

Impact of Types of Lymphocyte Chromosomal Aberrations on Human Cancer Risk: Results from Nordic and Italian Cohorts

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ABSTRACT

The frequency of cells with structural chromosomal aberrations (CAs) in peripheral blood lymphocytes is the first genotoxicity biomarker that has shown an association with cancer risk. CAs are usually divided into chromosome-type (CSAs) and chromatid-type aberrations (CTAs), with different mechanisms of formation. From a mechanistic point of view, it is of interest to clarify whether the cancer predictivity of CAs is different with respect to CSAs and CTAs. We report here cancer risk for cytogenetically tested, healthy subjects with respect to frequency of CAs, CSAs, and CTAs in peripheral blood lymphocytes, using Nordic (1981 subjects with CA data, 1871 subjects with CSA/CTA data) and Italian (1573 subjects with CA data, 877 subjects with CTA/CSA data) cohorts, with a median follow-up of 17 years. High levels of CAs at test were clearly associated with increased total cancer incidence in the Nordic cohorts and increased total cancer mortality in the Italian cohort. In the Nordic cohorts, significantly elevated cancer risks were observed for subjects with both high CSAs and high CTAs at test, and these variables showed equally strong cancer predictivity. The results of the Italian cohort did not indicate any clear-cut difference in cancer predictivity between the CSA and CTA biomarkers. There was no significant effect modification by age at test, gender, country, or time since test. The results suggest that both DNA double-strand breaks and other initial DNA lesions responsible for CSAs and CTAs are associated with cancer risk.

INTRODUCTION

Structural chromosomal aberrations (CAs) in peripheral blood lymphocytes (PBLs) have been applied for over 30 years in occupational and environmental settings (including radiation dosimetry) as a biomarker of early effects of genotoxic carcinogens (1, 2). CAs include chromosomal breaks and exchanges visible in arrested metaphase-stage cells and are usually divided into chromosome-type aberrations (CSAs) and chromatid-type aberrations (CTAs), which differ from each other morphologically. CSAs involve the same locus on both sister chromatids on one or multiple chromosomes, whereas CTAs affect one or several sister chromatids of a chromosome or several chromosomes.

The frequency of cells with structural CAs in PBLs is the first genotoxicity biomarker that has actually shown an association with overall cancer risk. An association between high CA frequency and increased cancer incidence was originally detected in a cohort of subjects examined in Nordic cytogenetic laboratories (3, 4). An independent Italian cohort study, based on cancer mortality data, arrived at

the same conclusion (5). The updated Nordic and Italian cohorts were pooled, and the cancer predictivity of the frequency of cells with CAs was corroborated (6, 7). Results from the pooled analyses also showed that the association between CA frequency and subsequent cancer incidence/mortality was not modified by sex, age, country, occupational carcinogen exposure, or smoking habits. This suggested that a high CA level, as such, is predictive of increased cancer risk, irrespective of the cause of the initial CA increase. The CA-related cancer risk did not change with time since the CA analysis, indicating that it does not reflect secondary effects of undetected cancer (6).

Another study to assess the predictive value of the CA assay for cancer was performed in a large cohort from the Czech Republic (8). After adjusting for gender, age at test, and occupational exposure, subjects with “high” CA scores had a significantly higher cancer incidence than those with “low” scores. However, this difference was especially seen in a subcohort of 225 radon-exposed miners. A more detailed analysis revealed that the frequencies of aberrant cells and chromatid breaks, but not the frequencies of CSA or chromatid exchanges, were predictive of cancer in the cohort of the radon-exposed workers (9). These results contrasted with the findings of a small case-control study, nested within a prospective Taiwanese cohort study of inhabitants in an area with arsenic-contaminated well water, in which the frequency of CSAs, but not CTAs, predicted cancer risk (10).

From both a mechanistic and a practical point of view, it is of interest to clarify whether the cancer predictivity of CAs is different with respect to CSAs and CTAs. CSAs and CTAs are induced by different types of environmental mutagens. In PBLs, which are mostly in a resting G₀ phase, agents that produce double-strand breaks, such as ionizing radiation and radiomimetic clastogenic chemicals, create CSAs. Other types of initial lesions (e.g., base alterations, cross-links, pyrimidine dimers, or single-strand breaks, depending on the inducer) induced by S-phase-dependent agents, including most chemical clastogens and UV light, give rise to CTAs (1).

