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ORIGINAL RESEARCH

# Micronuclei in the Oral Mucosa as a Measure of Genotoxic Damage in Dental Radiography: A Clinicopathologic Study

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## ABSTRACT

**Introduction:** The ill effects of X-rays have been well documented since the early days following their discovery. Conventional radiography is now being replaced by digital radiograph leading to reduced radiation doses. However, no amount of radiation exposure can be considered completely safe. A sensitive analysis and a specific approach are thereby required to detect the effect of low dose diagnostic radiation exposure.

**Aim:** To evaluate the frequency of micronuclei in buccal and palatal epithelium before and after digital panoramic radiography (DPR).

**Materials and methods:** The study was conducted in a private dental college, Faridabad, India. The Study group comprised of 60 patients (N = 60) which were randomly selected from those reporting to the Department of Oral Medicine and Radiology for digital panoramic radiography (DPR). For each individual, a scraping from buccal and palatal mucosa was taken using a wooden spatula. The prepared slides were viewed under magnification by light microscope for determination of micronuclei from the buccal and palatal epithelium.

**Results:** The comparison of the micronuclei count in the buccal and palatal mucosa before and 10–12 days after digital panoramic radiography revealed statistically significant ($p < 0.001$) results.

**Conclusion:** The application of the micronuclei test in epithelium cells is considered to be a sensitive tool for analyzing the genetic damage.


**K**eywords: Digital panoramic radiography, Micronuclei count, Oral mucosa.

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## INTRODUCTION

The fortuitous 'chance' discovery of X-rays by Wilhelm Conrad Roentgen on November 8, 1895, revolutionized the practice of medicine. Though accidental, this discovery was the culmination of years of path-breaking research by several physicists and scientists. The discovery of X-rays and their subsequent extensive use by the medical profession was followed by the evidence of their side effects. The ill effects of X-rays have been well documented since the early days following their discovery. Ionizing radiations are a renowned mutagen and carcinogen in human beings. Evolution has occurred from conventional to digital radiography leading to reduced radiation dose. However, no amount of radiation exposure can be considered completely safe. A sensitive analysis and a specific approach are thereby required to detect the effect of low dose diagnostic radiation exposure. Genetic alterations, such as chromosomal aberrations and formation of micronuclei in cell cytoplasm are the biological markers of early carcinogenesis.[1]

An increased frequency of chromosome breaks has been recently demonstrated to be an initial event in carcinogenesis, suggesting that these alterations may play a significant role in assessing the oncogenic risk of the patients exposed to carcinogens (e.g., radiation).[1] Among biomarkers that can be used for this purpose, the counting of micronuclei (MN) appears to be one of the most suitable. The measurement of MN in peripheral blood lymphocytes (PBL) is a well-established tool in human biomonitoring.[1] However, human lymphocytes, which are the most commonly used cells for cytogenetic monitoring, appear to be an inapt cell population for analyzing the genotoxic effects of radiographic examinations of the oral cavity as they are not the primary target for radiation-induced damage in the oral cavity.[2]

Buccal and palatal epithelial cells provide a substitute for monitoring occupational and environmental radiation exposures. They are inescapably exposed in dental radiography and thus are a primary target for radiation-induced damage. They are easily accessible for cytological exami-

nation using standard techniques.[3] Damage can lead to micronuclei formation in the basal layer of the epithelium, where cells undergo mitosis. Superficial buccal cells exfoliate continuously and are replaced by cell division of the basal stem cells. When the basal cells multiply; the damaged and fragmented chromosomes become lost during the anaphase stage of cell separation and are excluded from the reforming nuclei. The laggards are observed in the cytoplasm as micronuclei.[4] The maximum number of micronuclei formation is seen in exfoliated cells after 1–3 weeks of exposure to the genotoxic agent. Since it is known that radiation is genotoxic and mutagenic, it is important that any diagnostic radiography should be used only after careful consideration of the patient's history and consideration of both the dental and general health needs of the patient. Genotoxic effects subsequent to low dose radiation exposure have been observed in both patients[3] and exposed workers.[5] The assessment of micronuclei in exfoliated cells is a promising tool in monitoring the genotoxic effects caused due to ionizing radiations. These effects have been assessed in various studies using micronuclei test in patients exposed to radiography but evidence of genotoxic damage is not certain.[2,6,7] Hence this study was aimed to evaluate the frequency of micronuclei in the buccal and palatal epithelium in different age groups before and after digital panoramic radiography (DPR).

