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Cytogenetic Monitoring of Human Populations at Risk in Egypt: Role of Cytogenetic Data in Cancer Risk Assessment

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Somatic mutation plays a critical role in carcinogenesis. Numerous environmental agents can increase the probability that somatic mutation will occur. The use of genotoxicity testing is essential for assessing potential human toxicity so that hazards can be prevented. Cytogenetic monitoring of human populations exposed to chemicals has proved to be a useful tool for detecting the chemical mutagenic effects. Cytogenetic analysis of human chromosomes in peripheral lymphocytes allows direct detection of mutation in somatic cells. Different methods can be used for chromosomal analysis (conventional chromosomal analysis, sister chromatid exchange, micronucleus frequency detection). Micronucleus frequency can be detected either in peripheral blood lymphocytes or in exfoliated cells. Different examples of human population studies are presented. Several problems that are found in biomonitoring studies are discussed. These studies should help us learn about individual exposure assessment and biologically relevant doses, leading to quantitative assessment of human cancer risks.

Introduction

Although neoplasia is familiar in human populations, possible mechanisms for its causation remain limited to speculation. A relatively few situations exist in which the onset of cancer has been closely associated vith a specific causative agent, either environmental or genetic. For example, mesothelioma is now considered strongly suggestive of exposure to asbestos.

Humans are exposed to a large number of genotoxicants via ingestion, respiration, or absorption through the skin. Human exposure patterns are complicated with respect to exposure to single agent or complex mixtures. The situation is further complicated by agents acting synergistically or with inhibitory effects.

An enormous number of chemical or physical agents have been shown in experimental systems to be mutagenic or carcinogenic or both. Mutagenesis and carcinogenesis are frequently grouped together in discussions of possible risks to human health. Identification of mechanisms of cancer development has involved consideration of the somatic mutation hypothesis on the basis of the widespread occurrence of chromosomal abnormalities in cancer cells. Subsequent correlations between the mutagenicity and the carcinogenicity of radiation and chemicals have provided considerable support for the hypothesis (*1*).

Human Biomonitoring of Exposure to Genotoxicants

Epidemiologic studies on cancer in humans are necessary for risk assessment approaches. However, the epidemiologic approach is limited for two main reasons: first, only relatively high risks can be detected, and second, the observations on end effects are the consequence of exposures that may have occurred several decades earlier. Improved epidemiology, ideally, needs direct and accurate estimates of individual exposures. Biomonitoring has become an essential part of exposure assessment; its special objective is to define biologically relevant doses. It may be relevant to look for early effects directly in the exposed individuals or groups, especially from high exposure occupations (*2*). Currently, there is a need for multidisciplinary studies to evaluate the effect of different genotoxicants.

A general strategy for risk assessment of environmental genotoxicants is to determine the biological characteristics of

Table 1. Recommended methodology for assessing exposure and adverse effects of genotoxicants.[a]

External exposure	Environmental monitoring (e.g., lead in air)
Internal absorption	Biological monitoring (e.g., lead in blood)
Biological effect	Genetic monitoring (e.g., chromosomal aberrations)
Clinical response	Epidemiology of effects

[a] Modified from Sorsa et al. (*2*).

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genotoxicants and their toxic activity to the genetic material. Proper and relevant methods for genotoxicity assessment need to be used both at the experimental (*3,4*) and at the human exposure assessment levels (Table 1). Molecular epidemiology aims at combining laboratory and epidemiologic tools in a more analytical and sensitive approach for individual exposure assessment (*5*).

Cytogenetic Methods for Testing the Effect of Genotoxicants

Cytogenetic methods have become widely used in analyzing human chromosomes and screening various mutagens for their effects directly on human somatic cells *in vivo* (*6*).

Cytogenetic End Points

Conventional or Classical Cytogenetic Technique. Homogenous staining of chromosomes was the first classical cytogenetic technique for testing the mutagenic effects on human chromosomes. This technique permits rapid overall analysis of tested cells, i.e., checking the chromosomal number and registering chromosomal damage. The typical postradiation chromosomal aberrations are deletions, terminal and interstitial; dicentrics and rings, with or without fragments; translocations; and inversions. The aberrations induced by chemicals are quite different from postradiation changes. The most frequent of these aberrations are the chromatid and chromosome breaks. Chromatid and chromosomal exchanges and rearrangements are rare. Some types of chromosomal aberrations escape detection by this conventional technique, for example, peri- and paracentric inversions, small deletions, and reciprocal translocations. These can be detected by banding techniques. The automatic chromosomal analysis offers the possibility to screen systematically large groups of occupationally exposed people. However, this method is still in the experimental stage. It is expensive and is not yet ready for widespread use.

