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Individual Susceptibility to Induced Chromosome Damage and Its Implications for Detecting Genotoxic Exposures in Human Populations[1]

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ABSTRACT

In a previous study, we observed a bimodal distribution of sensitivity to sister chromatid exchange (SCE) induction by diepoxybutane (DEB) in lymphocytes from healthy individuals. Twenty-four % of the participants had increased sensitivity to *in vitro* induction of SCEs and chromosomal aberrations. These same participants also had significantly higher frequencies of uninduced or baseline SCE frequencies. In the present study, we measured baseline and DEB-induced SCE frequencies in 55 healthy female volunteers. Eleven of 55 [20%] women were relatively sensitive to DEB induction of SCEs. Baseline SCE frequencies in these sensitive individuals [10.4 ± 0.7 (SD) SCEs/cell] were significantly higher [$P < 0.001$; Student's t test] than baseline SCE frequencies in the remaining 44 individuals [8.0 ± 0.9 SCEs/cell]. Similar increases in SCEs were observed when the analysis was restricted to the upper 10% of the SCE distribution (high frequency SCE analysis). The phenotype of DEB sensitivity accounted for 58% of the variation among individual SCE scores. Given the population frequency of this sensitivity to SCE induction and the high proportion of variance in SCEs for which it accounts, failure to account for this factor could seriously distort conclusions about SCE measures associated with other environmental exposures. The most likely result of such unexplained variability (type II error) would be bias toward the null hypothesis. Also, the likelihood that individual variations contribute to false positive results is expected to be greatest in studies that compare small numbers of exposed and nonexposed individuals. To summarize, these results confirm our earlier study and show that increased baseline SCE frequencies can be indicative of increased sensitivity to certain classes of mutagenic carcinogens. Identification of DEB-sensitive persons could be used to increase the sensitivity of SCE analysis in monitoring studies to detect exposure to genotoxins.

INTRODUCTION

Recent epidemiological studies have sought to identify carcinogen exposure through the use of cytogenetic and molecular markers (1–6). The advantages of using laboratory-based biomonitoring in cancer epidemiology include reduction in exposure misclassification and estimation of biologically effective dose, which takes into account individual differences in sensitivity to carcinogen exposure (*e.g.*, polymorphic drug metabolism). One of the most widely used biomonitoring approaches has been the enumeration of SCEs[3] in peripheral blood lymphocytes (7). SCE analysis is a highly sensitive, although nonspecific, marker of exposure to genotoxins, particularly for those agents that induce stable covalent DNA adducts (8, 9). Because SCE frequency is a nonspecific marker, definitive identification of mutagen exposure requires exposure histories, longitudinal analyses, and, when feasible, confirmatory biochemical studies.

In healthy individuals, a wide range of SCE frequencies are observed; cigarette smoking is the single most important factor accounting for the largest identified component (approximately 20%) of interindividual variation in SCEs (10). Consequently, monitoring studies using SCE analysis must be designed and carried out to allow adjustments for the effects of cigarette smoking. Similar adjustments would be needed if an individual's intrinsic SCE frequency were to vary independently of exposure. We have recently discovered that sensitivity to SCE induction by the potent carcinogen DEB is bimodally distributed in human lymphocytes (11, 12) and that increased DEB sensitivity is associated with increased frequencies of baseline SCEs. Sensitivity to DEB appears to be independent of any other known mutagen exposure (*e.g.*, organic solvents, cigarette smoking). A pilot twin study of familial involvement in the bimodal response indicated that familial factors are associated with DEB sensitivity (13).

In the present study, we have examined an independent sample of normal individuals to confirm the presence of bimodal DEB sensitivity and to study its relationship to variations in baseline SCE frequencies. The results confirm the presence of a bimodal distribution of sensitivity to SCE induction in normal blood donors and that the phenotype of increased sensitivity to DEB induction of SCEs is an important source of variation in baseline SCE frequencies. An improved understanding of this trait may greatly increase the power of human SCE monitoring studies to detect carcinogen-exposed individuals.

MATERIALS AND METHODS

Experimental Subjects. Participants were 55 healthy female volunteer employees of the University of California, San Francisco, taking part in an epidemiological study of the natural history of breast disease. Volunteers were selected through a mass mailing to all female university employees inviting them to participate in the study. The women studied consisted of 55 consecutive volunteers. Each woman completed a questionnaire and provided a blood sample. The questionnaire elicited demographic data, age, occupation, medical status (including history of cancer), diet, smoking history, and prior or current exposure to medications or environmental agents that could affect the SCE assay (*e.g.*, X-rays, birth control pills, estrogens, thyroid hormones, anticancer chemotherapy).

