

XRCC3 THR241MET POLYMORPHISM INFLUENCE ON NUCLEAR BUDS FREQUENCY IN EXPOSED TO FORMALDEHYDE



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INTRODUCTION

Formaldehyde (FA), also known as formalin, formal and methyl aldehydes, is a colorless, flammable, strong-smelling gas. It has an important application in embalming tissues and that result in exposures for workers in the pathology anatomy laboratories and mortuaries. Occupational exposure to FA has been shown to induce nasopharyngeal cancer and has been classified as carcinogenic to humans (group 1) on the basis of sufficient evidence in humans and sufficient evidence in experimental animals. Manifold in vitro studies clearly indicated that FA is genotoxic. FA induced various genotoxic effects in proliferating cultured mammalian cells. The cytokinesis-block micronucleus (CBMN) assay was originally developed as an ideal system for measuring micronucleus (MN), however it can also be used to measure nucleoplasmic bridges (NBP) and nuclear buds (NBUD). Over the past decade another unique mechanism of micronucleus formation, known as nuclear budding has emerged. NBUDS is considered as a marker of gene amplification and/or altered gene dosage because the nuclear budding process is the mechanism by which cells removed amplified and/excess DNA. Shimizu et al. (1998) showed that amplified DNA is localised selectively to specific sites at the periphery of the nucleus and eliminated via nuclear budding to form MN during the S phase of cell cycle. The gene XRCC3 is involved in homologous recombination repair of cross-links and chromosomal double-strand breaks and at least one polymorphism has been reported in codon 241, a substitution of a methionine for a threonine.

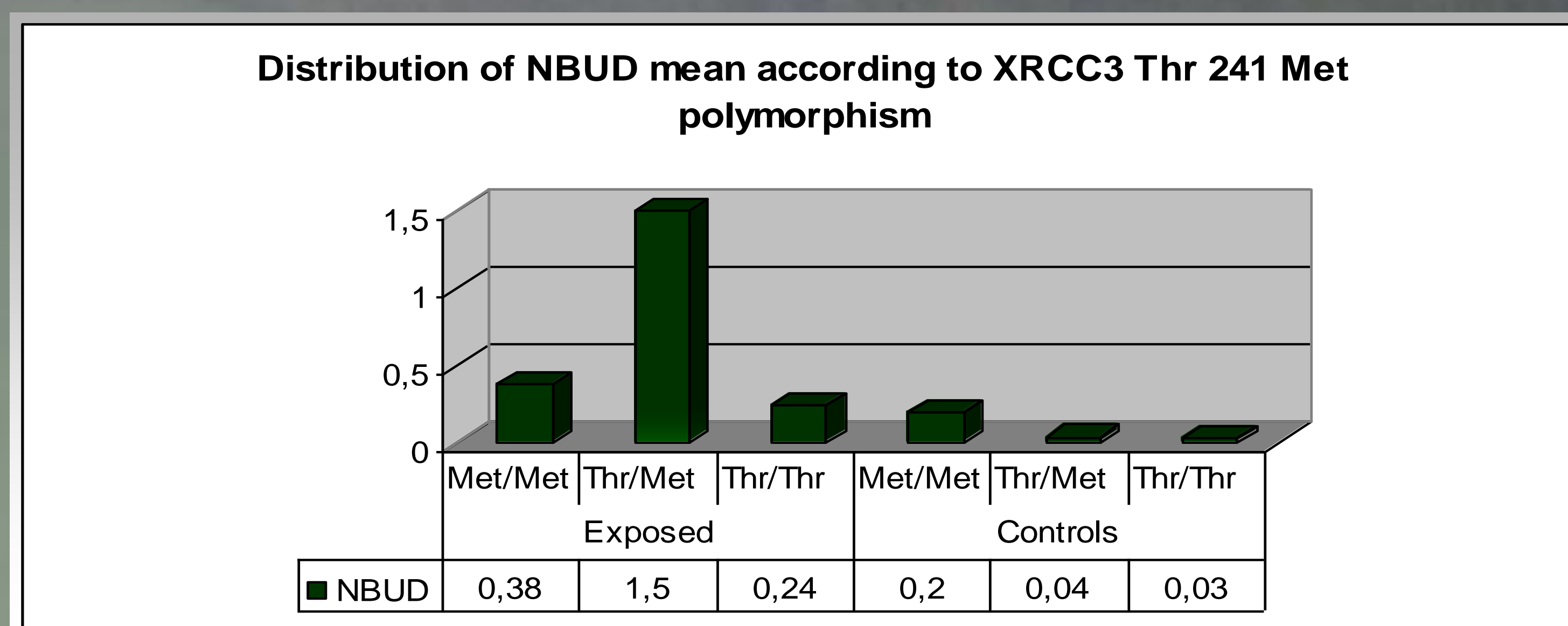
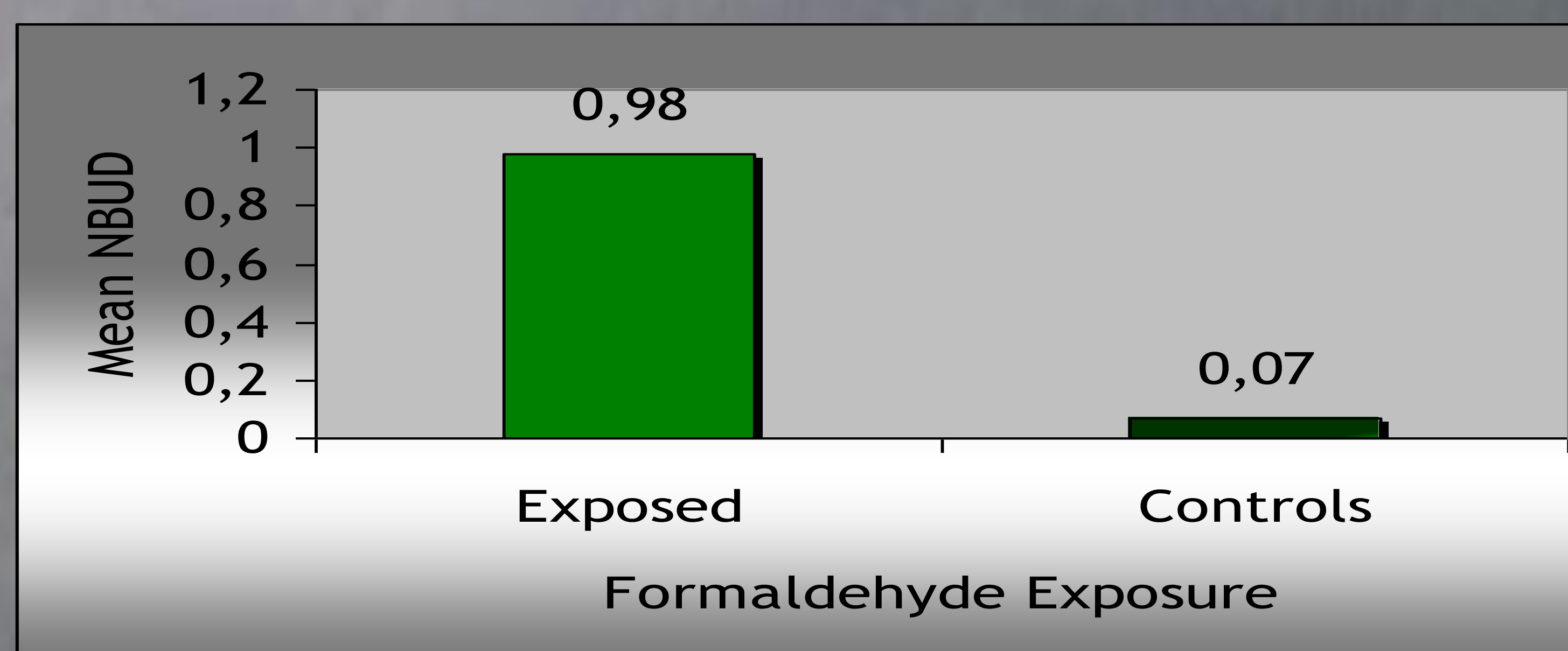
AIM OF THE STUDY

