RESEARCH ARTICLE

Increased Sister Chromatid Exchange in Peripheral Blood Lymphocytes from Humans Exposed to Pesticide: Evidence Based on a Meta-analysis

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Abstract

Background: Sister chromatid exchange (SCE) in human peripheral blood lymphocytes is one of the most extensively studied biomarkers employed to evaluate genetic damage subsequent to pesticide exposure. Objective: To estimate the pooled levels of SCE in human peripheral blood lymphocytes among population exposed to pesticide. Materials and Methods: Meta-analysis on the association between SCE frequency and pesticide exposure was performed with STATA 10.0 software package and Review Manager 5.0.24 in this study. Results: The overall means of SCE were 7.88 [95% confidence intervals (95%CI): 6.71-9.04] for exposure group and 6.05 (95%CI: 5.13-6.95) for controls, respectively. There was statistically significant difference in the SCE frequency in human peripheral blood lymphocytes between pesticide-exposed groups and control groups, and the summary estimate of weighted mean difference was 1.69 (95%CI: 1.01-2.38). We also observed that pesticide-exposed population had significantly higher SCE frequency than control groups among smokers, nonsmokers, pesticide applicator, pesticide producer, other exposure population and Asian population in stratified analyses. Conclusions: Data indicate that the SCE frequency in human peripheral blood lymphocytes might be an indicator of early genetic effects for pesticide-exposed populations.

Keywords: Sister chromatid exchange - pesticide - peripheral blood lymphocytes - meta-analysis

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Introduction

Pesticides are a group of natural or synthetic chemical substances including insecticide, herbicide and fungicide, being designated to combat plagues that generally attack, harm or transmit illness to living organisms including humans. Since the mid-1940s, a large number of synthetic pesticides have been introduced in the market. At present, the pesticide manual includes 900 main entries and lists over 2600 products (Bolognesi et al., 2011). Each year, large amounts of pesticides are set free into the environment and many of them are known to have adverse biological effects on non-target organisms including humans. Human exposure to pesticides can occur via dermal contact, inhalation, ingestion, or across the placenta (Gilden et al., 2010).

Most pesticides are acutely and chronically toxic to humans. Chronic health effects associated to pesticide exposures included neurological effects, reproductive or developmental problems and carcinoma. Epidemiological studies have shown that there was an association between pesticide exposure and increased risk of several human cancers (Alavanja et al., 2004; Mink et al., 2008; Shim et al., 2009; Shakeel et al., 2010; Balasubramaniam et al., 2013; Rajabli et al., 2013; Uysal et al., 2013; Yildirim et al., 2013; Kumar et al., 2014; Zendehdel et al., 2014). Human biomonitoring is a useful tool of great interest in cancer risk assessment. The genotoxic effects of pesticides are primary factors for carcinogenesis, and thus, cytogenetic biomonitoring will become useful in human population exposed to pesticide. Sister chromatid exchange (SCE) in human peripheral blood lymphocytes is one of the most extensively studied biomarkers of cytogenetic damage. However, the results from epidemiological studies remained inconsistent and controversial (Bauchinger et al., 1982; Linnainmaa, 1983; Rupa et al., 1988; Jablonicka et al., 1989; De Ferrari et al., 1991; Rupa et al., 1991; Gomez-Arroyo et al., 1992; Carbonell et al., 1993; Lander et al., 1995; Hoyos et al., 1996; Kourakis et al., 1996; Pasquini et al., 1996; Scarpato et al., 1996; Joksic et al., 1997; Steenland et al., 1997; Gomez-Arroyo et al., 2000; Hatjian et al., 2000; Padmavathi et al., 2000; Shaham et al., 2001; Zeljezic et al., 2002; Suarez et al., 2003; Costa et al., 2006; Ergene et al., 2007; Rowland et al., 2007; Martinez-Valenzuela et al., 2009). In order to obtain a precise estimate of the association of SCE frequency with pesticide exposure, we collected published data to evaluate the validation of SCE in human peripheral blood

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lymphocytes as a cytogenetic biomarker of pesticide-exposed population.