## MATERIALS AND METHODS

The study was conducted in a private dental college, Faridabad (India). The Study group, which comprised of 60 patients (N = 60), were randomly selected from those reporting to the Department of Oral Medicine and Radiology for DPR. Subjects were divided into three subgroups depending upon age. These groups comprised of group 1 (20 subjects with age ranging from 10–25 years), group 2 (20 subjects with age ranging from 26–40 years) and group 3 (20 subjects above 40 years of age).

**Table 1:** Parameters for cell inclusion in cells to be scored

| | |
|---|---|
| (a) | Intact cytoplasm and relatively flat cell position on the slide. |
| (b) | Little or no overlap with adjacent cells |
| (c) | Little or no debris. |
| (d) | Nucleus normal and intact, nuclear perimeter smooth and distinct. |

The study was approved by the Institutional Ethical Committee, and informed consent was taken from each participant of the study.

Inclusion Criteria included any individual reporting to the department for digital panoramic radiography. Exclusion criteria included patients who have undergone any diagnostic radiography in the past 1 month, patients with a history of past or present potentially malignant disorders/malignancy of the oral cavity or orofacial region, patients with history of tobacco/alcohol in any form, patients with history of radiotherapy in Head & Neck area and pregnancy.

The mucosal cell sample for analysis was taken in which loose cells were scraped off from the buccal mucosa, and hard palate with the help of a wooden spatula and the two pairs of cytosmears were made at two different times, i.e., before and 10–12 days after the patients underwent Digital Panoramic Radiography. Method of staining procedure was PAS stain using Fuelgen-Rossenbeck reaction. The feulgen stain was favored in this study because of its DNA specificity and easy identification of micronuclei.

### Scoring of Micronuclei

The criteria developed by Tolbert et al. was used for micronucleus scoring (Table 1).[7]

For screening of slides zigzag method was used. In this method, for each individual, a minimum of 500 cells each from buccal and palatal epithelium was studied by blind analysis. The prepared slides were viewed under magnification by light microscope for determination of micronuclei using 40x Objective lens and 10x Eyepiece; thus a total Magnification of 400x (Fig. 1).

### Statistical Analysis

The statistical analysis was carried out using Statistical Package for Social Sciences (SPSS version 18.0 for Windows) with suitable statistical formula's. A *p* value of less than 0.05 was considered to be statistically significant.

## RESULTS

Table 2 shows the comparison of micronuclei count in the buccal and palatal mucosa before and 10–12 days after Digital Panoramic Radiography which was found to be statistically significant.

Table 2: The comparison of micronuclei (MN) count in buccal and palatal mucosa before and 10-12 days after digital panoramic radiography (DPR) in study group

| | | *Mean MN count* | *Total sample size (N)* | *Std. deviation* | *p value* |
|---|---|---|---|---|---|
| Buccal Mucosa | MN count before DPR | 1.55 | 60 | 0.910 | <0.001 |
| | MN count 10–12 days after DPR | 3.75 | 60 | 1.230 | |
| Palate | MN count before DPR | 0.98 | 60 | 0.792 | <0.001 |
| | MN count 10–12 days after DPR | 2.03 | 60 | 0.736 | |

Graph 1 shows the comparison of micronuclei count between buccal and palatal mucosa. The *p* value of micronuclei counts in buccal and palatal mucosa before and 10–12 days after Digital Panoramic Radiography was less than 0.001 which was statistically significant.

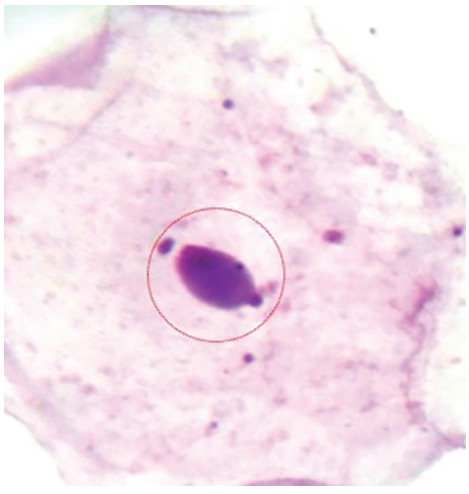
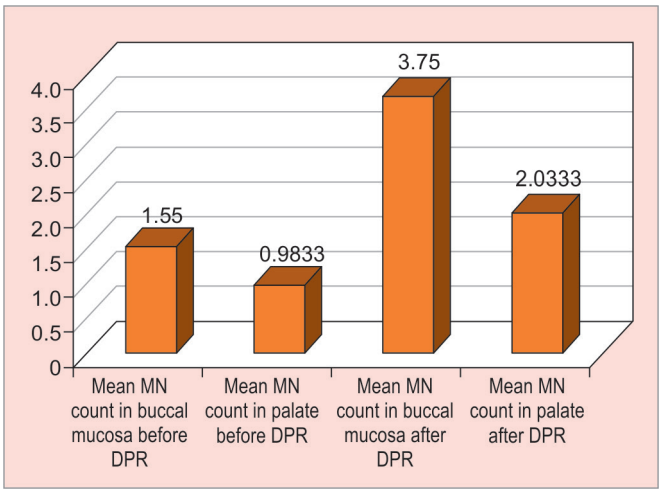