It is obvious that CA generation requires one or several DNA double-strand breaks, but their formation schedule is different for CSAs and CTAs. A double-strand break is the primary lesion for CSAs (11), and CSAs observed in cultured PBLs are expected to reflect double-strand breaks mostly generated *in vivo* in G₀ stage. For lymphocyte CTAs, however, double-strand breaks are probably formed from the initial DNA lesions *in vitro* in S phase.

The formation mechanisms for CSAs and CTAs also appear to be different and involve different DNA repair systems. In G₀-G₁ lymphocytes, the formation of chromosome-type exchanges is believed to be mainly due to the repair of double-strand breaks by nonhomologous DNA end-joining and nonconservative homologous recombination repair, chromosome-type breaks representing incompletely repaired double-strand breaks, or unrepaired double-strand breaks (11). When cultured PBLs go through DNA synthesis and chromosomes are duplicated, the aberrations formed in G-G₁ are doubled, and typical CSAs can be seen in metaphase. Chromosome-type breaks are more common than exchanges, and mostly asymmetrical exchanges

Received 10/27/03; revised 12/22/03; accepted 1/7/04.

Grant support: Supported by the European Union Quality of Life Program (Contract QLK4-CT-2000-00628); the Swedish Medical Research Council; the Swedish Cancer Society; the Finnish Work Environment Fund; Associazione Italiana per la Ricerca sul Cancro (AIRC); and the Research Centre for Environmental Health, Danish Ministry of the Interior and Health. Ethical Committees approved the study in each of the participating countries.

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(such as dicentric chromosomes) can be distinguished in the traditional CA analysis (1). Chromatid-type exchanges are formed, possibly by homologous recombination, in the S phase of the cultured lymphocyte, from base modifications and single-strand breaks that are enzymatically turned into double-strand breaks; chromatid breaks would result from incomplete or failed repair (11). Most CTAs are chromatid breaks. The rare chromatid-type exchanges seen in CA analysis involve mislocation of chromosomal material to another chromosome or within the chromosome and should not be confused with sister chromatid exchanges, which are found in most cells and considered to represent symmetrical exchange of DNA segments (1).

CAs can also be formed spontaneously from double-strand breaks generated by cellular events such as topoisomerase action, DNA replication, V(D)J recombination, transposable elements, and fragile sites, and in excision repair of oxidative DNA damage, apurinic and apyrimidinic sites, and deamination products (11). When double-strand breaks are formed in unreplacated DNA in G₀ and G₁ phases of the cell cycle, CSAs may be formed, whereas double-strand breaks generated in duplicated DNA in the S phase and G₂ give rise to CTAs. S-phase-dependent genotoxic substances formed in cells (e.g., ethylene oxide from ethylene) will also generate CTAs.

Thus, CSAs and CTAs have different mechanisms of formation resulting from different kinds of DNA lesions induced by different types of clastogens. Therefore, information on whether the cancer predictivity of CAs is due to CSAs, CTAs, or both provides important indications as to the origin of the cancer-predicting CAs.

In the present study, we have collected new data on CA type from the individual laboratories contributing to the Nordic and Italian cohorts, and have prolonged the follow-up periods of the cohorts. Our major objective was to evaluate whether the cancer predictivity of CAs is different with respect to CA type.

MATERIALS AND METHODS

The Nordic Cohorts. Cohorts of subjects tested for CAs were established in Sweden, Finland, Norway, and Denmark (3, 4, 6). Altogether, the Nordic cohorts included 1981 subjects. In the Swedish and Danish cohorts, seven and six additional subjects, respectively, were included after our previous report was published (6), because complementary individual data had been registered.

The percentage males in the cohort varied between 69 and 100% for the different countries, and median age at test varied between 34 and 39 years. The median calendar year at test varied between 1981 and 1987. Information on malignant tumors diagnosed from the date of the cytogenetic testing until the end of 1999 (Sweden and Denmark) or 2000 (Norway and Finland) was obtained from the National Cancer Registries. The median follow-up time was 16.5 (80% central range, 12.6–22.0) years, considering all subjects.