Materials and Methods

Literature source and analytical methods

We conducted a systematic search through the database of Medline/PubMed, Embase and web of science, the search terms utilized were: "sister chromatid exchange", "pesticide", "insecticide", "fungicide", "herbicide" and "lymphocyte". The ending date of search was up to September 30, 2013. Additional relevant references quoted in the searched articles were also selected.

Criteria of literature inclusion: (a) The papers should be published in English; (b) The papers should include pesticide exposure and the frequency of SCE in human peripheral blood lymphocytes; (c) The paper must contain the exposed groups and control groups; (d) The paper must have the sample size, arithmetic means and standard deviations (SD) or the information that can be used to infer the results. Accordingly, reviews and overlapping or repeated literatures were excluded. For repeated studies or overlapping studies, the publication with more information was selected.

In total, 33 published studies were identified with the frequency of SCE in human peripheral blood lymphocytes of pesticide-exposed population. We reviewed all papers in accordance with the criteria defined above and excluded four overlapping articles and two papers without offering full information. Therefore, twenty-seven studies were determined to enter our study. Among them, data from two studies (Rupa et al., 1989; Carbonell et al., 1990) were included in the stratified analysis by smoking status only, owing to that they had the same population as Rupa et al's study (Rupa et al., 1991) and Carbonell et al's study (Carbonell et al., 1993), respectively.

Data extraction

For each study, characteristics such as first author, year of publication, country of studied population, duration, arithmetic means and standard deviations or standard errors, sample size of exposed groups and control groups and covariates accounted for were noted. Two of the authors independently tabulated the data and inputted them from these eligible studies to an electronic database. We estimated the summary arithmetic means and standard deviations, if the study provided stratum information, the data coming from similar stratum were combined to make a full use of them. Characteristics of individual study were summarized in Table 1.

Quantitative data synthesis

To assess the relationship between SCE frequency and exposure to pesticide, we conducted a meta-analysis of identified studies. Data were combined using either a fixed-effects model or a random-effects model

Table 1. General Information on the Studies Included in this Meta-analysis

Author	Year	Type of work	Duration (mean±SD)	Country	Covariates accounted for
Bauchinger (Bauchinger et al., 1982)	1982	Workers in plant	11.41±6.37 years	Germany	Smoking
[a]Carbonell (Carbonell et al., 1990)	1990	Agricultural workers	More than 10 years	Spain	Smoking
Carbonell (Carbonell et al., 1993)	1993	Agricultural workers	170.7 ± 179.1 hours per year	Spain	Agricultural activity and duration
Costa (Costa et al., 2006)	2006	Agricultural explorations and greenhouses	Range from 0.5 to 48 years	Portugal	Sex and smoking
[c]Ergene (Ergene et al., 2007)	2007	Subjects living in region contaminated with pesticides	34.56±10.47 years	Turkey	Smoking
De Ferrari (De Ferrari et al., 1991)	1991	Floriculturists	Unknown	Italy	Age and smoking
Gomez-Arroyo (Gomez-Arroyo et al., 1992)	1992	Agricultural workers	Range from 1 to 35 years	Mexico	Smoking, drinking and duration
Gomez-Arroyo (Gomez-Arroyo et al., 2000)	2000	Floriculturists in greenhouses	7.7±3.8 years	Mexico	Sex
[c]Hatjian (Hatjian et al., 2000)	2000	Agricultural college students dipping sheep	Short exposure	Unite Kingdom	
Hoyos (Hoyos et al., 1996)	1996	Farm workers	16.5±8.8 years	Colombia	Age, cigarette smoking and drinking
Jablonicka (Jablonicka et al., 1989)	1989	Pesticides production	Unknown	Czechoslovakia	Unknown
Joksic (Joksic et al., 1997)	1997	Agricultural workers	12.1± 6.02 years	Yugoslavia	Unknown
Kourakis (Kourakis et al., 1996)	1996	Pesticides sprayers	Unknown	Greece	Unknown
Lander (Lander et al., 1995)	1995	Greenhouse sprayers	An average of 17 (range 1-50) years	Denmark	Smoking and age
Linnaimaa (Linnainmaa, 1983)	1983	Pesticides sprayers	Unknown	Finland	Smoking
Martinez-Valenzuda (Martinez-Valenzuela et al., 2009)	2009	Agricultural workers	7.00±3.95 years	Mexico	Smoking and drinking
Padmavathi (Padmavathi et al., 2000)	2000	Pesticide industry	Range from 1 to 24 years	India	Smoking and duration
Pasquini (Pasquini et al., 1996)	1996	Farmers	18.35±12.42 years	Italy	Age, smoking and duration
[c]Rowland (Rowland et al., 2007)	2007	War veterans	Unknown	New Zealand	Age, smoking and drinking
Rupa (Rupa et al., 1988)	1988	Vegetable gardens	20.24±7.77 years	India	Smoking and duration
[b]Rupa (Rupa et al., 1989)	1989	Applicators in cotton fields	8 hours per day in the spring and winter seasons (range 1-25 years)	India	Duration and smoking
Rupa (Rupa et al., 1991)	1991	Applicators in cotton fields	8 hours per day and 9 months per year	India	Duration
Scarpato (Scarpato et al., 1996)	1996	Greenhouse floriculturists	Unknown	Italy	Smoking and sex
Shaham (Shaham et al., 2001)	2001	Greenhouse farmers	Mean exposure period: 28.3 years (range 2.5–55.5 years)	Israel	Age, smoking, education and origin
Steenland (Steenland et al., 1997)	1997	Applicators	Unknown	Mexico	Age and smoking
[c]Suarez (Suarez et al., 2003)	2003	Workers exposed pesticides by tap water	Unknown	Spain	Unknown
Zeljezic (Zeljezic et al., 2002)	2002	Pesticide industry	Mean exposure period: 22.25 years (range from 4 to 30 years)	Croatia	Smoking

