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Cancer Risk in Humans Predicted by Increased Levels of Chromosomal Aberrations in Lymphocytes: Nordic Study Group on the Health Risk of Chromosome Damage[1]

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ABSTRACT

Cytogenetic assays in peripheral blood lymphocytes (PBL) have been used extensively to survey the exposure of humans to genotoxic agents. The conceptual basis for this has been the hypothesis that the extent of genetic damage in PBL reflects critical events for carcinogenic processes in target tissues. Until now, no follow-up studies have been performed to assess the predictive value of these methods for subsequent cancer risk. In an ongoing Nordic cohort study of cancer incidence, 3182 subjects were examined between 1970 and 1988 for chromosomal aberrations (CA), sister chromatid exchange or micronuclei in PBL. In order to standardize for the interlaboratory variation, the results were trichotomized for each laboratory into three strata: low (1–33 percentile), medium (34–66 percentile), or high (67–100 percentile). In this second follow-up, a total of 85 cancers were diagnosed during the observation period (1970–1991). There was no significant trend in the standardized incidence ratio with the frequencies of sister chromatid exchange or micronuclei, but the data for these parameters are still too limited to allow firm conclusions. There was a statistically significant linear trend ($P = 0.0009$) in CA strata with regard to subsequent cancer risk. The point estimates of the standardized incidence ratio in the three CA strata were 0.9, 0.7, and 2.1, respectively. Thus, an increased level of chromosome breakage appears to be a relevant biomarker of future cancer risk.

INTRODUCTION

Chromosomal rearrangements play an important role in the activation of protooncogenes (1) and inactivation of tumor suppressor genes (2). Several types of genetic predisposition to cancer may be associated with constitutional chromosome instability (3). Moreover, alterations of the karyotype have been found in all types of neoplastic cells and are often highly specific for particular diagnostic categories (4, 5). Thus, it is generally accepted that chromosomal mutations are causal events in the development of neoplasia.

PBL[4] are extensively used in biomonitoring of populations exposed to various mutagenic or carcinogenic compounds. This is because of the ease of sampling, the possibility of obtaining large numbers of scorable cells, and the documented sensitivity of this system in detecting chromosome damage induced by exposures, particularly ionizing radiation. The conceptual basis for using CA in PBL as a biomarker has been the hypothesis that the extent of genetic damage in PBL reflects similar events in the precursor cells for carcinogenic processes in the target tissues. At the population level, an increased frequency of CA has thus generally been considered indicative of increased cancer risk for those exposed to the damage-inducing agent (6, 7).

In addition to CA, two other cytogenetic end points in PBL have been used as indicators of chromosomal damage: SCE and MN. SCEs represent symmetrical exchanges between sister chromatids; generally, they do not result in alteration of the chromosome morphology (8). MN in PBL represent small, additional nuclei formed by the exclusion of chromosome fragments or whole chromosomes lagging at mitosis. Therefore, MN rates indirectly reflect chromosome breakage or impairment of the mitotic spindle. The health significance of increased levels of CA, SCE, and MN is unknown (7, 9).

In order to answer the important question, whether a high frequency of CA, SCE, or MN in PBL indicates an increased risk for subsequent cancer, a prospective Nordic cohort study has been initiated (10, 11). The conditions for undertaking such a study in the Nordic countries were optimal. A large number of cytogenetic surveillance studies of occupationally and environmentally exposed groups had been performed in these countries during the last decades. The national cancer incidence registries are also of a high quality; they have existed since at least the 1950s and use similar classification criteria.

In a first follow-up until 1985, 34 cancers had been diagnosed in the cohort, and there was a trend for a positive association ($P = 0.06$) between the frequency of CA and subsequent cancer risk (10). There was no such trend for SCE. The follow-up period for subjects tested with the MN test was too short to allow even tentative conclusions.

We now report a second follow-up of the cohort, consisting of 85 incident cancer cases.

PATIENTS AND METHODS

Cohort and Cytogenetic End Points. Adult individuals (>15 years of age) examined during 1970–1988 in four Swedish, two Finnish, two Norwegian, and one Danish laboratory constituted the study cohort ($n = 3182$ subjects). The subjects were originally selected for cytogenetic studies because of various, mainly occupational, exposures to mutagens or carcinogens or as unexposed referents. Subjects with cancer diagnosed before the cytogenetic analysis were not included in the cohort. Of the 3182 subjects, 1984 were studied for CA, 2019 for SCE, and 760 for MN in PBL. The distribution of modifying factors such as age, smoking habits, gender, and exposure, with respect to laboratory, is given in Table 1. A more detailed description of the exposure has been given previously (11).

