

Final Report Summary

Title of the project		Cytogenetic Biomarkers and Human Cancer Risk	
Acronym of the project		CancerRiskBiomarkers	
Type of contract RTD		Total project cost	
		€1,828,058	
Contract number	Duration	EU contribution	
QLK4-CT-2000-00628 NAS extension: QLK4-CT-2002-02831	47 months (with NAS extension)	€1,300,000	
Commencement date		Period covered by the final report	
1 January 2001		1 January 2001 - 30 November 2003	
<u>PROJECT COORDINATOR</u>			
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http://www.ttl.fi/NR/rdonlyres/42077A6B-31AF-4DB8-994D-5296FC64CBB2/0/canriskbio.PDF			
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Objectives:

Cytogenetic analyses of peripheral blood lymphocytes have been used for decades to show the genotoxic effects of chemical and radiation exposure in humans. A recent Nordic-Italian study revealed that a high frequency of chromosome aberrations (CAs), but not of sister chromatid exchanges (SCEs) or micronuclei (MN), in lymphocytes is predictive of an increased cancer risk. A thorough individual exposure assessment of the cancer cases and their matched healthy controls indicated that the association between CAs and cancer risk was not explained by smoking or known occupational exposure to carcinogens. High CA level was associated with increased cancer risk also in non-smokers and in subjects with no history of occupational contact with carcinogens. Thus, high CA frequency appeared to predict increased cancer risk regardless of the reason for the elevated CAs.

An important conclusion from these studies is that individual susceptibility factors probably play an important part in determining the CA-cancer association. The existing cohort provides an exceptional opportunity to characterise these factors by a molecular epidemiological approach, since archived cell specimens are available on most of the subjects - in addition to the cytogenetic results, exposure information, and cancer status already included in the database. The objectives are:

To clarify which common genetic polymorphisms of carcinogen metabolism, DNA repair, and folate metabolism affect the baseline or induced frequency of cytogenetic biomarkers in human lymphocytes.

To evaluate in a nested case-control study (a) if such polymorphisms could explain the cancer risk predictivity of CA frequency and (b) if smoking and other carcinogen exposure influence cancer risk predictivity of CAs when the genotype information is taken into account. Detailed individual exposure profiles, prepared in the previous study, are already available.

To evaluate if chromosome-type (induced by radiation) and chromatid-type (induced by chemical mutagens) CAs have different cancer risk predictivity.

To re-evaluate if lymphocyte SCE frequency, which has previously shown no association with cancer risk, could have better predictive value when disturbing experimental details are taken into account.

To examine the cancer association of CAs and SCEs in new cohorts from Czech Republic and other Newly Associated States (NAS)

To obtain, from pooled European cohorts (Nordic, Italian, Czech, NAS) reliable estimates for the association between CA frequency and (a) total cancer risk, and (b) risk for cancer at specific sites.

To assemble a cohort of subjects screened for MN frequency in lymphocytes using the cytokinesis-block method, based on data from European laboratories participating in an international MN network and to estimate the extent of the association between the frequency of MN and subsequent risk of cancer.

Results and Milestones:

Studies of genetic polymorphisms and cytogenetic damage indicated that the effect of genetic polymorphisms on the level of CAs and apparently also of MN is complex, with several polymorphisms of xenobiotic metabolism, DNA repair proteins, and folate metabolism enzymes showing an influence. This probably reflects the multiple external and internal exposures inducing a multitude of DNA lesions eventually resulting in CAs and MN. Few polymorphisms appeared to have an impact on the frequency of SCEs. Polymorphisms affecting the level of cytogenetic biomarkers can be viewed as potential factors influencing the cancer risk predictivity of CAs and the possible cancer risk predictivity of MN. The magnitude of this tentative effect on cancer risk could not, however, be estimated.

The study provided the first direct information about the possible role of genetic polymorphisms in modulating cancer risk in early stages of carcinogenesis. The findings, restricted to *GSTM1* and *GSTT1* genotypes, were negative. The result thus seemed to support the idea that the ability of CAs to predict cancer is independent on genotypes. However, conclusions are limited by the small study group and availability of only two major polymorphisms of similar nature. GST polymorphisms, similar to other polymorphisms of xenobiotic metabolism, may be important especially in connection with specific exposures. The negative outcome can also be explained through the effect of many polymorphisms affecting CA level. Thus, single polymorphism may have only a low effect on cancer predictivity.

Studies on the role of CA type in cancer predictivity suggested that both chromatid- and chromosome-type CAs may be predictive of cancer risk, although chromosome-type CAs appeared to have a more important influence. SCEs did not appear to be indicative of cancer risk, and a full scale analysis of the cancer risk predictivity of SCEs with the supplemental information collected was not feasible.

The cohort studies on the cancer risk predictivity of CAs clearly showed that CA frequency is predictive of cancer. This predictivity was not due to undetected cancer, because it did not depend on the time elapsed from the CA analysis to the cancer detection. Both the Czech and the new NAS cohorts showed an association especially with stomach cancer. In the NAS cohort, a strong association also existed to colorectal cancer. The ongoing analysis of the pooled European cohort will shed more light on this matter.

Studies of MN and cancer predictivity revealed a clear association between the frequency of MN and subsequent risk of cancer. The extent of risks observed was close to that measured for CAs. Thus, MN analysis which is easier, cheaper, and faster than CA scoring, may provide an alternative for CAs in cancer risk prediction. The issue of specific tumour sites is still open for MN, given the short follow-up of most cohorts (and the consequent small number of cancer cases).

In conclusion, the results convincingly showed that CA frequency is predictive of cancer risk at the group level and suggested cancer predictive value also for MN frequency. Both chromosome-type and chromatid-type CAs appeared to predict cancer, but the former showed a more pronounced effect. CAs particularly appeared to predict stomach cancer and colorectal cancer. Although various genetic polymorphisms were observed to affect the level of CAs and MN, the two polymorphisms (*GSTM1* and *GSTT1*) for which association to cancer risk predictivity could be assessed did not show a modifying effect. The findings are expected to be useful in development of strategies for cancer risk management and in risk assessment of genotoxic carcinogens.

Benefits and Beneficiaries:

The project provided information about the effect of major polymorphisms on the frequency of chromosome damage. This information can directly be utilised in design, method selection, and interpretation of genotoxicity surveys of exposure to occupational and environmental carcinogens, including biological dosimetry of radiation exposure. The results will be useful for occupational physicians and toxicologists, radiation surveillance professionals, geneticists, and epidemiologists.

The project confirmed and thoroughly characterised the cancer predictivity of chromosome damage. This information can be utilised in development of strategies for cancer risk management and in risk assessment of genotoxic carcinogens by EU, WHO, and national regulatory bodies. The study yielded the first data on the possible modifying effect of genetic polymorphisms on cancer, providing valuable directions for future efforts in assessing the various factors contributing to cancer risk.

Future Actions (if applicable):

The results confirm that CAs predict cancer risk at the group level. In future projects, it should be assessed (a) how this information could be taken into account in regulation, (b) what are the prospects for individual risk assessment, (c) what could explain the apparent preferential prediction of stomach cancer, and (d) if stable CAs (translocations) could provide a superior measure for cancer risk. The scientific basis for genotype effect on CA and MN level and relationships to cancer prediction should further be characterized in combined European cohorts.