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Micronuclei in humans induced by exposure to low level of ionizing radiation: influence of polymorphisms in DNA repair genes

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Abstract

Understanding the risks deriving from protracted exposure to low doses of ionizing radiation has remarkable societal importance in view of the large number of work settings in which sources of IR are encountered. To address this question, we studied the frequency of micronuclei (MN), which is an indicator of DNA damage, in a population exposed to low levels of ionizing radiation and in matched controls. In both exposed population and controls, the possible influence of single nucleotide polymorphisms in *XRCC1*, *XRCC3* and *XPD* genes on the frequency of micronuclei was also evaluated. We also considered the effects of confounding factors, like smoking status, age and gender. The results indicated that MN frequency was significantly higher in the exposed workers than in the controls [8.62 ± 2.80 versus 6.86 ± 2.65; $P = 0.019$]. Radiological workers with variant alleles for *XRCC1* or *XRCC3* polymorphisms or wild-type alleles for *XPD* exon 23 or 10 polymorphisms showed a significantly higher MN frequency than controls with the same genotypes. Smoking status did not affect micronuclei frequency either in exposed workers or controls, while age was associated with increased MN frequency in the exposed only. In the combined population, gender but not age exerted an influence on the yield of MN, being higher in females than in males. Even though

Abbreviations: CA, chromosomal aberrations; MN, micronuclei; BER, base excision repair; HRR, homologous recombination repair; SNPs, single nucleotide polymorphisms; NER, nucleotide excision repair; EPIC, European prospective investigation into cancer and nutrition; FFQ, food frequency questionnaire; *Hwb*, dose equivalent of ionizing radiation to the whole body; BN, binucleated; NDI, nuclear division index; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; SSCP, single strand conformation polymorphism; S.D., standard deviation; FISH, fluorescence in situ hybridization

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there is a limitation in this study due to the small number of subjects, these results suggest that even exposures to low level of ionizing radiation could have genotoxic effects and that *XRCC3*, *XRCC1* and *XPD* polymorphisms might contribute to the increased genetic damage in susceptible individuals occupationally exposed to chronic low levels of ionizing radiation. For a clear conclusion on the induction of DNA damage caused by protracted exposure to low doses of ionizing radiation and the possible influence of genetic polymorphism in DNA repair genes larger studies are needed.

Keywords: Ionizing radiation; Occupational exposure; Micronuclei; Genetic polymorphisms; DNA repair genes

1. Introduction

Over the years ionizing radiation has become a universal diagnostic and therapeutic tool, making the largest man-made contribution to the population dose [1]. Thus, medical personnel represent the group most consistently exposed to low dose of ionizing radiation. The high doses of ionizing radiation are clearly known to produce deleterious consequences in humans, including, but not exclusively, cancer induction. However, the effect of such radiations at lower doses, as in occupational work settings, is less clear. The scientific community is primarily concerned with the biological consequences from protracted exposure at low doses [2]. In particular, in spite of the deepening scientific knowledge about radiation adverse health effects, there is a particular need to introduce new epidemiological approach in radioprotection programs for the health surveillance of hospital workers chronically exposed to ionizing radiation [3–5].

In the last decade, several biomarkers, such as cytogenetic analysis, have been developed to perform biomonitoring of populations occupationally exposed to ionizing radiation. Chromosomal aberrations (CA) have been widely accepted as reliable biomarkers for evaluating damage induced by ionizing radiation in humans. Increased frequencies of CA are well known among radiological workers, as compared to controls. However, since the technique is time consuming and demands skilled personnel, the biomonitoring of large groups of workers is difficult. Thus, micronuclei (MN) analysis in human lymphocytes using the cytochalasin B technique [6] has found its place in performing large-scale studies as a valuable easier and faster procedure than the CA assay [7]. MN consists of acentric chromosome fragments or whole chromosomes that are not distributed to the main nuclei during anaphase. Consequently, MN formation is a reliable biomarker of exposure to both clastogenic and aneugenic agents, such as ionizing radiation [8]. The method has already been successfully employed to assess cytogenetic damage in groups occupationally exposed to ionizing radiation [9,10] or population living in areas with a high background of radioactivity [11].

Ionizing radiation interacts with mammalian cells by inducing a wide range of detrimental effects, with the most important damage occurring to the cellular DNA. Ionizing radiation damages cellular DNA in many ways requiring the concerted action of a number of DNA repair enzymes for the maintenance of its structural integrity [12]. Thus, DNA repair plays a vital role in faithful maintenance of genomic integrity, and deficiencies in repair function, as recently highlighted in several reviews, are known to promote cancer development [13,14]. The deleterious clinical consequences of inherited defects in DNA repair systems are apparent from several human cancer predisposition syndromes, some of which shows a hypersensitivity towards ionizing radiation [15]. A significant variation in radiosensitivity between healthy individuals has also been documented [16,17] and the genetic polymorphisms existing in a number of DNA repair enzymes have been proposed as a source of this individual variability (susceptibility). These polymorphisms may be important in determining an individual's ability to repair cellular DNA after ionizing radiation exposure, and therefore, to modulate the toxicological outcome. Oxidative base damage and strand breaks induced by ionizing radiation are repaired mainly by the base excision repair (BER) and homologous recombination repair (HRR) pathways [18,19]. *XRCC1* plays an important role in BER, and *XRCC3* functions in the HRR pathway. Since *XRCC1* and *XRCC3* mutant cells show increased and moderate sensitivity to ionizing radiation, respectively, SNPs in these two genes have been attracting research interest [20–22]. Several studies also suggest a possible