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Chromosomal aberrations and SCEs as biomarkers of cancer risk

H. Norppa [a,*], S. Bonassi [b], I.-L. Hansteen [c], L. Hagmar [d], U. Strömberg [d], P. Rössner [e,f], P. Boffetta [g], C. Lindholm [h], S. Gundy [i], J. Lazutka [j], A. Cebulska-Wasilewska [k], E. Fabiánová [l], R.J. Šrám [f], L.E. Knudsen [m], R. Barale [n], A. Fucic [o]

[a] New Technologies and Risks, Finnish Institute of Occupational Health, FI-00250 Helsinki, Finland
[b] Unit of Molecular Epidemiology, National Cancer Research Institute, 16132 Genoa, Italy
[c] Department of Occupational and Environmental Medicine, Telemark Hospital, 3710 Skien, Norway
[d] Division of Occupational and and Psychiatric Epidemiology, Lund University, SE-22185 Lund, Sweden
[e] Laboratory of Genetic Toxicology, National Institute of Public Health, 100 42 Prague 10, Czech Republic
[f] Institute of Experimental Medicine AS CR and Health Institute of Central Bohemia, 142 20 Prague 4, Czech Republic
[g] Unit of Environmental Cancer Epidemiology, International Agency for Research on Cancer, 69008 Lyon, France
[h] STUK, Radiation and Nuclear Safety Authority, FI-00881 Helsinki, Finland
[i] Department of Diagnostic Onco-Cytogenetics, National Institute of Oncology, 1122 Budapest, Hungary
[j] Department of Botany and Genetics, Vilnius University, 03101 Vilnius, Lithuania
[k] Department of Epidemiology, Jagiellonian University Medical School, 31-034 Kraków, Poland
[l] Department of Occupational Health, State Health Institute, 975 56 Banská Bystrica, Slovakia
[m] Institute of Public Health, University of Copenhagen, DK-2200 Copenhagen N, Denmark
[n] Dipartimento di Scienze dell'Uomo e dell'Ambiente, University of Pisa, 56100 Pisa, Italy
[o] Institute for Medical Research and Occupational Health, 10000 Zagreb, Croatia

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Abstract

Previous studies have suggested that the frequency of chromosomal aberrations (CAs), but not of sister chromatid exchanges (SCEs), predicts cancer risk. We have further examined this relationship in European cohorts comprising altogether almost 22,000 subjects, in the framework of a European collaborative project (CancerRiskBiomarkers). The present paper gives an overview of some of the results of the project, especially as regards CAs and SCEs. The results confirm that a high level of CAs is associated with an increased risk of cancer and indicate that this association does not depend on the time between CA analysis and cancer detection, i.e., is obviously not explained by undetected cancer. The present evidence indicates that both chromatid-type and chromosome-type CAs predict cancer, even though some data suggest that chromosome-type CAs may have a more pronounced predictive value than chromatid-type CAs. CA frequency appears to predict cancers at various sites, although there seems to be a particular association with gastrointestinal cancers. SCE frequency does not appear to have cancer predictive value, at least partly due to uncontrollable technical variation. A number of genetic polymorphisms of xenobiotic metabolism, DNA repair, and folate metabolism affect the level of CAs and might collectively contribute to the cancer predictivity of CAs. Other factors that may influence the association between CAs and cancer include, e.g., exposure to genotoxic carcinogens and internal generation of genotoxic species. Although the association between CA level and cancer is seen at the group level, an association probably also exists for the individual, although it is not known if an individual approach could be feasible. However, group level evidence should be enough to support the use of CA analysis as a tool in screening programs and prevention policies in occupational and environmental health.

Keywords: Biomarker; Cancer; Chromosomal aberration; Genotoxicity; Genotype; Sister chromatid exchange

* Corresponding author. Tel.: +358 30 474 2336; fax: +358 30 474 2110.
E-mail address: hannu.norppa@ttl.fi (H. Norppa).