Cell Culture and Cytogenetic Studies. Venous blood was drawn from donors into sodium-heparinized vacutainers. For cell cultures, 0.5 ml of whole blood was added to a final volume of 5 ml of RPMI 1640 tissue culture medium containing 10% fetal calf serum, 0.1 ml of phytohemagglutinin (DIFCO Laboratories, Detroit, MI), penicillin (100 units/ml), and streptomycin (100 μg/ml) in 1-oz glass prescription bottles. Lymphocytes were treated with DEB ([±]-1,3-butadiene diepoxide; Aldrich Chemical Company, Milwaukee, WI) at 21 h of culture. DEB was diluted in sterile water and a fresh stock solution was prepared for each experiment. At 24 h of culture, 50 μM bromodeoxyuridine was added to each culture. Cells were cultured for 72 h at 37.5°C in 5% CO_2 with 98% relative humidity. Two h before fixation, Colcemid (2 ×

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[3] The abbreviations used are: SCE, sister chromatid exchange; DEB, diepoxybutane; HFC, high frequency cell.

10^{-7} M, final concentration; CIBA Pharmaceuticals, Summit, NJ) was added. Cells collected by centrifugation were exposed for 8 min to 0.075 M KCl at 37°C to spread the chromosomes and fixed three times in methanol:acetic acid (3:1). The resulting suspension was dropped onto microscope slides and differentially stained by a modification of the fluorescence-plus-Giemsa technique (14). The slides were immersed for 15 min in a solution of 5 μg Hoechst 33258 (Riedel-De Haen AG, Hannover, Federal Republic of Germany) per ml in Sorensen's buffer, pH 6.8, and then washed, dried, mounted with buffer under the coverslip, and exposed for 8 min to black light 2 cm from 2 BLB GE tubes at 55°C. The slides were then stained for 4 min in a 3% Giemsa solution made in the same Sorensen's buffer. All SCE analyses were performed on coded slides and scored blindly.

Statistical Analysis. The mean SCE/cell was calculated by scoring 50 cells/individual for baseline SCEs and by scoring 30 cells for DEB-induced SCEs. DEB-sensitive and -resistant groups were defined as: DEB sensitive, >90 SCEs/cell; and DEB resistant, <90 SCEs/cell. The mean baseline SCE/cell, as well as the mean SCE in the upper 10% of the SCE distribution (HFC), in resistant and sensitive individuals were compared using Student's *t* test. An alternative method of comparing HFC frequencies was also applied in which HFC numbers are pooled within groups and compared using χ^2 analysis (15). Comparisons were also made using a log transformation of individual SCE scores. Linear regression assessed the effects of age on baseline SCEs/cell and DEB-induced SCEs. Analysis of variance assessed the relative contribution of factors (*e.g.*, race, smoking, DEB sensitivity) to the variance in SCE scores. Analyses of variance were also carried out following logarithmic transformation of the SCE data. Statistical runs were performed using statistical analysis system (SAS) software. SAS is a registered trademark of the SAS Institute Inc..

RESULTS

The study group consisted of 55 women (42 white, 6 black, 7 Asian) with a mean age of 44 ± 7 (SD) years. There were 9 current smokers in the group and 46 nonsmokers, including 16 former smokers. None of the participants had a history of cancer or exposure to medications or agents known to affect SCE frequencies. Eleven individuals (20%) had DEB-induced SCE scores that were >90 SCEs/cell and were classified as relatively sensitive to DEB induction of SCEs, whereas the remaining 44 were classified as relatively resistant to SCE induction (Fig. 1; Table 1). The resistant subgroup had a mean of 65.6 ± 7.4 SCEs/cell (range, 52.6–82.2) compared with a mean of 110.6 ± 6.5 (range, 103.2–124.8) in the sensitive subgroup. The difference between the two modes of the DEB-treated SCE distribution was 45 SCEs/cell; in our previous study, the difference observed was 46.7 SCEs/cell (11). The difference in induced SCEs between the two modes of the SCE distribution is large compared with the within-subject variation in SCE induction which we have estimated to be approximately 10% (11). Neither race nor age was correlated with either DEB-induced or baseline SCEs/cell. Because of the small number of nonwhites examined, the present study cannot adequately assess the role of race in DEB sensitivity. Also, there was no significant increase observed in baseline SCEs associated with smoking in the present study. However, when the study group was stratified according to DEB sensitivity (Table 1), smokers who were DEB resistant had higher baseline SCE frequencies. This result may be due to the fact that nonsmokers who are DEB sensitive have higher baseline SCE scores than smokers who are DEB resistant (See Table 1, Footnotes *l* and *h*).