**Fig. 1:** Photomicrograph with micronuclei in buccal mucosa after DPR

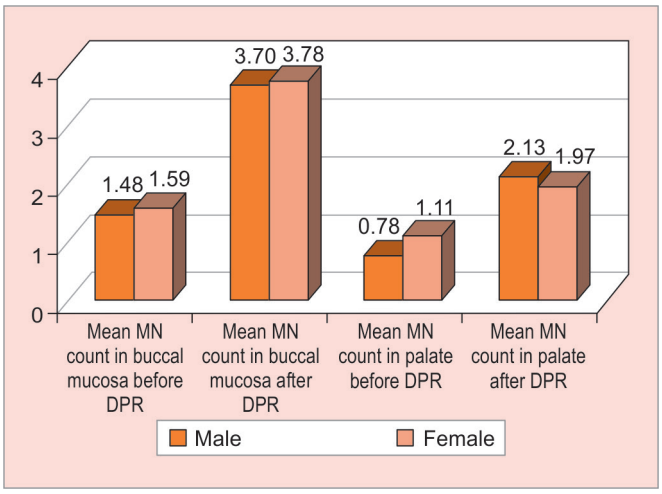
Graph 2 shows the comparison of micronuclei count in both the genders in buccal and palatal mucosa before and 10–12 days after Digital Panoramic Radiography. The *p* values of micronuclei count in males and females in buccal and palatal mucosa before and 10-12 days after DPR were statistically insignificant.

Table 3 shows the intergroup comparison of mean micronuclei count in three age groups (groups 1–3) containing 20 subjects each in buccal and palatal mucosa before and 10–12 days after DPR. This depicts that mean values of MN count was higher in older age groups as compared to younger age groups.

Table 4 depicts the comparison of micronuclei counts within three age groups using analysis of variance (ANOVA) test in buccal and palatal mucosa before and 10–12 days after DPR. Though the mean values of MN




Graph 1: Shows the comparison of micronuclei (MN) counts in buccal and palatal mucosa




**Graph 2:** The estimation of micronuclei (MN) count in both genders in buccal mucosa and palate before and 10-12 days after DPR

**Table 3:** The intergroup comparison of micronuclei (MN) count in three age groups in buccal and palatal mucosa before and 10-12 days after digital panoramic radiography (DPR)

| *Age groups* | | *Sample size (N)* | *Mean MN count* | *Std. deviation* |
|---|---|---|---|---|
| MN count in buccal mucosa before DPR | 10–≤25 Years | 20 | 1.65 | 1.09 |
| | 26–40 Yrs | 20 | 1.30 | 0.80 |
| | >40 Yrs | 20 | 1.70 | 0.80 |
| | Total | 60 | 1.55 | 0.91 |
| MN count in buccal mucosa 10–12 days after DPR | 10–≤25 Years | 20 | 3.45 | 1.50 |
| | 26–40 Years | 20 | 3.75 | 1.29 |
| | >40 Years | 20 | 4.05 | 0.76 |
| | Total | 60 | 3.75 | 1.23 |
| MN count in palate before DPR | 10–≤25 Yrs | 20 | 0.95 | 0.76 |
| | 26-40 Years | 20 | 0.80 | 0.77 |
| | >40 Years | 20 | 1.20 | 0.83 |
| | Total | 60 | 0.98 | 0.79 |
| MN count in palate 10–12 days after DPR | 10–≤25 Years | 20 | 1.95 | 0.60 |
| | 26-40 Years | 20 | 2.05 | 0.76 |
| | >40 Years | 20 | 2.10 | 0.85 |
| | Total | 60 | 2.03 | 0.74 |

**Table 4:** The comparison of micronuclei (MN) count in study group within age groups using ANOVA test

| | | *p value* |
|---|---|---|
| MN count in buccal mucosa before DPR | Between Groups<br>Within Groups | 0.323 |
| MN count in buccal mucosa 10–12 days after DPR | Between Groups<br>Within Groups | 0.309 |
| MN count in palate before DPR | Between Groups<br>Within Groups | 0.276 |
| MN count in palate 10-12 days after DPR | Between Groups<br>Within Groups | 0.811 |

count were higher in older age groups, it was not statistically significant.