The Italian Cohort. A cohort of 1573 subjects tested for CAs was established in Italy (6). Seventy-six % were males; their median age at test was 39 years, and the median calendar year at test was 1983. The follow-up data with specific reference to cancer mortality were updated during 2002. Causes of death were obtained from the municipality of residence. The median follow-up time was 16.6 (80% central range, 9.2–25.4) years.

Collection of Data on CA Type. Data on the type of CAs were collected from the participating Nordic and Italian cytogenetic laboratories, including the number of cells scored, chromatid breaks, chromosome breaks, dicentrics (including possible multicentrics), chromatid exchanges, ring chromosomes, marker chromosomes, and aberrant cells, in addition to birth date, CA sample collection date, and culture time. The data were obtained either from written documents of individual analysis results or computerized databases by the cytogenetic personnel of each laboratory. Whenever necessary, the figures were checked from the original scoring sheets, if available. Information on individual CTA and CSA frequencies was obtained for all cohort participants, except for 110 Swedish and 696 Italian subjects, for whom the original records contained insufficient information or could not be retrieved.

Definitions of CA, CTA, and CSA. CA was defined as the number of cells with aberrations, excluding gaps, per 100 cells (3, 4, 6). At least 100 metaphases had been scored from each individual. CSA was defined to include chromosome-type breaks, ring chromosomes, marker chromosomes, and dicentrics, and CTA included chromatid-type breaks and chromatid exchanges. The numerics of CTA and CSA were based on the number of corresponding aberrations (not cells with aberrations) per 100 cells, because, in general, the type of aberrations could not be linked to the specific scored cells based on the information in the original records.

The results on CA were trichotomized with respect to laboratory and culture time (48–50 or 60–80 h), to standardize for those sources of variation (3, 4, 6). Before the statistical analyses, we decided to dichotomize the CTA and CSA variables, based on the median values with respect to laboratory and culture time (Table 1), because the data on these variables were heavily concentrated to low, mostly zero, values. Subjects with CTA/CSA results equal to the corresponding median value were categorized into the “low” group. Each subject could be allocated in one of the four categories “CTA low, CSA

Table 1 Distributions of chromatid-type aberrations (CTAs; number of chromatid-type breaks and chromatid exchanges per 100 cells) and chromosome-type aberrations (CSAs; number of chromosome-type breaks, ring chromosomes, marker chromosomes, and dicentrics per 100 cells) among the tested subjects, with respect to laboratory and culture time

Cohort	Laboratory	Culture time (h)	No. of subjects	CTA		CSA	
				Median	Range	Median	Range
Sweden ^a	A	48	180	0.5	0.0–6.0	0.0	0.0–7.0
	A	72–80	235	0.5	0.0–3.0	2.0	0.0–9.0
	B	72–80	231	0.0	0.0–5.0	0.0	0.0–12.0
Finland	C	48–50	375	1.0	0.0–9.0	1.0	0.0–8.0
	C	60–72	54	1.0	0.0–10.0	1.0	0.0–10.0
	D	48	126	0.4	0.0–4.4	0.4	0.0–2.8
	D	72	2	0.6	0.0–1.2	2.0	1.7–2.3
Norway	E	48	112	0.8	0.0–6.0	0.0	0.0–4.0
	E	66–72	19	1.0	0.0–5.0	0.0	0.0–4.0
	F	48	340	0.5	0.0–5.0	0.5	0.0–8.0
Denmark	G	48	197	1.0	0.0–4.0	1.0	0.0–5.0
Italy ^b	H	48	55	0.0	0.0–6.0	0.0	0.0–2.7
	I	48	327	1.3	0.0–12.0	1.0	0.0–7.0
	I	72	127	2.0	0.0–13.0	1.3	0.0–6.0
	J	48	69	0.0	0.0–7.0	0.0	0.0–4.0
	K	48	58	0.0	0.0–3.0	0.0	0.0–3.0
	L	72	56	4.0	0.7–27.3	2.0	0.0–7.3
	M	48	42	0.0	0.0–0.0	0.0	0.0–2.0
	M	72	97	0.0	0.0–4.0	0.0	0.0–7.0
	N	48	46	1.0	0.0–4.0	0.0	0.0–3.0

^a Data on CTA and CSA were available for 646 of the 756 Swedish subjects.

^b Data on CTA and CSA were available for 877 of the 1573 subjects.