Table 1 *Baseline and HFC SCE frequencies in smokers and nonsmokers according to in vitro DEB sensitivity*

		Baseline SCE frequency		HFC[a] SCE frequency	
	N	Mean ± SD	Range	Mean ± SD	Range
Nonsmokers	46	8.4 ± 1.3[b]	6.3–11.3	15.9 ± 2.8	10.8–23.8
Smokers	9	9.1 ± 0.9[c]	8.0–10.9	16.9 ± 2.6	14.2–22.6
DEB resistant[d]	44	8.0 ± 0.9[e]	6.3–10.7	15.3 ± 2.3[f]	10.8–21.4
Nonsmokers	37	7.8 ± 0.8[g]	6.3–10.7	15.1 ± 2.4	10.8–21.4
Smokers	7	8.8 ± 0.6[h]	8.0–9.6	16.3 ± 1.6	14.2–18.2
DEB sensitive[i]	11	10.4 ± 0.7[j]	9.3–11.3	19.1 ± 2.6[k]	15.4–23.8
Nonsmokers	9	10.5 ± 0.7[l]	9.5–11.3	19.1 ± 2.3	16.0–23.8
Smokers	2	10.1 ± 1.1	9.3–10.9	19.0 ± 5.1	15.4–22.6

[a] Mean SCE frequency in the 10% of the cells in the SCE distribution with the highest number of SCEs.
[b] Comparison value for Footnote *c*.
[c] Not significantly greater than Footnote *b*; $P = 0.130$ (Student's *t* test).
[d] Individuals whose DEB-induced SCE frequency is in the lower of the two modes in the population.
[e] Comparison value for Footnote *j*.
[f] Comparison value for Footnote *k*.
[g] Comparison value for Footnote *h*.
[h] Significantly greater than Footnote *g*. $P = 0.003$ (Student's *t* test).
[i] Individuals whose DEB-induced SCE frequency is in the higher of the two modes in the population.
[j] Significantly greater than Footnote *e*; $P < 0.001$ (Student's *t* test).
[k] Significantly greater than Footnote *f*; $P < 0.001$ (Student's *t* test).
[l] Significantly greater than Footnote *h*; $P < 0.001$ (Student's *t* test).

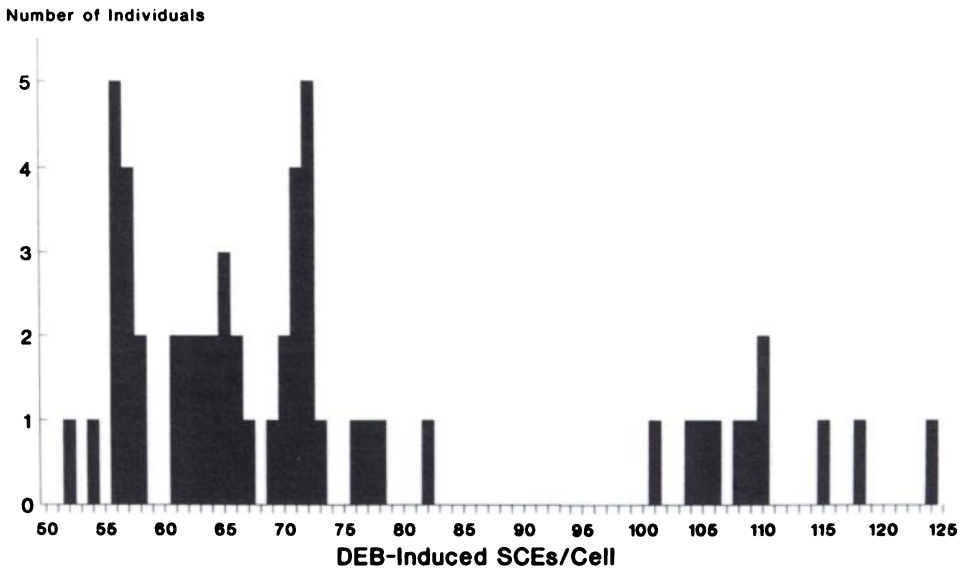

Fig. 1. Distribution of DEB-induced sister chromatid exchange frequencies in 55 healthy female blood donors.

