched control groups. Only studies in English where the full text was available were considered. Full text articles were assessed for the inclusion in the analysis independently by three reviewers (C. B.; M.C.; M.B.) with all the discrepancies resolved through a discussion. The selected articles were analyzed with respect to their quality and included in the review if the experimental protocol and the scoring criteria applied was adequate, and the exposed-control matching was based on the main confounding factors for the assay (age, sex and smoking status).

2.2. Statistical methods

We computed for each study the Mean Ratio (MR_i) as the effect estimate:

$$MR_i = \frac{MN \text{ mean}(\text{patients})}{MN \text{ mean}(\text{controls})}$$

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