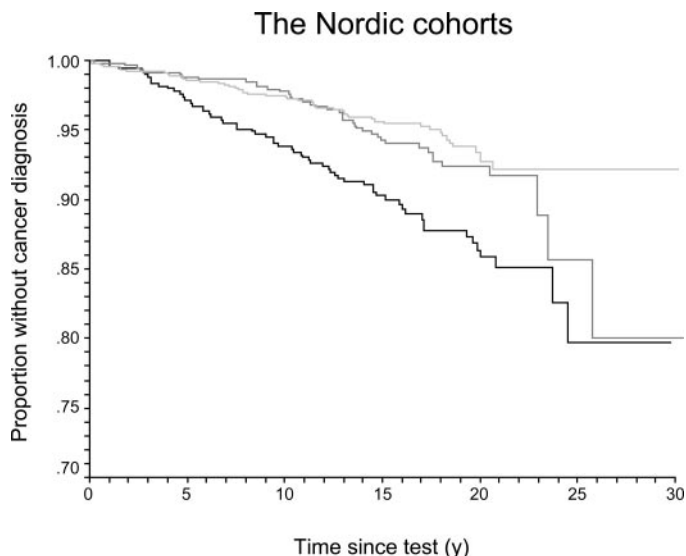


Fig. 1. Kaplan-Meier curves for total cancer incidence observed in the Nordic cohorts, with respect to the chromosomal aberration results at test (light gray curve, low; dark gray curve, medium; black curve, high).

low; “CTA low, CSA high,” “CTA high, CSA low,” and “CTA high, CSA high.” This categorization of CTA/CSA did not yield overlapping categories (each subject is placed in one of the four categories), in contrast to considering CTA and CSA separately. However, we also present effect estimates based on each type of aberration (CTA high versus low and CSA high versus low).

Statistical Methods. The Kaplan-Meier method was used to describe total cancer incidence/mortality during the follow-up of the cohorts. The log-rank test was used to compare the crude incidence or mortality between the defined CA groups and CTA/CSA groups of subjects. The effect of CA as well as of CTA/CSA on total cancer incidence or mortality was estimated by Cox’s regression modeling (12). Hence, the effect measure was an incidence ratio (IR) or a mortality ratio (MR). The reported effect estimates were adjusted for age at test (five age groups, ≤45, 46–50, 51–55, 56–60, and 61+ years), gender, and, for the Nordic cohorts, country. Modification of the effects of CA and CTA/CSA by each covariate was tested by using Wald’s test for the relevant interaction term included in the model (12). We stratified the follow-up data by time since test <12 and ≥12 years (the median follow-up time among the cancer cases was 10.9 years in the Nordic cohorts and 13.1 years in the Italian cohort), to test for possible effect modification by time since test (alternative cutoff points between 10–14 years yielded similar results).

RESULTS

The Nordic Cohorts. During the follow-up, 150 Nordic subjects examined for CAs were diagnosed with cancer (Sweden, *n* = 52;

Finland, *n* = 39; Norway, *n* = 53; and Denmark, *n* = 6). The total cancer incidence observed in the low, medium, and high CA groups differed (Fig. 1; *P* < 0.001; log-rank test). The adjusted IR estimates indicated elevated cancer risk for subjects with increased levels of CAs at test (Table 2). No significant effect modification by age at test (*P* = 0.3), gender (*P* = 0.22), country (*P* = 0.6), or time since test (*P* = 0.3) was found.

Among the 1871 subjects examined for CTA/CSA, 143 were diagnosed with cancer. Regardless of type of aberration, a significant effect was found (CTA high versus low IR_{adjusted} = 1.46 [95% confidence interval, 1.05–2.03]; CSA high versus low IR_{adjusted} = 1.42 [1.02–1.99]). The total cancer incidence observed in the four CTA/CSA groups differed (Fig. 2; *P* = 0.003). The adjusted IR estimates indicated significantly elevated cancer risk for subjects with high CTAs and high CSAs at test (Table 2). The estimated IR for the subjects with low CTAs and high CSAs (reference group: low CTA and low CSA) was similar to the IR for those tested with high CTA and low CSA. Thus, a significantly elevated risk of cancer was associated with both high CTA and high CSA in the Nordic cohort. No significant effect modification by age at test (*P* = 0.6), gender (*P* = 0.12), country (*P* = 0.6), or the time since test (*P* = 0.5) was found.