[a, b]were included in the stratified analysis on smoking status only; [c]other exposure to pesticide

Table 2. Summary Results of Meta-analysis on Sister Chromatid Exchange Induced by Pesticides Exposure

Population	Exposure/control	Heterogeneity test		Summary estimate of weighted mean difference (95%CI)	Hypothesis test		df	Egger's test		Begg's test	
		Q	*P*		*Z*	*P*		*t*	*P*	*Z*	*P*
Total	1214/1068	1303.13	<0.00001	1.69 (1.01-2.38)	4.83	<0.00001	24	0.40	0.695	0.40	0.691
Stratification by smoking											
Smoking	307/248	171.46	<0.00001	1.87 (0.92-2.83)	3.83	0.0001	12	1.56	0.147	1.04	0.300
Nonsmoking	366/321	273.32	<0.00001	1.59 (0.62-2.57)	3.22	0.001	10	2.26	0.050	1.56	0.119
Stratification by the type of work											
Pesticides application	896/794	645.36	0.000	1.44 (0.64-2.24)	3.54	0.000	16	0.31	0.761	0.87	0.387
Pesticides production	220/183	43.89	0.000	2.73 (1.51-3.95)	4.38	0.000	3	1.10	0.386	1.02	0.308
Other exposure	98/91	201.96	0.000	1.91 (0.17-3.65)	2.15	0.031	3	1.58	0.255	0.34	0.734
Stratification by origin of country											
Europe	579/547	676.73	<0.00001	0.88 (-0.06-1.83)	1.83	0.07	13	0.68	0.510	0.99	0.324
Asia	380/285	32.48	<0.00001	3.82 (3.15-4.48)	11.22	<0.00001	5	0.79	0.474	0.38	0.707
America	255/236	222.72	<0.0001	1.35 (0.02-2.67)	1.99	0.05	4	0.90	0.435	0.24	1.000