## DISCUSSION

The saddest aspect of life right now is that science gathers knowledge faster than society gathers wisdom–Issac Asimov.

Ionizing radiation has been portrayed as a double-edged sword. Although the radiation is extensively used for diagnostic and therapeutic purposes, there is a great concern about the potential harmful effects. exposure to high doses of ionizing radiation has been found to act as a carcinogen and evidently cause adverse effects in humans. On the contrary, the effect of a very low dose of radiation is not very clear, and no amount can be considered completely safe. Chromosomal aberrations are a frequent and significant response on exposure to mutagenic agents. They are of significance from the standpoint of inherited human disease and have been implicated in carcinogenesis. The oral cavity/oral mucous membrane is subjected to the burden of radiation during diagnostic dental imaging (intraoral periapical radiography, bitewing radiography, occlusal radiography, panoramic radiography, skull views, TMJ views and specialized radiographic techniques of head and neck).

Panoramic dental radiography is being considered less harmful than taking multiple periapical radiographs as in a full-mouth survey. However, it is of concern that panoramic radiography is widely used because of its easy availability. Though this technique allows for the reduction of radiation exposure to the patient, radiation genotoxic effects following low-dose medical exposure have been detected in both patients and exposed workers.[8] Since it is known that radiation is genotoxic and mutagenic, it is important that any diagnostic radiography should be used only after careful consideration of both the dental and general health needs of the patient.

Currently, there are many established methods for assessing the mutagenic potential of physical and chemical agents. These include DNA aneuploidy, Barr bodies, and other nuclear abnormalities. A sensitive analysis and a specific approach are thereby required to detect the effect of low dose diagnostic radiation exposure. Among biomarkers that can be used for this purpose, the counting of micronuclei (MN) appears to be one of the most suitable. Micronuclei originate from chromosome fragments or whole chromosomes that are not included in the main daughter nuclei during nuclear division. They reflect chromosome damage and may thus provide a marker of early-stage carcinogenesis. Genetic damage is the most important fundamental cause of developmental and degenerative diseases. The genomic damage is caused by environmental exposure to genotoxins, radiation and chemicals, micronutrient deficiency, lifestyle factors such as alcohol, smoking, drugs and stress and defects in DNA.[9] Micronucleated cell indexes may reveal unstable genome, although the exact mechanisms are unknown.[10] On the whole, an increased frequency of micronuclei indicates an increased risk of malignancy.[11] The assessment of micronuclei in exfoliated cells is a promising tool in monitoring the genotoxic effects caused due to ionizing radiations. These effects have been assessed in various studies using micronuclei test in patients exposed to radiography, but evidence of genotoxic damage is not certain.[2,6] Hence the requirement of the study was to evaluate the frequency of micronuclei in buccal and palatal mucosa in different age groups before and after DPR.

The comparison of the micronuclei count in the buccal and palatal mucosa before and 10–12 days after Digital Panoramic Radiography revealed that the mean micronuclei count in buccal mucosa was 1.55 pre-exposure, and it was 3.75 post-exposure. Similarly, the mean micronuclei count in palatal mucosa was 0.98 before Digital Panoramic Radiography (DPR) and 2.03 after DPR. The prepared slides were viewed under magnification by light microscope for determination of micronuclei the increase in the mean micronuclei counts in both the sites post-exposure to DPR was statistically significant ($p < 0.001$) (Table 2) (Graph 1). This was in concurrence with studies carried out by Madhavan et al. in 2012[12] and Waingade et al. in 2012[13] who also found a statistically significant increase in the micronucleus frequency in cells of non-keratinized mucosa after 10 ± 2 days post-exposure. The findings are suggestive that panoramic dental radiography may induce genotoxic effects on the oral mucosal cells. The population characteristics and methodological aspects like differences in the sites, collection of the cells, fixing techniques, various staining procedures, number of cells counted and scoring criteria for MN, etc., may also affect the results.[14] Alterations in DNA repair genes may influence an individual's DNA restoring ability and risk of