The Italian Cohort. During the follow-up, 90 Italian subjects examined for CAs died from a malignant tumor. The total cancer mortality observed in the low, medium, and high CA groups differed (Fig. 3; *P* = 0.02). The adjusted MR estimates indicated elevated risk of dying from a malignant tumor for subjects with increased levels of CAs at test (Table 2). No significant effect modification by age at test (*P* = 0.9), gender (*P* = 0.8), or time since test (*P* = 0.8) was found.

Among the 877 subjects examined for CTA/CSA, 67 died from a malignant tumor. CTAs indicated a somewhat more pronounced effect on total cancer mortality (high versus low MR_{adjusted} = 1.46 [0.90–2.37]) than CSA (high versus low MR_{adjusted} = 1.12 [0.68–1.85]). The total cancer mortality observed in the four CTA/CSA groups (Fig. 4; *P* = 0.05) differed. The adjusted MR estimated did not reveal a clearly consistent effect pattern of CTA/CSA at test; only the subjects with CTA high and CSA low had significantly higher total cancer mortality than did the reference subjects (with both CTA and CSA low; Table 2). No significant effect modification by age at test (*P* = 0.7), gender (*P* = 0.3), or time since test (*P* = 0.9) was found.

DISCUSSION

A major result of the present study was that the type of CAs (CSAs or CTAs) has no obvious modifying impact on the cancer predictivity

Table 2 Total cancer incidence ratio (IR) and mortality ratio (MR) estimates comparing the subjects previously studied for chromosomal aberrations (CAs), chromatid-type aberrations (CTAs), and chromosome-type aberrations (CSAs)

The estimates were obtained from multivariate Cox regression analyses with adjustment for age at test (≤45, 46–50, 51–55, 56–60, and 61+ years), gender, and country (Sweden, Finland, Norway, and Denmark)

Group of subjects	Nordic cohorts		Italian cohort	
	No. of cases/ No. of subjects	IR ^a (95% CI) ^b	No. of cases/ No. of subjects	MR ^c (95% CI)
Model with CA				
CA low ^d	49/894	1.00	23/593	1.00
CA medium	41/591	1.21 (0.79–1.83)	33/555	1.42 (0.82–2.44)
CA high	60/496	1.87 (1.28–2.74)	34/425	1.93 (1.12–3.30)
Model with CTA/CSA				
CTA low, CSA low ^d	40/756	1.00	14/355	1.00
CTA low, CSA high	28/328	1.35 (0.83–2.20)	17/157	1.84 (0.90–3.78)
CTA high, CSA low	34/451	1.39 (0.87–2.20)	21/203	2.35 (1.19–4.62)
CTA high, CSA high	41/336	1.91 (1.23–2.96)	15/162	1.58 (0.75–3.32)

^a Wald’s test for a multiplicative trend of IR across the CA groups yielded *P* = 0.001.

^b CI, confidence interval.

^c Wald’s test for a multiplicative trend of MR across the CA groups yielded *P* = 0.016.

^d Reference category.

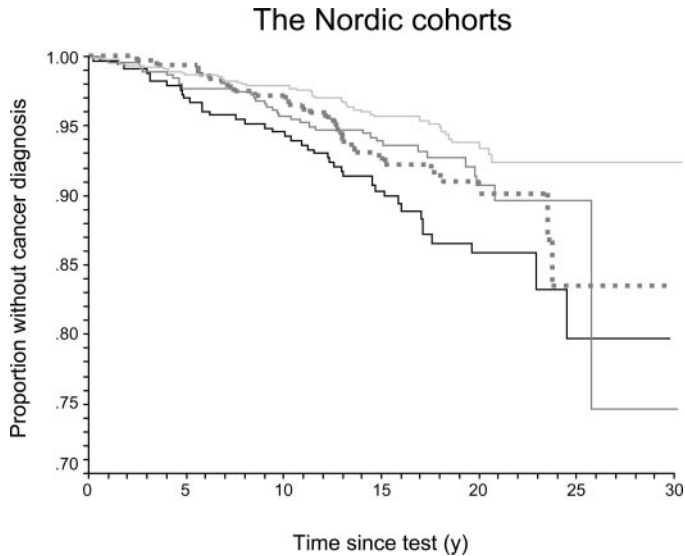


Fig. 2. Kaplan-Meier curves for total cancer incidence observed in the Nordic cohorts, with respect to the chromatid-type aberration (CTA)/chromosome-type aberration (CSA) results at test (light gray curve, low CTA, low CSA; dotted curve, low CTA, high CSA; dark gray curve, high CTA, low CSA; black curve, high CTA, high CSA).