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1. Introduction

The frequency of chromosomal aberrations (CAs) in peripheral blood lymphocytes has been applied for decades as a biomarker of the early effects of genotoxic carcinogens, in occupational and environmental settings (including biodosimetry of radiation) [1–4]. CAs in lymphocytes are thought to represent a surrogate endpoint for more specific chromosome alterations in target tissues of carcinogenesis. Assuming that the mechanisms of chromosome damage formation are similar in different tissues, the level of damage in lymphocytes can be expected to reflect the level of damage in cancer-prone tissues and to indicate cancer risk [1–4].

The extensive use of the CA assay has resulted in the accumulation of analysis data in many European laboratories. This has enabled the examination of the potential association between previously measured CA frequency and subsequent cancer outcome. An association between high CA frequency and increased cancer incidence was originally detected by the Nordic Study Group on the Health Risk of Chromosome Damage in a collaborative project of 10 Nordic cytogenetic laboratories [5–8]. No association could be shown for sister chromatid exchanges (SCEs) or micronuclei (MN), two other cytogenetic biomarkers which can also be analyzed from lymphocytes. An independent study among 10 laboratories from Italy, based on cancer mortality data, also concluded that CAs are predictive of cancer risk [9]. The Nordic and Italian cohorts were subsequently combined by the European Study Group on Cytogenetic Biomarkers and Health for an updated analysis, which confirmed the cancer risk predictivity of CA frequency but suggested no such association for SCEs or MN [10–13].

A case–control study nested within the Nordic–Italian cohort, involving individual assessment of occupational carcinogen exposure and smoking for the cancer cases and their matched healthy controls, indicated that the association between CAs and cancer was not merely a reflection of smoking or occupational exposure to carcinogens, but was similarly seen in apparently unexposed subjects [13]. Thus, these results suggested that a high CA level as such is predictive of increased cancer risk, irrespective of the cause of the initial CA increase. This result could have several explanations. Despite the thorough exposure assessment, some carcinogenic exposures were missed, such as those related to diet, the general environment, and endogenous generation. Low dietary intake of micronutrients such as folate which may have contributed to the findings could not be constructed retrospectively. One possibility is that genetic instability and individual susceptibility factors play a part in determining the association between CAs and cancer. As archival cell specimens are available on many of the subjects included in the existing cohorts, it should be possible to characterise these factors by a molecular epidemiological approach. Previous studies have suggested that various common polymorphisms of carcinogen-metabolising enzymes, proteins affecting DNA repair, and enzymes of folate metabolism may influence both the levels of chromosome damage (see [14]) and cancer risk [15–30].

A European collaborative research project, "Cytogenetic Biomarkers and Human Cancer Risk" (CancerRiskBiomarkers) was established in 2001 to further study cancer risk prediction by cytogenetic biomarkers. The project had a number of scientific objectives which can be reduced to simple questions:

(1) Is cancer risk predicted by CAs also in other cohorts than those studied thus far?
(2) Do chromosome-type and chromatid-type CAs have different cancer risk predictivity?
(3) What types of cancer do CAs predict?
(4) Do lymphocyte SCEs predict cancer if disturbing experimental details are taken into account?
(5) Do genetic polymorphisms affect the level of cytogenetic biomarkers?
(6) Do genetic polymorphisms explain the cancer risk predictivity of CAs?

The present paper gives an overview of the results of the project, some still preliminary, and tries to give answers to the questions shown above, especially as regards CAs and SCEs. An additional objective of the project, answering the question "Does lymphocyte MN frequency predict cancer if data from cytokinesis-block MN assay are primarily used for the evaluation?" is not a topic of the present review.

2. Is cancer risk predicted by CAs in other cohorts?

One of the goals of the project was to obtain, from European cohorts, reliable estimates for the association between CA frequency and total cancer risk. This was done by updating the existing cohorts and by examining the cancer association of CAs in new cohorts from Czech Republic and other countries that had associated with the EU (Newly Associated States, NAS) at the time of the project. These countries included Hungary, Lithuania, Poland, and Slovakia (presently full members of the EU), and Croatia. Table 1 shows a short summary of the CA cohorts included. The establishment of the Czech cohort