Harlequin Technique. The harlequin technique was described as a sensitive, convenient method for routine chemical mutagenicity testing (*7*). An increased number of sister chromatid exchanges (SCE) was noticed even when the dose of a chemical was below the concentration required for detecting the classical chromosomal aberrations. The increase in incidence after radiation *in vitro* and *in vivo* is very low. The detection of SCE in cells requires a lower level of technical skills and is more rapid than scoring the classical aberrations; SCEs occur by different mechanisms than the classical aberrations; therefore, we are testing two different types of DNA damage. For these reasons, the harlequin technique is convenient for large screening studies.

Micronucleus Technique. IN BINUCLEATED PERIPHERAL BLOOD LYMPHOCYTES. The micronucleus testing procedure has a number of important advantages over the analysis of metaphase chromosomes. Preparing cells as well as scoring slides is simpler and quicker than chromosome analysis, but not at the expense of accuracy. The micronucleus (MN) test is at least as sensitive as the metaphase method (chromosomal breakage analysis). In addition, MN can be used to screen for effects on the spindle apparatus. It is highly suitable for routine toxicological screening (*8*). Micronuclei enclose acentric chromosome fragments or whole chromosomes that have not been incorporated in the main nuclei at cell division. Micronuclei require one cell division to be expressed. Consequently, the conventional MN technique (*8*) is imprecise because the cells that have undergone only one division and contain the micronuclei cannot be identified separately from the total population of lymphocytes. To overcome this problem, cytokinesis was blocked using cytochalasian B. Cytokinesis-blocked cells are easily recognizable by their binucleated appearance. They are dividing cells that have completed nuclear but not cytoplasmic division (*9*).

IN EXFOLIATED HUMAN CELLS. This approach involves a modification of the micronucleus test to use on exfoliated human cells (MEC test). Micronuclei present in these cells represent chromosomal breakage occurring in the dividing cell populations of the basal epithelial layers. The daughter cells containing the micronuclei migrate up through the epithelium and are exfoliated. The biological relevance of employing the MEC test to study carcinogen-exposed populations is that the approach serves as an endgenous dosimeter of genotoxic damage directly in the tissue that is the target for the carcinogens and from which tumors will later arise. Furthermore, the fact that the assay provides an estimate of the frequency of chromosomal breakage is itself significant. Although the MEC test will not indicate whether a specific required chromosome change has occurred in a carcinogen-exposed tissue, a chronic increase in the level of MEC in a tissue may suggest an increase in the probability of the necessary chromosomal change occurring (*10*).

Relevance of Cytogenetic Damage

Evidence suggests chromosomal changes may be intrinsically linked to cancer development. Chromosomal instability is characteristic of dysplasias and many premalignant conditions, and specific chromosomal aberrations appear to be associated with many types of cancer (*11*). These abnormalities are usually represented by a translocation or a loss of a chromosome band. Furthermore, individuals having to genetic syndromes in which chromosomal breakage rates are elevated, such as the chromosomal breakage syndromes, Bloom's syndrome, ataxia-telangictasia, Fanconi's anemia, and xeroderma pigmentosum, are also characterized by an increase in the risk for cancer (*12,13*). Finally, a role for chromosomal breakage, translocation, or loss is implicated in the sequence of events leading to development of neoplasia, as such changes can activate oncogenes or result in the loss of tumor anti-oncogenes or suppressor genes (*14,15*).

Studies of Humans Exposed to Chemicals

Population cytogenetic monitoring is one of the ways in which the effects of environmental mutagens may be detected in man. In Egypt, workers who have undergone long-term occupational exposure to high levels of a test chemical are supposed to be at high risk. A cytogenetic analysis is suitable for this purpose. A small peripheral blood sample provides enough cells to be scored for chromosomal aberrations. Blood collections are technically easy and it is therefore possible to carry out repeated periodical sampling of exposed workers.