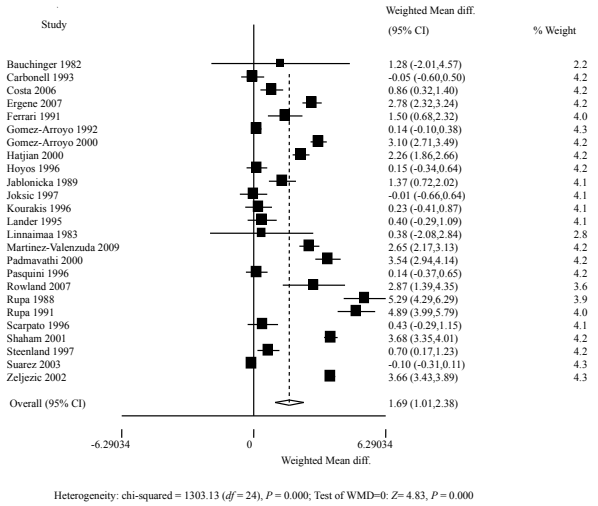


Figure 1. Meta-analysis is Conducted on Sister Chromatid Exchange (SCE) Among Total Population. Each estimate of weighted mean difference on SCE per cell is designated by a solid square, and the 95% confidence intervals (95%CI) of each subgroup is shown by transverse line. The blank rhombus at the bottom is the pooled estimate of weighted mean difference by a random-effects model.

(DerSimonian et al., 1986). The Cochrane Q statistics test was performed for the assessment of heterogeneity among studies. A fixed-effects model is employed when the effects are assumed to be homogenous, while a random-effects model is employed when they are heterogeneous. We computed the weighted mean difference and 95% confidence intervals (95%CI) for each study. Egger's test was used to test publication bias (Egger et al., 1997). Begg's rank correlation test was also used to check the publication bias (Begg et al., 1994).

The meta-analysis was performed with Review Manager (Version 5.0.24, The Cochrane Collaboration) and STATA 10.0 software package (Stata Corporation, College Station, Texas). All the tests were two-sided, and a P value of <0.05 for any test or model was considered to be statistically significant difference.

Results

Meta-analysis database

We established a database according to the extracted information from each article. Some general information was listed in Table 1. It indicates first author, year of publication, exposure to pesticide, duration, country of studied population and covariates accounted for. There were a total of 25 studies with 1214 exposures and 1068 controls.

Test of heterogeneity

Table 2 shows the difference in SCE frequency between pesticide-exposure groups and control groups. The heterogeneity of the 25 studies was analyzed. Our results showed that all meta-analyses on SCE frequency had heterogeneity with P value<0.05. Therefore, we estimated the summary weighted mean difference for them with a random-effects model.

Quantitative data synthesis

The overall mean of SCE frequency was 7.88 (95%CI: 6.71-9.04) for exposure group, and 6.05 (95%CI: 5.14-6.96) for controls. Table 2 indicates the summary estimates of weighted mean difference of the SCE frequency. There was statistically significant difference in the frequency of SCE in human peripheral blood lymphocytes between pesticide-exposed groups and controls, and the summary estimate of weighted mean difference was 1.69 (95%CI: 1.01-2.38) (Figure 1). We performed subgroup analyses on SCE stratified by smoking status, pesticide exposure and country of studied population. Our findings showed that there were statistically significant differences in the frequency of SCE in human peripheral blood lymphocytes between pesticide-exposed groups and control groups among smokers, nonsmokers, pesticide applicator, pesticide producer, other exposure population and Asian population, and the summary estimates of weighted mean difference were 1.87 (95%CI: 0.92-2.83), 1.59 (95%CI: 0.62-2.57), 1.44 (95%CI: 0.64-2.24), 2.73 (95%CI: 1.51-3.95), 1.91 (95%CI: 0.17-3.65) and 3.82 (95%CI: 3.15-4.48), respectively (Table 2). We did not observe any association between SCE frequency and pesticide exposure among European population and American population, the summary estimates of weighted mean difference were 0.88 (95%CI: -0.06-1.83) and 1.35 (95%CI: 0.02-2.67), respectively (Table 2).