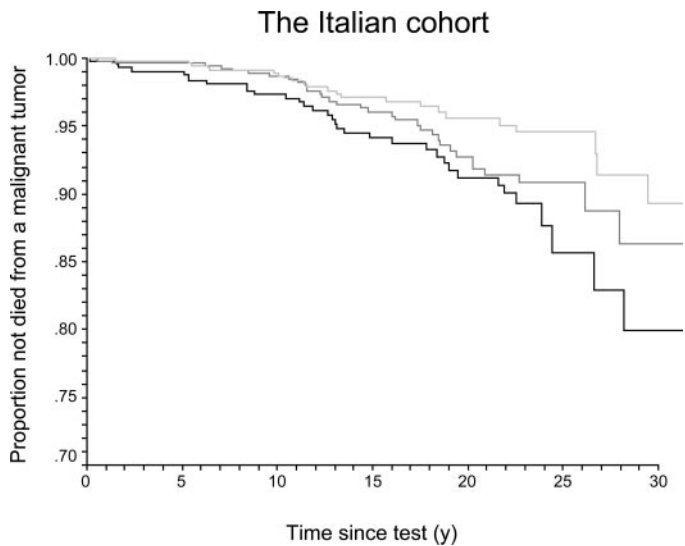


Fig. 3. Kaplan-Meier curves for total cancer mortality observed in the Italian cohort, with respect to the chromosomal aberrations results at test (light gray curve, low; dark gray curve, medium; black curve, high).

of CAs. Findings from the Nordic cohort indicated cancer predictivity of similar strength for CSAs and CTAs. The results of the Italian cohort were more difficult to interpret. Nevertheless, focusing on the 95% confidence intervals around the effect estimates, no difference in cancer predictivity between CSAs and CTAs could be confirmed. A possible explanation for the less clear-cut Italian results may be that for five of the nine cytogenetic laboratories (providing 26% of the subjects), both median CTA and CSA values were zero (Table 1), resulting in too crude a classification of the cytogenetic biomarkers for these subjects. This was much less of a problem in the Nordic cohort.

Our results suggest that both DNA double-strand breaks leading to CSAs and other types of DNA lesions converted into CTAs in the S phase are associated with cancer predictivity. The present findings are in contrast to the small Taiwanese study, in which the frequency of CSAs, but not CTAs, predicted cancer risk in a population exposed to

arsenic in well water (10). The difference might be explained assuming that, in the Taiwanese cohort, the arsenic exposure was associated with CSA increase and that many of the cancers observed were due to the arsenic exposure, whereas the factors responsible for the cancer predictivity of chromosome damage in the Nordic-Italian cohort were unknown and probably complex.

In the Czech subcohort of 225 radon-exposed workers, cumulative radiation dose was weakly correlated with the percentage of cells with CAs (Spearman's correlation, $r_s = 0.16$) and with the frequency of chromatid breaks ($r_s = 0.22$), but not with CSAs (9). These results are surprising, because ionizing radiation is known to cause CSAs rather than CTAs in PBLs (1). The associations in the Czech radon cohort between CA frequency and total cancer and lung cancer, respectively, were not mediated through CSAs, but through the frequency of chromatid breaks and the percentage of cells with CAs (9). Again, this is an unexpected result, as an effect of radiation-induced CSA, rather than of chromatid breaks, would have been expected. The finding might reflect the effects of other occupational exposures in the mines such as engine exhaust (13). In general, the results from the Czech study are, however, difficult to interpret, because the cancer predictive value of the CA test in the radon-exposed cohort was obtained by using the mean value of all individual CA tests for categorizing the subjects (8, 9). Most of the subjects in the radon-exposed cohort had been cytogenetically examined several times over the years. When only the first CA test result was used, as in the Nordic and Italian studies (6, 7), the cancer predictivity of the CA score disappeared (8). The drawback with the analysis of the Czech cohort is that using the mean value of all CA tests (including those after the start of follow-up for cancer) for categorizing subjects prevents time-related analyses of the association between CA score and cancer.