Examples of Monitoring Studies

Several studies have been conducted in Egypt for cytogenetic monitoring (Fig. 1).

Cytogenetic Effects in Traffic Policemen. The aim of this study was to evaluate the cytogenetic effects in humans exposed to automobile exhaust. The induction of chromosomal damage was studied in an exposed group of 28 traffic policemen with exposure of more than 10 years and a control group of 15 policemen trainers from the Faculty of the Police. The percentage of chromosomal aberrations (7.7 ± 3.1) as well as the mean sister chromatid exchanges (7.5 ± 3.4) were significantly higher among the traffic policemen than in the control group. The percentage of chromosomal aberrations was 2.8 ± 2.1 and the mean sister chromatid exchanges was 4.8 ± 2.9 in the control group. The cause for this elevated chromosome damage is most likely due to their exposure to pollutants from automobile exhaust; however, the increase is not correlated with the blood lead level or the duration of employment. On the other hand, the increase in chromosome damage among the traffic policemen is enhanced further by smoking (*16*).

Cytogenetic Study in Workers Occupationally Exposed to Mercury. This study was conducted to evaluate the cytogenetic effects in male workers exposed to mercury fulminate. A total of 29 male workers and 29 age- and sex-matched controls were examined. The mean mercury level in urine of the exposed workers was 123.2 ± 54.1 μg/L compared to 39.2 ± 11.1 μg/L in the control group. The difference was statistically significant ($p <$ 0.001). Metaphase chromosomes were studied. Micronucleated peripheral blood lymphocytes were also analyzed in cytochalasian-B blocked binucleated lymphocytes. The percentage of metaphases with chromosomal aberrations was significantly higher ($p < 0.001$) in the exposed group (6.1 ± 2.3) compared to the control group (2.8 ± 0.7). The chromosomal aberrations detected were in the form of gaps, breaks, and fragments. A significant increase in the incidence of micronucleated lymphocytes was found among the exposed group (7.1 ± 4.2) compared to the control group (5.4 ± 2.2) ($p < 0.01$). The detected chromosomal damage correlated neither with the duration of exposure nor with the urinary mercury level (*17*).

Cytogenetic Study among Workers Packing Pesticides. The aim of this study was to investigate cytogenetic changes among workers packing a variety of pesticides. Twenty-eight workers from two companies in Egypt were selected for this study. Exposed workers were matched by age and sex to 20 controls, who worked as clerks. Duration of exposure was 12.9 ± 6.2 years. Lymphocytic cultures were set up and harvested at 48 hr for chromosomal aberration assay and 72 hr for sister chromatid exchange assay. The mean frequency of chromosomal aberrations was 4.58% among the exposed group versus 2.55% among controls. The difference was statistically significant ($p < 0.05$). The exposed workers who were smokers showed elevated frequency of aberrations compared to nonsmokers (5.07% and 3.85%) ($p > 0.05$). No significant correlation was observed regarding chromosome aberrations and duration of exposure. Types of aberrations were mainly chromatid gaps and breaks. Sister chromatid exchanges were not significantly elevated among exposed group compared to the controls (*18*).

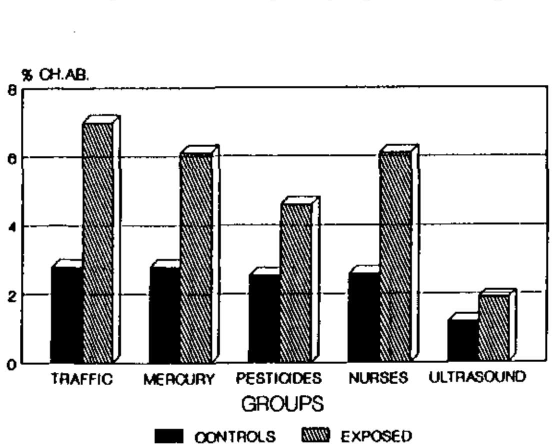

FIGURE 1. Chromosomal aberrations (CH.AB) in different populations at risk in Egypt.