Bias diagnosis

Publication bias was assessed in this study. The result for SCE in total population was an asymmetric funnel plot (Figure 2). Our results from both Egger's test and Begg's test suggested that publication bias might not have a significant influence on the summary estimate of SCE among total population, smokers, pesticide applicator, pesticide producer, other exposure population,

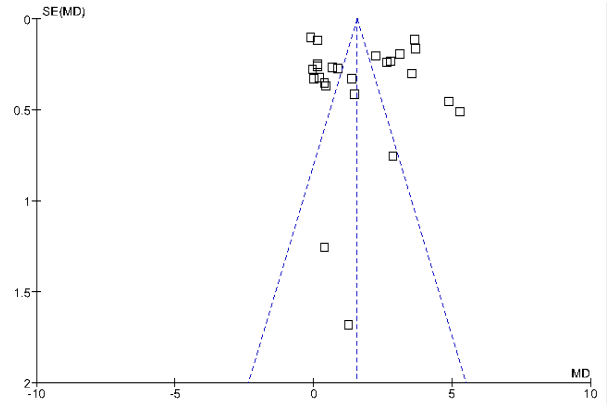
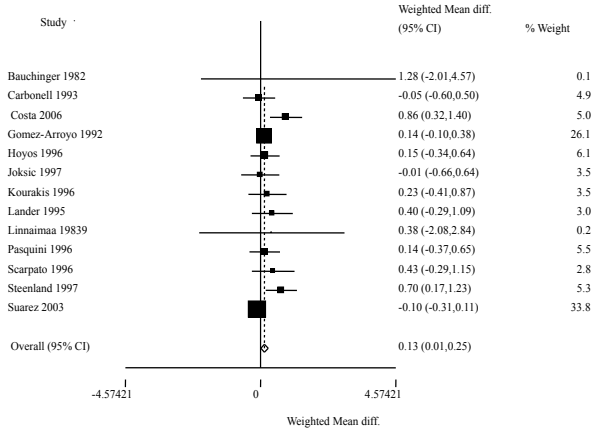


Figure 2. Funnel Plot Analysis is Used to Detect Publication Bias on SCE. Each point represents a separate study for the indicated association. For each study, the mean difference (MD) is plotted on as size-effect against the precision (standard error, SE). The line in the centre indicates the summary diagnostic MD. If bias is absent, small studies will have MD that are widely scattered but still centered round the MD estimates provided by large, more precise studies



Heterogeneity: chi-squared = 18.67 (*df* = 12), *P* = 0.097; Test of WMD=0: *Z*= 2.13, *P* = 0.033

Figure 3. Sensitivity Analysis is Conducted on SCE. Each estimate of weighted mean difference on SCE per cell is designated by a solid square, and the 95% confidence intervals (95%CI) of each subgroup is shown by transverse line. The blank rhombus at the bottom is the pooled estimate of weighted mean difference by a fixed-effects model

Asian population, European population and American population. Maybe, there was publication bias in the meta-analysis for nonsmokers because there was some uncertainty with a P value being equal to 0.05 in Egger's test.

Sensitivity analysis

We conducted the sensitivity analysis and found that the study including Bauchinger et al. (1982), Carbonell et al. (1993), Costa et al. (2006), Gomez-Arroyo et al. (1992), Hoyos et al. (1996), Joksic et al. (1997), Kourakis et al. (1996), Lander et al. (1995), Linnaimaa (1983), Pasquini et al. (1996), Scarpato et al. (1996), Steenland et al. (1997) and Suarez et al. (2003) was homogenous for SCE among total population, and the Q value for test of heterogeneity was 18.67 (df=12, *p*=0.097) (Figure 3).

Discussion

Sister chromatid exchange was first visualized by Taylor in plant cells using tritium and autoradiography, which provided poor spatial resolution. It was later discovered that incorporation of the DNA base analog 5'-bromodeoxyuridine, in combination with Hoechst dye 33258 staining, would differentiate sister chromatids and reveal SCE (Wilson et al., 2007). SCE results from S-dependent lesions which during S-phase are eventually transformed to double strand break (DSB) and these can be repaired by a homologous recombination mechanism that may give rise to SCE. It has been described as a sensitive convenient method for monitoring exposure to environmental genotoxic agents (Anwar, 1994).