In both the Nordic and Italian cohorts, there were clear effects of CAs on cancer incidence and cancer mortality, respectively. Moreover, there was no indication that the strength of the cancer predictivity decreased with time since test. Decreasing cancer predictivity with respect to time since test would have supported the view that undetected cancer may have increased the CA frequencies. Our results are coherent with two alternative hypotheses: that longstanding exposure to carcinogens in the diet, in the general environment, or through endogenous sources might affect both the CA frequency and cancer

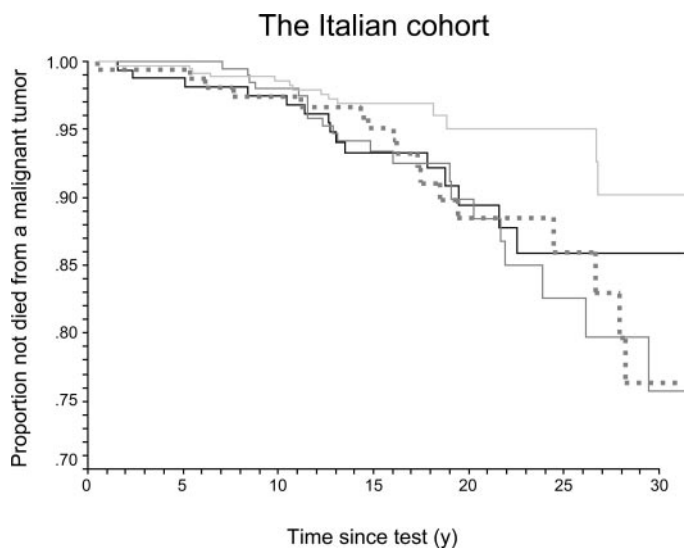


Fig. 4. Kaplan-Meier curves for total cancer mortality observed in the Italian cohort, with respect to the chromatid-type aberration (CTA)/chromosome-type aberration (CSA) results at test (light gray curve, low CTA, low CSA; dotted curve, low CTA, high CSA; dark gray curve, high CTA, low CSA; black curve, high CTA, high CSA).

risk, or that individual susceptibility factors may determine the association between CA and cancer incidence. The observed slight (non-significant) increase in CA cancer predictivity with time would actually suggest the involvement of exposure to genotoxic carcinogens, unidentified in our previous analysis of occupational exposures and smoking (7). Unfortunately, there is no information available on dietary parameters or environmental exposures in the Nordic and Italian cohorts. Thus, this hypothesis cannot be tested in the present database. With respect to the other hypothesis, previous studies have suggested that various common polymorphisms of carcinogen-metabolizing enzymes influence both the level of chromosome damage (14–20) and cancer risk (see 21–25). Furthermore, several studies have indicated a cancer association for the recently discovered genetic polymorphisms of DNA repair and folate metabolism (26–51). Evidence has also started to appear suggesting that some of these polymorphisms could influence the rate of chromosome damage (Refs. 52–60; see also Footnote 7⁷). Genetic susceptibility factors may directly affect the CA frequency in PBLs.

To sum up, the results of the present study support the conclusion that CA frequency in PBLs, as a biomarker of cancer risk, will not be improved by separating CSAs from CTAs. This suggests that both DNA double-strand breaks and other DNA lesions responsible for CSAs and CTAs, respectively, are associated with cancer risk. Because the findings were not entirely consistent between the Nordic and Italian cohorts with respect to CTAs and CSAs separately predicting cancer risk, additional studies with larger cohorts and consistent data on CA classification are warranted. It may be especially interesting to evaluate the possible effect of carcinogen exposure on the cancer risk predictivity of CTAs and CSAs, dividing the exposing agents in S-phase-dependent and S-phase-independent clastogens. The strength of the cancer predictivity by CA frequency did not decrease with time since test, which is circumstantial evidence in favor of individual susceptibility factors or long-standing exposure to dietary, environmental, or endogenous carcinogens explaining the association between CA frequency and cancer incidence.

ACKNOWLEDGMENTS

We are indebted to Aage Andersen, Cecilia Lando, Zoli Mikoczy, Anneli Ojajarvi, and Eero Pukkala for epidemiological assistance and Hilikka Järventaus and Thorkil Boisen for compilation of historical scoring data.

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Cancer Res 2004;64:2258-2263.

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