For each subject, a personal identification code and the time and result of the cytogenetic analysis(es) were registered. Eight Swedish, 5 Norwegian, and 3 Danish subjects, whose personal identification codes could not be retrieved, were not included in the cohort.

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[4] The abbreviations used are: PBL, peripheral blood lymphocytes; CA, chromosomal aberrations; SCE, sister chromatid exchange; MN, micronuclei; SIR, standardized incidence ratio; CI, confidence interval.

Table 1 *Distribution of modifying factors, at the time of the initial enrollment, among the 3182 subjects in the cohort*

Laboratory[a]	No. of subjects	Median age (yr)	% Smokers	% Males	% Exposed
Sweden					
DCGL+DOMH	719	38	43	84	60
DCGS	367	37	36	50	11
IOHS	343	39	36	62	13
IMGU	232	32	20	63	83
Finland					
IOHH	699	33	43	57	51
FCRNSH	104	37	38	73	70
Norway					
DOMP	341	37	66	91	53
NRHO	159	41	40	45	68
Denmark					
IOHC	218	39	60	100	65

[a] DCGL, Department of Clinical Genetics, Lund; DOMH, Department of Occupational Medicine, Halmstad; DCGS, Department of Clinical Genetics, Karolinska Institutet, Stockholm; IOHS, Department of Occupational Medicine, National Institute of Occupational Health, Solna; IMGU, Institute of Medical Genetics, Umeå; IOHH, Institute of Occupational Health, Helsinki; FCRNSH, Finnish Centre for Radiation and Nuclear Safety, Helsinki; DOMP, Laboratory of Genetics, Department of Occupational Medicine, Porsgrunn; NRHO, the Norwegian Radium Hospital, Oslo; IOHC, Institute of Occupational Health, Copenhagen.

When the relationship between rate of chromosomal change and cancer incidence was estimated, each cytogenetic end point was evaluated separately. In order to standardize for the interlaboratory variation, the end point variables were trichotomized as follows: the 33rd and 67th percentiles were determined for each end point and each subject was classified as "low" (1–33 percentile), "medium" (34–66 percentile), or "high" (67–100 percentile) by comparing each individual end point value with the relevant percentile values (Table 2).

When CA, which were classified according to the recommendations of the International System for Human Cytogenetic Nomenclature (12), were determined, at least 100 metaphases had been scored for each individual. Gaps were not included. The culture time had been 48 or 72 h (Table 2). The CA data based on a 48-h culture time were trichotomized separately from those with a 72-h culture time.

The scoring of mean SCE was based on the analysis of 20–50 cells/individual. The MN estimate was based on the analysis of at least 1000 interphase mononuclear cells.

Information concerning Cancer Incidence. Information concerning malignant tumors (coded according to the International Classification of Diseases, revision 7) diagnosed from the start of the national cancer registries (Denmark, 1945; Norway, 1953; Finland, 1955; Sweden, 1958) up to 1990 (Sweden and Denmark) or 1991 (Finland and Norway) was obtained. However, only subjects with no cancer diagnosis at the time of the cytogenetic analysis were included in the cohort, as pointed out above.

Risk Estimates. Expected cancer incidence from the date of sampling for the cytogenetic analysis up to 1990 (Sweden and Denmark) or 1991 (Finland and Norway) was calculated using calendar year-, gender-, and 5-year age group-specific incidence for each country. These rates were obtained from the national cancer registries. Date of death, tumor diagnosis, emigration, or the 85th birthday of a person were used as individual end points, whichever occurred first.

Vital Status. Vital status was determined as of December 31, 1990, for the Swedish and Danish cohorts and as of December 31, 1991, for the Finnish and Norwegian cohorts (Table 3). The final cohort comprised 3182 subjects, of which 95.4% were still alive at the end of the observation periods. Only 20 subjects had emigrated, and 2 had been lost to follow-up.

Statistical Methods. SIRs and 95% CIs were calculated according to the Poisson distribution or according to the χ^2 distribution if the expected values were >10. The relationships between the level of cytogenetic end points and cancer risk were analyzed by linear modeling of trends in SIR (13). The test for trend was one tailed. The term "statistically significant" refers to $P \leq 0.05$ or that the 95% CI does not include 1.00.