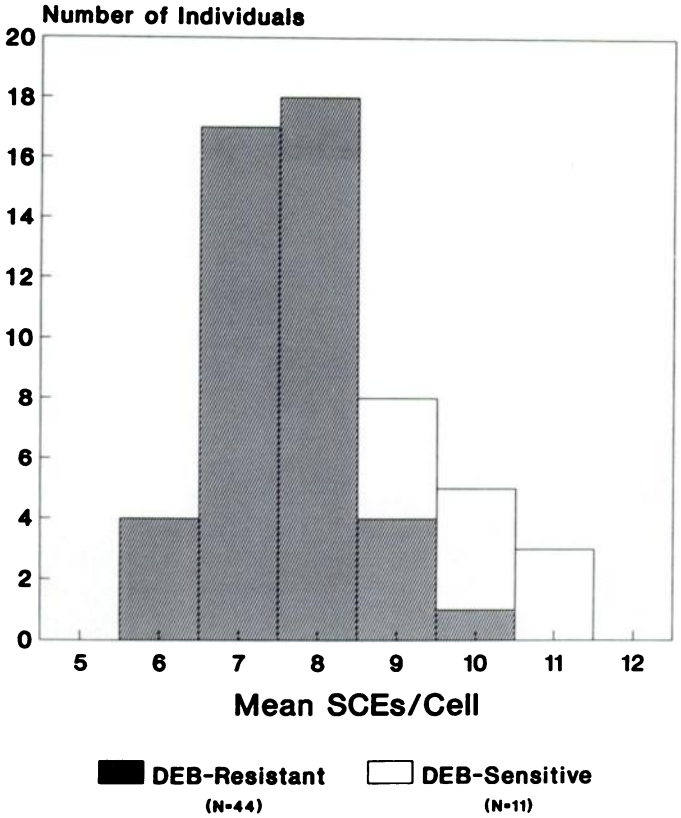

Fig. 2. Distribution of baseline SCE frequencies in 55 blood donors. □, SCE scores for individuals relatively sensitive to SCE induction by DEB; ▨, SCE scores for individuals relatively resistant to SCE induction by DEB (see text for definition of DEB sensitivity).

Smokers in the DEB-sensitive group were not found to have high baseline SCEs compared with nonsmokers; however, this may have been due to the small number of DEB-sensitive smokers examined (*i.e.*, 2). The mean baseline SCE/cell in DEB-sensitive individuals was increased compared with DEB-resistant individuals. Similar results were observed in high frequency SCE analyses when HFC frequencies were calculated for each individual (Table 1) or when HFC numbers are pooled over all individuals within each group (data not shown). Baseline SCE frequencies for persons sensitive to DEB induction of SCEs fell in the upper tail of the distribution of SCE scores (Fig. 2). ANOVA (Table 2) indicated that smoking contributed little to the variance in individual SCE scores, whereas DEB sensitivity accounted for up to 58% of the variance in baseline SCE scores. In our first study, DEB sensitivity accounted for 12–15% of the variation (12). In the present analysis, the combination of DEB sensitivity and smoking explained approximately 61% of the variance in baseline SCEs. Similar results were obtained in analyses of log-transformed data.

DISCUSSION

In our first study, we observed a bimodal distribution of SCEs induced *in vitro* by DEB. Although hypersensitivity to the induction of chromosomal damage *in vitro* has been well documented in rare genetic syndromes (16), with the exception of SCE induction by epoxide substrates in glutathione *S*-transferase deficiency (17), we know of no other example of segregation of the SCE marker into distinct groups in the general population. Consequently, in the present study, we wanted to confirm the existence of the bimodal response in an independent sample of normal blood donors. In several respects, the data from the present study are similar to those of the initial study, although some differences were observed. The prevalence of DEB sensitivity in the present study (20%) is very similar to our previous estimate of 24% (12). The absolute number of SCEs induced and the differences in SCEs between sensitive and resistant subgroups are almost identical (within 5%) to the previous measurements. Thus, the present study indicates that bimodal sensitivity to DEB is a reproducible phenomenon. In this sample, however, the contribution of the phenotype of DEB sensitivity to variations in baseline SCEs was 4 times greater than in the previous study. These differences may be related to the characteristics of the present study group, which consisted solely of women, in contrast to the previous study group which consisted mainly of men. Moreover, there were fewer smokers in the present study population. Future studies should consider gender and smoking in greater detail in relation to baseline SCEs in DEB-sensitive individuals.

The mechanisms underlying increased sensitivity to DEB and the associated increase in baseline SCE frequencies are unknown. Factors such as age, smoking, alcohol use, and RBC or WBC counts do not appear to be related to the bimodal distribution of DEB sensitivities (12). Twin studies have indicated that familial factors are associated with the bimodal distribution of chromosome damage induced by DEB. Further studies are needed to determine the heritability of the phenotype of DEB sensitivity and its possible mode of inheritance. If genetic factors are implicated, then the marker of DEB sensitivity could provide a means of studying how genetics contribute to baseline SCE frequencies in nonexposed and carcinogen-exposed persons.