cancer.[15] It should also be taken into consideration that each patient has a unique level of contact with genotoxic agents capable of producing changes in cells in the oral mucosa. The results reported by different studies vary because genotoxic effects depend on the type, amount and radiation dose absorbed, on the type of cell affected, and on the individual's capacity to withstand the action of genotoxic agents.[16] Biomonitoring studies of subjects exposed to radiation are relatively hard and specific because each population is exposed to different radiation doses. Thus explaining why some researchers found an increase of genetic damage in populations exposed to X-rays.[17] On intersite comparison, the mean micronuclei count was higher in the buccal mucosa both before (1.55 *vs.* 0.98) and after DPR (3.75 *vs.* 2.03) when compared to the palatal mucosa. Both these differences were statistically significant. The pre-exposure Mean MN count difference between buccal and palatal mucosa though statistically significant would need further investigation for confirmation. In this study, a higher frequency of micronuclei obtained from the buccal epithelial cells after radiation exposure can be explained by the direct absorption of X rays by epithelial cells. Studies carried out by Cerqueira et al. in 2004[9] and Angeliri et al. in 201018 also found an increase in the micronuclei count in exfoliated buccal epithelial cells, immediately before and 10–12 days after exposure during panoramic dental radiography though their results were not statistically significant. Hence, here findings were in accordance with literature that showed the ionizing radiation due to panoramic imaging was capable of inducing genotoxic effects in the oral mucosal cells.

The study also compared the micronuclei (MN) counts between two genders in buccal mucosa and palatal mucosa before and 10–12 days after DPR. There were 23 males and 37 females out of a total of 60 subjects. The mean micronuclei count in buccal mucosa before DPR was 1.48 and 1.59 in males and females respectively ($p$ = 0.634) and 10-12 days after DPR, counts increased to 3.70 and 3.78 respectively ($p$ = 0.79). The mean MN count in palatal mucosa before DPR was 0.78 and 1.11 in males and females respectively ($p$ = 0.122) and 10–12 days after DPR, the counts increased to 2.13 and 1.97 respectively ($p$ = 0.425). The comparisons revealed the $p$ values to be statistically insignificant (Graph 2). In this study, no significant correlation was found between the gender and MN count. Cerquira et al.[19] and Popova et al.[20] have reported results that are concordant with this study. The mean MN count in the buccal mucosa before and after DPR in group 1 (10–≤25 years of age) was 1.65 and 3.45, in group 2 (26–≤40 years of age) was 1.30 and 3.75 and in group 3 (over 40 years of age) was 1.70 and 4.05, respectively. The mean MN count in the palatal mucosa before and after DPR in group 1(10–≤25 years of age) was 0.95 and 1.95, in group 2 (26-≤40 years of age) was 0.80 and 2.05 and in group 3 (over 40 years of age) was 1.20 and 2.03, respectively (Table 3). The ANOVA was applied to evaluate the variations in the mean MN counts both within each group and intergroup, and these results were found to be statistically insignificant (Table 4). However, the results revealed that the mean MN count was higher in older age groups as compared to younger age groups. These results were in accordance with Duffaud et al.,[21] Bolognesi et al.,[22] Waingade et al.[13] and Pai et al.[23] The increase in spontaneous chromosomal instability with age, as reflected with a higher basal level of micronuclei frequency, is associated with an accumulation of DNA damage, due to progressive impairment of overall DNA repair capacity.[24] A positive relationship with age was also obtained by Fenech and Morley[25] while investigating the spontaneous frequency of micronuclei in peripheral lymphocytes as well. This study assessed the frequency of MN and did not find any statistically significant difference between the different age groups in MN frequencies. This probably may be due to the small sample size of the study population. The results of the present study suggest that digital panoramic imaging induces genotoxic effects on oral epithelial cells of buccal and palatal mucosa leading to the formation of micronuclei. The buccal epithelium showed a higher susceptibility to genotoxic damage as evidenced by increased MN counts in comparison on to the palatal mucosa. Therefore, panoramic dental radiographs should only be advised when obligatory because it cannot be considered as a risk-free procedure.

Panoramic radiographic examination is an important part of dental practice. However, it is tantamount that need for the radiological examination, use of appropriate exposure factors, the accuracy of the technique and appropriate radiation protection practices in accordance with as low as reasonably achievable (ALARA) are strictly followed to minimize the risk of genotoxic damage and its potential consequences. This study was performed on individuals who were prescribed a digital panoramic radiograph. Evaluation of MN in the buccal and palatal mucosa has an advantage that it is a relatively non-invasive procedure. It is obvious that epithelial cells of the oral mucosa appear to be target cells for panoramic X-ray exposure. In addition, these epithelial cells are highly proliferative and about 90% of all human cancers are malignancies of epithelial cells. Therefore, the use of the micronucleus test in epithelium cells is considered to be a sensitive tool for biomonitoring the genetic damage in human population.[26]

## CONCLUSION

Further research is necessary to address the various sources of variability such as differences in methodology. Large prospective studies combining exposure data with lifestyle factors and health status should be conducted. Strict criteria should be adopted for assessing cytotoxic damage, which involves not only micronuclei but also other types of nuclear damages, that may act as valuable markers.

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