Table 2 *Definitions of low (1–33 percentiles), medium (34–66 percentiles), and high (67–100 percentiles rates of CA, SCE, and MN in PBL for the four Swedish, two Finnish, two Norwegian, and one Danish laboratory*

	CA (%)			SCE (%)			MN (‰)		
Laboratory[a]	Low	Medium	High	Low	Medium	High	Low	Medium	High
Sweden									
DCGL + DOMH[b]	≤1.0	>1.0–2.0	>2.0	≤8.4	>8.4–9.8	>9.8	≤3.0	>3.0–5.0	>5.0
DCGL + DOMH[c]	≤1.5	>1.5–3.0	>3.0						
DCGS[c]	≤1.0	>1.0–3.0	>3.0	≤13.1	>13.1–16.1	>16.1			
IOHS[b]	≤1.0	>1.0–2.0	>2.0	≤7.9	>7.9–9.2	>9.2	≤3.5	>3.5–5.5	>5.5
IMGU[c,d]	≤1.0	>1.0–2.0	>2.0	≤7.0	>7.0–9.0	>9.0	≤2.0	>2.0–3.0	>3.0
Finland									
IOHH[b]	≤1.0	>1.0–3.0	>3.0	≤7.8	>7.8–9.3	>9.3			
FCRNSH[b]	≤0.5	>0.5–1.3	>1.3	≤8.2	>8.2–9.2	>9.2			
Norway									
DOMP[b]	≤1.0	>1.0–2.0	>2.0	≤5.6	>5.6–6.8	>6.8			
NRHO[b]	0	>0–1.1	>1.1	≤5.2	>5.2–6.4	>6.4			
NRHO[c]	≤0.9	>0.9–2.3	>2.3						
Denmark									
IOHC[b,d]	≤1.0	2	≥3.0	≤7.0	>7.0–8.0	>8.0			

[a] For abbreviations, see Table 1.
[b] Culture time for CA scoring, 48 h.
[c] Culture time for CA scoring, 72 h.
[d] Does not follow the percentile limits for CA, since 155 of 231 samples studied at IMGU were 0 and only 46 were ≥2.0 and since 98 of 197 samples studied at IOHC were ≤1.0 and only 48 were ≥3.0.

Table 3 *Vital status at the end of the follow-up periods[a] in the cohorts of previously cytogenetically tested subjects*

	Sweden		Finland		Norway		Denmark		Total	
Vital status	No.	%	No.	%	No.	%	No.	%	No.	%
Living	1591	95.8	781	97.5	453	90.6	212	97.3	3037	95.4
Dead	64	3.9	20	2.5	37	7.4	4	1.8	125	3.9
Emigrated	6	0.4	2	0.3	10	2.0	2	0.9	20	0.6
Total	1661	100.0	803	100.0	500[b]	100.0	218	100.0	3182	100.0

[a] For Sweden and Denmark, December 31, 1990, and for Norway and Finland, December 31, 1991.
[b] Another two subjects had been lost to follow-up and were not included in the cohort.

Table 4 *Number and site of cancers diagnosed after cytogenetic testing in the Swedish cohort of 1661 subjects, in the Finnish cohort of 803 subjects, in the Norwegian cohort of 500 subjects, and in the Danish cohort of 218 subjects*

Site	International Classification of Diseases, revision 7	No. of diagnosed cancers				
		Sweden	Finland	Norway	Denmark	Total
Lip	140	1				1
Tonsil	145.0	1				1
Stomach	151		1	2		3
Colon	153	5		3		8
Rectum	154	1	2	1		4
Liver	155			1		1
Pancreas	157	1		1		2
Larynx	161		1			1
Lung	162	1	6	2		9
Breast	170	2	2	3		7
Cervix uteri	171			1		1
Corpus uteri	172	2				2
Prostate	177	6	1	4		11
Testis	178	1				1
Kidney	180		2	2		4
Urinary bladder	181			2	1	3
Melanoma	190	1	1	1		3
Other skin	191	3		2		5
Brain	193	4			1	5
Parathyroid	195.1	1				1
Pituitary	195.3	1				1
Insuloma of pancreas	195.5	1				1
Bone	196			1		1
Unspecified	199			1		1
Non-Hodgkin's lymphoma	200	2	1			3
Hodgkin's lymphoma	201		1			1
Multiple myelomas	203			1		1
Lymphatic leukemia	204	1	2			2
All	140–209	35	20	28	2	85

RESULTS

A total of 85 cancers had been diagnosed in the cohort during the observation period (Table 4). Their median calendar year of birth was 1927 (range, 1901–1963), as compared with 1946 (1895–1970) for the total cohort. The mean time lags between the time for the cytogenetic analysis and the date for cancer diagnosis were 4.7 years in the Swedish cohort, 6.0 years in the Finnish cohort, 7.9 years in the Norwegian cohort, and 2.2 years in the Danish cohort.