Regardless of the mechanisms involved in DEB sensitivity, the population frequency of this trait and the impact of the trait on SCE measures have substantial implications for the use of SCEs as an end point in biomonitoring studies of chemical exposures. Because such a large portion of the variation in baseline SCE frequencies (58%) is attributable to DEB sensitivity, potential differences in SCEs due to other exposures will be obscured if the trait is not considered in analyses. The most likely result of such unexplained variability is bias toward the null hypothesis (type II error, false negatives). This effect was illustrated, in our study, by the failure to observe a significant smoking effect on baseline SCE frequencies until adjustments for the phenotype of DEB sensitivity were made. Using the DEB marker in the present study allowed the detection of a subtle 12% increase in smoking-related SCE frequencies which otherwise would have remained undetected.

Identification of DEB-sensitive individuals in exposed and nonexposed populations can thus be used to increase the power of SCE analysis to detect exposure-related effects. It is important, however, to determine if SCEs associated with DEB

Table 2 *Analysis of sources of variation in baseline SCE frequencies without and with logarithmic transformation*

Source of variation	d.f.	% of variance in SCEs explained	*F*	*P*
Baseline SCE				
Smoking[a]	1	3.4	4.6	0.036
DEB class (high/low)[b]	1	57.6	78.3	0.0001
Log-transformed baseline SCE				
Smoking	1	3.6	4.8	0.032
DEB class (high/low)	1	56.8	75.9	0.0001

[a] Smoking was modeled as a dichotomous variable.
[b] DEB sensitivity was modeled as a dichotomous variable.

sensitivity are independent of the exposures under study. For example, in the present and previous studies, increases in SCE frequency associated with cigarette smoking appear to be independent of those increases associated with DEB sensitivity, although larger studies are needed to confirm this observation. When SCEs associated with DEB sensitivity are independent of exposure, more accurate assessment of exposure effects can be obtained by stratifying the populations of exposed and nonexposed persons by DEB sensitivity and analyzing SCE frequencies within sensitivity groups.

Under some circumstances, the phenotype of DEB sensitivity may also contribute to false-positive results in exposure studies. For example, in small samples of individuals (5–10 persons), it is possible, by random chance, for the study group to consist primarily of sensitive individuals and to erroneously attribute their higher SCE frequencies to environmental exposures. Therefore, depending on the study design and sample size, unexplained subgroup sensitivity to SCE induction may increase both type I and type II errors.

Interaction of chemical exposure and the trait of DEB sensitivity is likely to occur in some cases and should also be considered. For example, exposure to DEB itself would be expected to result in interactive effects on SCE frequencies. Although direct exposure to DEB is rare, the potential for exposure does exist as a result of the metabolism of 1,3-butadiene. 1,3-Butadiene is a widely used industrial chemical and environmental pollutant (18, 19) which is metabolized by P-450 mixed function oxidases in mammals to highly reactive metabolites including monoepoxybutene and DEB (20, 21), which are thought to be the activated forms of this carcinogen responsible for SCE induction. Because the trait of DEB sensitivity may be associated with a hypersensitivity to induction of SCEs by 1,3-butadiene as a result of its conversion to DEB, population exposure to 1,3-butadiene may lead to greater-than-additive effects on SCE frequencies in the DEB-sensitive subgroup. Consequently in 1,3-butadiene exposure, identification of DEB-sensitive individuals may increase the power to detect genotoxic effects by allowing for stratification of the population by DEB sensitivity and incorporating an interactive term into the model during analysis. Further studies are required to determine which chemical exposures interact with the phenotype of DEB sensitivity to result in greater-than-additive increases in SCE frequencies.

A number of molecular and biological markers are currently being evaluated as tools for epidemiological studies of carcinogenesis in human populations. A full appreciation of genetic and environmental factors that influence the background levels of these markers in unexposed referent populations is necessary to maximize their utility in molecular epidemiological studies. For example, many researchers are seeking to identify the source of polyaromatic-DNA adducts that have been detected in tissues from nonexposed individuals (22–26). In the case of the SCE marker, numerous studies have been undertaken to identify the factors responsible for variations in baseline SCEs in nonexposed individuals; only cigarette smoking has been consistently shown to influence SCEs. The present studies have identified an additional factor that is likely to be more important than cigarette smoking and which occurs frequently in normal blood donors. On the basis of our findings, we propose that SCE analysis, presently considered a highly sensitive method for detecting mutagen exposures, can be made even more sensitive through the incorporation of the DEB sensitivity marker into the design and interpretation of human monitoring studies.

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