Several studies have shown that pesticide produced genotoxic effects in assays performed *in vitro*. Nikoloff et al reported that herbicide flurochloridone induced a significant and equivalent increase in SCEs regardless of the concentration in Chinese hamster ovary cells treated for 24h within the 0.25-15μg/ml concentration range (Nikoloff et al., 2012). Afugan induced a significant increase in the frequency of SCE in cultured human lymphocytes at all concentrations (2.5, 5, 10 and 20 μg/ml) at both 24h and 48h treatment periods, compared with the negative controls (Yuzbasioglu et al., 2006). Federico et al reported that a statistically significant increase of SCE was observed in epithelial liver cell lines by four phenylurea herbicides (fenuron, chlorotoluron, diuron and difenoxuron), compared with the negative controls (Federico et al., 2011). 200.0μg/ml of Permethrin induced a significant increase in SCE frequency over control values in cultured human lymphocytes (Turkez et al., 2012). Fipronil, a phenylpyrazole pesticide induced a statistically significant increase in the SCE frequency in a dose-dependent manner in human peripheral blood lymphocytes, compared with a negative control (Celik et al., 2014).

Our meta-analysis showed that the frequency of SCE in human peripheral blood lymphocytes was significantly higher in the pesticide-exposed groups than control groups as evidenced by a random-effects model, where the summary estimate of weighted mean difference was 1.69 (95%CI: 1.01-2.38). Our findings indicated that exposure to pesticide could induce significantly increased levels of chromosome damage in human peripheral blood lymphocytes measured by SCE, which might be an indicator of early genetic effects for pesticide-exposed population.

The availability of reference values is important for laboratories and research teams to validate protocols and analytical procedures and for epidemiologists to estimate the statistical power of field studies and assess the quality of data (Neri et al., 2005). Baseline Micronuclei frequencies for the cytokinesis block assay in adults and children have been published (Bonassi et al., 2001; Neri et al., 2005). In this paper, we provided the SCE baseline values of referent population from 25 papers included in this meta-analysis at the same time, which might be used for the planning phase of a study, but not for a standard to select proper controls in the conduct of future studies.

There are some limitations inherent in this meta-analysis. Firstly, only published literatures were included in this study, which might cause publication bias. Both Egger's test and Begg's test were carried out to address this issue. Our results showed that the likelihood of key publication bias might not be present in this meta-analysis except for nonsmokers since there was some uncertainty with the P value being equal to 0.05 in Egger's test. Secondly, several factors such as age, sex, cigarette smoking, duration, exposure type and levels of environmental exposure might affect the frequency of SCE in human peripheral blood lymphocytes (Bonassi et al., 1995; Bolognesi et al., 1997; Martinez-Valenzuela et al., 2009; Ben Salah et al., 2011). Cigarette smoking and exposure type were stratified in this meta-analysis for SCE frequency further, and we also observed significantly higher frequency of SCE in human peripheral blood lymphocytes among smokers or nonsmokers, applicator, producer and other exposure population in comparison with their corresponding control groups, respectively. However, other confounders were not stratified in this meta-analysis, since only a few investigators reported such results and stratified range was not uniform for some factors. Thirdly, since studies included in this meta-analysis were heterogeneous, we performed sensitivity analysis further, and found that the studies were homogenous for SCE among total population while some studies were excluded.

Considering that the origin of studied population might have an effect on the SCE frequency among subjects exposed to pesticide, country of studied population was stratified in this meta-analysis further. We only observed that there was significantly increased frequency of SCE in exposed groups among Asian population, compared with control groups. The association was not found in European population and American population, maybe due to the different level of environmental exposure to pesticide among the different origin of country.

In summary, the findings show a significant increase in frequency of SCE in human peripheral blood lymphocytes of pesticide-exposed population. However, our meta-analysis was conducted on population-based studies, meta-analysis based on individual data might provide more precise and reliable results. Therefore, it is necessary to construct an international database on genetic damage among population exposed to pesticide that may contain all raw data of studies examining pesticide-genetic toxicity. It is required for authors of all of the published papers to share their raw data. With sufficient individual data, it may be likely to resolve this problem of confounding factors including age, sex, cigarette smoking, duration, exposure type and levels of environmental pesticide exposure.

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