Cytogenetic Study in Nurses Occupationally Exposed to Antineoplastic Drugs. This study evaluated the effects of low-level occupational exposure of nursing personnel to antineoplastic drugs. Twenty nurses who constantly handled these drugs and 20 controls matched according to age and sex were examined. Micronucleated peripheral blood lymphocytes were analyzed in cytochalasian B-treated binucleated lymphocytes. Metaphase chromosomes were also studied. A significant increase in micronuclei ($p < 0.001$) was found for nurses (10.05 ± 4.71) as compared to the matched controls (5.42 ± 2.22). The number of micronucleated lymphocytes was significantly related to the duration of exposure ($p < 0.001$). The percentage of metaphases with chromosomal aberrations was significantly higher ($p <$ 0.05) in the exposed group (6.1 ± 2.7) compared to the control group (2.6 ± 1.6). The detected chromosomal aberrations were in form of gaps, breaks, and fragments (*19*).

Cytogenetic Effect of* In Utero *Exposure to Diagnostic Ultrasound on Maternal and Fetal Lymphocyte Chromosomes. In this study, metaphase chromosomes were studied from 16 women and 16 fetuses exposed *in utero* to diagnostic ultrasound. The exposure ranged from one to ten times during different periods of gestation. Sixteen unexposed women and 18 fetus were investigated as control groups. The detected chromosomal aberrations were in the form of gaps, breaks, and fragments. The changes (including gaps) in the exposed groups (1.19% maternal, 0.67% fetal) were not statistically significant compared to the control groups (1.89% maternal, 1.61% fetal). Excluding gaps, the changes were also not significant. The percentage of chromosomal changes were 0.4% in the maternal-exposed group and 0.29% in the fetal-exposed group. In the control groups, the percentage were 0.83% and 0.3% in the maternal and fetal groups, respectively. No correlation could be detected between chromosomal aberrations and the frequency or the type of exposure (*20*).

Chromosomal Breakage in Urothelial Cells of Individuals with* Schistosoma haematobium *Infections. Individuals infected with the parasite *Schistosoma haematobium* have an elevated risk of bladder cancer. The underlying mechanism by which this elevation in cancer risk is produced is unresolved. The aim of this research was to determine whether inflammatory reactions triggered by these chronic infections would produce DNA damage to urothelial cells, a possible mechanism whereby precancerous changes could be induced. The study was based in a village in the Fayoum goverorate in Egypt. The prevalence of infection in this village is approximately 40%. The study involved sampling 50 infected males who had schistosoma ova in their urine. The urine was centrifuged, and the pellet, containing exfoliated urothelial cells, was fixed in methanol. As controls for these individuals, 25 local villagers were matched with the study group. These villagers had no clinical symptoms of schistosomiasis and no ova or inflammatory cells in their urine. A second control group was taken from 25 individuals of the same socioeconomic status from Cairo. The mean micronucleus frequencies for urothelial cells in the infected population was significantly greater than observed among either control populations. However, interindividual variation was observed among the studied groups. Further studies examining the effect of antischistosomal therapy on micronucleus frequencies in these infected individuals are currently ongoing (manuscript in preparation).

Micronucleus Frequencies in Exfoliated Cells Obtained from Different Sites in the Oral Cavity of Xeroderma Pigmentosum Patients. Xeroderma pigmentosum (XP) patients are predisposed to skin cancer. They also have a high prevalence of squamous cell carcinoma of the tip of the tongue. Mechanistically, this enhanced risk has been attributed to a defect in the repair of DNA damage induced by ultraviolet rays from sunlight. To determine whether a relationship exists between exposure to ultraviolet light and the level of chromosomal breakage occurring in epithelial tissue in five XP patients, the exfoliated cell micronucleus test was applied to different sites in the oral cavity of patients. These sites were the right buccal mucosa, the left buccal mucosa, the dorsal tip of the tongue, and the palate. Five controls matched according to age and sex were examined concurrently. The frequency of micronucleated cells was determined in each exfoliated cell sample. An unequal distribution of the frequency of micronucleated cells was found in the different sample sites of the oral cavity in XP patients, with the greatest elevation in frequencies among cells collected from the dorsal tip of the tongue. In contrast, the frequency of micronucleated cells did not vary in samples from different sites obtained from the controls. Samples from the tip of the tongue were significantly lower in controls than in XP patients ($p < 0.05$). This observation may have some significance because this site in the oral cavity would receive the greatest sunlight exposure. These data suggest that the exfoliated cell micronucleus test can be used to study the extent to which genotoxic damage in a tissue results from the complex interplay of host and environmental factors (manuscript in preparation).