Sixty-six subjects with cancer had previously been monitored for CA (Table 5). There was a significant positive trend ($P = 0.0009$) in SIR with CA frequency. Among those with a high frequency of CA, a cancer was diagnosed subsequently 2.5-fold as often as among those with low or medium CAs. If we break the data down by each country, significant trends were still seen for both Sweden ($P = 0.006$) and Norway ($P = 0.019$) but not for the Finnish subcohort ($P = 0.21$).

Forty-nine of the cancer cases in the cohort had been monitored for SCE before their diagnoses. No association was seen between the SCE frequency and subsequent cancer incidence in any of the national cohorts or in the total material (Table 6).

Eleven of the cancer cases in the Swedish subcohort had been monitored for MN before their diagnoses. No association was seen between the MN frequency and subsequent cancer incidence (Table 7).

DISCUSSION

The findings support the hypothesis that an elevated CA frequency in PBL predicts an increased cancer risk. The caveat still applies that this assessment is based on a relatively limited number of cases. Nevertheless, the results indicate that an increase in CA frequency among exposed subjects in a cross-sectional cytogenetic study ought to lead to the implementation of preventive measures in the environment in order to avoid future cancers.

Many factors, exogenous as well as endogenous, influence the individual CA, SCE, and MN values, *e.g.*, age, sex, genetic constitution, and different occupational and life style exposures. Several of these factors have been recorded, on individual basis, for the members of the cohort, and their impact on the cytogenetic end points has been evaluated (11). The influence of these modifying factors on the cancer predictability of the different end points may be possible to study in connection with future follow-ups of the cohort.

Table 5 *Relationship between frequency of chromosomal aberrations (low, 1–33 percentiles; medium, 34–66 percentiles; high, 67–100 percentiles) in peripheral lymphocytes and subsequent risk of total cancer morbidity*

O, observed number of cancers; E, expected number of cancers. The calculations were based on 755 subjects and 6712 person-years from the Swedish cohort, on 556 subjects and 5609 person-years from the Finnish cohort, on 471 subjects and 4601 person-years from the Norwegian cohort, and on 197 subjects and 744 person-years from the Danish cohort; total of 1979 subjects and 17666 person-years.

Frequency of CA	Sweden				Finland				Norway				Denmark				Total			
	O	E	SIR	95% CI	O	E	SIR	95% CI	O	E	SIR	95% CI	O	E	SIR	95% CI	O	E	SIR	95% CI
Low	4	5.2	0.9	0.2–2.0	6	4.1	1.5	0.5–3.2	6	8.3	0.7	0.3–1.6	0	0.8	0.0	0.0–4.4	16	18.4	0.9	0.5–1.4
Medium	3	5.7	0.5	0.1–1.5	4	3.8	1.0	0.3–2.7	4	6.6	0.6	0.7–1.5	0	0.5	0.0	0.0–7.5	11	16.6	0.7	0.3–1.2
High	15	6.2	2.4	1.4–4.0	8	3.6	2.2	1.0–4.4	15	8.5	1.8	1.0–2.9	1	0.6	1.7	0.0–9.3	39	18.9	2.1	1.5–2.8
All	22	17.1	1.3	0.8–2.0	18	11.5	1.67	0.9–2.5	25	23.4	1.1	0.7–1.6	1	1.9	0.5	0.0–2.9	66	53.9	1.2	1.0–1.6
P value for trend (one sided)			0.006				0.21				0.019				[a]				0.0009	

[a] No trend test was performed on the Danish data because of too few observations.