Determine whether there is an in vivo association between the XRCC3 Met 241 Thr polymorphism and the mean of nuclear buds (NBUD) in occupationally workers exposed to formaldehyde

METHODOLOGY

The study was carried out in Portugal in a sample of 56 workers occupationally exposed to FA in pathology anatomy laboratories and in 85 non-exposed subjects. The evaluation of the frequency of NBUD was conducted by applying cytokinesis blocked micronucleus assay in peripheral blood lymphocytes

RESULTS



The mean of NBUD was higher in exposed workers (0.98 ± 0.273) in comparison with controls (0.07 ± 0.028), a statistically significant difference (Mann-Whitney test, $p < 0.001$). Binary logistic regression indicated that the exposure to FA was an important variable affecting the frequency of NBUD and the polymorphism of XRCC3 at codon 241 were found statistically significant ($p = 0.006$). The exposed workers carrying the Thr/Met XRCC3 241 genotype were found to have higher mean NBUD (1,50 vs 0,21) and in controls it was the Met/Met genotype, NBUD (0,20 vs 0,03). Met/Met (OR=4.342, 95% CI 1.087-17.339) and Thr/Met (OR= 5.864, 95% CI 1.648-20.865) polymorphisms showed to be risk factors in comparison with Thr/Thr.

CONCLUSIONS

NBUD should be considered as a genotoxic biomarker, with an origin comparable to that of MN. It appears to originate from interstitial or terminal acentric fragments, possibly representing nuclear membrane entrapment of DNA that has been left in cytoplasm after nuclear division, or excess of DNA that is being extruded from the nucleus. Chromosomal instability has been associated to XRCC3 gene mutation and other genes involved in repair. Manifold studies suggest a direct role of XRCC3 Thr241Met polymorphism maybe associated, but not significant, to a reduce capacity of DNA repair.

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