Problems in Cytogenetic Monitoring Studies of Populations Exposed Environmentally

Different Individual Sensitivity

Different individual sensitivity is not surprising because the mutagen undergoes a long and complicated process between the first contact with the human body and the appearance of the ultimate chromosomal change, which we are able to detect as a chromosomal aberration in the lymphocyte. According to Vogel (*21*), this process proceeds at three levels: *a*) entrance of the mutagen into the human body and its excretion have a strong influence on the actual dose of the mutagen, i.e., its concentration in different tissues. Inherited or acquired changes in the function of the lungs, digestive tract, kidneys and the other organs can change the quantitative effects of the mutagen; *b*) metabolism of the mutagen, the detoxicating or the activating ability of the liver and the other organs in the body are important and can be influenced genetically or by environmental factors; *c*) direct contact with DNA. Each individual differs most probably in the ability to repair DNA damage.

Problem of Valid Controls

An evaluation of chromosomal changes detected in the cells of exposed workers requires reliable control data. It is more convenient to use the cells from the same person before exposure as control and then, if possible, at various time intervals during and after exposure to the chemical tested (*22*). This will avoid the difficulties encountered with differing sensitivities of individuals tested. Such controls are optimal but they are seldom available when occupationally exposed persons are tested. Therefore, blood samples from other persons must be used as controls. If possible the control should be matched in term of sex, age, and race. Control blood samples should be cultured under exactly the same conditions as samples from exposed people, and slides should be coded before scoring. The average percentage of aberrant cells in peripheral blood lymphocytes of healthy adult people, who are not exposed to unusual doses of mutagens, is 1 or 2% in most laboratories if gaps are not included. Young children and infants usually have less than 1% aberrant cells (*5*).

Confounding Factors

A number of factors, such as the use of drugs, drinking alcohol, smoking habits, radiation, and viral or other infections in the last 3 months before sampling, need to be taken into account because they can have a profound influence on the results. Those individuals who may not recall exposure to any of these factors may have an elevated level of chromosomal aberrations. In addition, individuals exposed to elevated levels of radiation and chemicals in the remote past are not suitable as controls because some types of aberrations may survive for years in the human body (*1*).

Number of Persons Examined

The use of chromosomal aberrations for monitoring means that we are studying the response of single, randomly chosen cells; each aberrant cell is a member of the lymphocyte population. Therefore, it is possible to obtain significant data from a few persons if enough randomly chosen cells are scored. Cytogenetic monitoring is, in fact, the monitoring of a population (cells) in a population (group of people) (*6*).

Evaluation of the Real Consequence of Chromosomal Damage

The danger of the neoplastic process is supposed to be greater in individuals with clones of aberrant cells. Even if the persons with high levels of aberrant cells are healthy, we must accept this finding as an indication that these persons have been exposed to some kind of mutagen. The interindividual variability to chemicals makes the proper dose estimate from chromosomal changes impossible. Therefore, chromosomal aberrations are at present only a qualitative indicator of mutagenic effects.

Possible Use of Results from Cytogenetic Studies in Occupational Health Service

If it appears that chromosomal aberrations have increased, exposure must be reduced because these individuals may also have other types of genetic damage (e.g., point mutation or chromosomal aberrations in germinal cells). Workers should be advised not to plan to conceive a child within 1 year for women or within the next 3 months for men (*5*). Results of some studies have demonstrated that chromosomal changes are reversible and that chromosomal aberrations may revert to control levels in 2 to 3 years after reducing exposure to the mutagen.

Obtaining Statistically Significant Results and Predicting Future Health Effects

An additional problem in cytogenetic surveys of populations exposed environmentally is in obtaining statistically significant results with regard to very low-level exposures and then determining the meaning of such results for health effects in the population as a whole and in the individuals on which the observations were made. Thus, although chromosomal changes are an indicator of cellular genetic damage in a population, they cannot be used quantitatively to predict future health effects for a given individual (*25*).

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