Table 6 *Relationship between frequency of sister chromatid exchanges (low, 1–33 percentiles; medium, 34–66 percentiles; high, 67–100 percentiles) in peripheral lymphocytes and subsequent risk of total cancer morbidity*

O, observed number of cancers; E, expected number of cancers. The calculations were based on 850 subjects and 6906 person-years from the Swedish cohort, on 669 subjects and 6292 person-years from the Finnish cohort, on 289 subjects and 2707 person-years from the Norwegian cohort, and on 208 subjects and 785 person-years from the Danish cohort; total of 2016 subjects and 15873 person-years.

Frequency of SCE	Sweden				Finland				Norway				Denmark				Total			
	O	E	SIR	95% CI	O	E	SIR	95% CI	O	E	SIR	95% CI	O	E	SIR	95% CI	O	E	SIR	95% CI
Low	3	7.4	0.4	0.1–1.2	7	3.4	2.1	0.8–4.3	6	3.3	1.8	0.7–3.9	0	0.6	0.0	0.0–5.8	16	14.7	1.1	0.6–1.8
Medium	6	7.6	0.8	0.3–1.7	3	4.0	0.8	0.2–2.2	5	4.2	1.2	0.4–2.8	0	0.6	0.0	0.0–6.1	14	16.4	0.9	0.5–1.4
High	6	7.7	0.8	0.3–1.7	6	5.1	1.2	0.4–2.6	5	4.4	1.1	0.4–2.6	2	0.8	2.4	0.3–8.6	19	18.0	1.1	0.6–1.7
All	15	22.7	0.7	0.4–1.1	16	12.4	1.3	0.7–2.1	16	11.9	1.3	0.8–2.2	2	2.1	1.0	0.1–3.5	49	49.1	1.0	0.7–1.3
P value for trend (one sided)			0.19				>0.5				>0.5				[a]				>0.5	

[a] No trend test was performed on the Danish data because of too few observations.

Table 7. *Relationship between rate of micronuclei (low, 1–33 percentiles; medium, 34–66 percentiles; high, 67–100 percentiles) in peripheral lymphocytes and subsequent risk of total cancer morbidity.*

O, observed number of cancers; E, expected number of cancers. The calculations were based on 686 subjectes and 4772 person-years from the Swedish cohort.

Frequency of MN	O	E	SIR	95% CI
Low	1	3.3	0.3	0.0–1.7
Medium	7	3.8	1.8	0.7–3.8
High	3	5.3	0.6	0.1–1.7
All	11	12.4	0.9	0.4–1.6
P value for trend (one tailed)			0.47	

In the Swedish and Norwegian subcohorts, the association between CA frequency and cancer risk was statistically significant, but in the Finnish cohort it was not. This discrepancy is probably spurious, because the number of observations in each subcohort is limited. In the first follow-up (10) the positive trend was actually strongest in the Finnish subcohort.

Although the data may indicate that SCE has less, or no, predictive value with regard to cancer, one must acknowledge that the data are still too limited to allow firm conclusions. The mechanisms by which SCE and CA arise are not well known (reviewed in Ref. 14) and the predictive value of the two assays may very well be different (15). Unlike CA, SCE is detected after replication of a DNA template containing bromodeoxyuridine, an agent that by itself induces SCE (14). Although there is an overlap in the type of agents inducing CA and SCE in PBL *in vivo* and *in vitro*, there are numerous examples of agents prompting one, but not the other, of the two events (16). The lack of an association between high SCE frequency and cancer outcome in the present study does not necessarily diminish the value of SCE as an exposure indicator, since events reflecting exposure and events related to cancer outcome may very well be unlinked (17).

As for SCE, there was no indication of any association between the MN frequency and subsequent cancer risk. Only 11 of the cancer cases had, however, been monitored for MN before diagnosis. Thus, we have to wait for future follow-ups before any conclusion can be drawn about the predictive value of this test method.

The present analysis was based on trichotomized data, and the range of CA frequency in the high group was wide. Because of the limited number of cases it is not yet meaningful to study whether very high CA scores are associated with a particularly high cancer risk. Other questions that should be possible to address in future follow-up studies of this cohort include the predictive values of the cytogenetic end points with regard to specific cancer types, the influence of age at cytogenetic testing for the predictive value of the end points, and the effects of methodological differences in sampling and laboratory procedures for the predictive value of the different end points.

We are presently forming a new study base, on the same principles as the present one, containing information concerning repeated samplings on the included subjects. Data from this cohort will also allow us to address the question of the precision of the predictive values from a single cytogenetic scoring as compared to a joint measurement from repeated sampling in the same individual.

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