HHS Public Access

Author manuscript

Mutat Res. Author manuscript; available in PMC 2021 March 01.

Published in final edited form as:

Mutat Res. 2019 ; 781: 207–217. doi:10.1016/j.mrrev.2017.08.002.

Meta-analysis of chromosomal aberrations as a biomarker of exposure in healthcare workers occupationally exposed to antineoplastic drugs

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Abstract

Many antineoplastic drugs used to treat cancer, particularly alkylating agents and topoisomerase inhibitors, are known to induce genetic damage in patients. Elevated levels of chromosomal aberrations, micronuclei, and DNA damage have been documented in cancer patients. Elevations in these same biomarkers of genetic damage have been reported in numerous studies of healthcare workers, such as nurses and pharmacists, who routinely handle these drugs, but results vary across studies. To obtain an overall assessment of the exposure effect, we performed a meta-analysis on data obtained from peer-reviewed publications reporting chromosomal aberration levels in healthcare workers exposed to antineoplastic drugs. A literature search identified 39 studies reporting on occupational exposure to antineoplastic drugs and measurement of chromosomal aberrations in healthcare workers. After applying strict inclusion criteria for data quality and presentation, data from 17 studies included in 16 publications underwent meta-analysis using Hedges' bias-corrected g and a random-effects model. Results showed the level of chromosomal aberrations in healthcare workers exposed to antineoplastic drugs was significantly higher than in controls. The standardized mean differences (difference of means divided by within sd) from all studies were pooled, yielding a value 1.006 (unitless) with $p < 0.001$. Thus, in addition to the documented genotoxic effects of antineoplastic drugs in cancer patients, this meta-analysis confirmed a sig nificant association between occupational exposure to antineoplastics during the course of a normal work day and increases in chromosomal aberrations in healthcare workers. Based on the studies reviewed, we were unable to accurately assess whether appropriate use of protective measures might reduce the incidence of genetic damage in healthcare workers. However, given the potential for increased cancer risk linked to increases in chromosomal aberrations, the results of this study support the need to limit occupational exposure of healthcare workers to antineoplastic drugs as much as possible.

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Conflict of interest

None.

Keywords

Genetic damage; Antineoplastic drugs; Healthcare workers; Cancer risk

1. Introduction

Concerns regarding occupational exposures to antineoplastic drugs became an issue for healthcare workers in the late 1970s and early 1980s when secondary malignancies were identified in cancer patients following treatment with these drugs, and workers experienced acute health effects when preparing them [1–3]. Over the past 35 years, a wealth of information has been published concerning the carcinogenicity of anticancer drugs, workplace contamination and worker exposure, adverse health effects associated with these exposures, and observations of genotoxic effects in exposed workers [4–7]. Although antineoplastics are a heterogeneous group of chemicals, their cytotoxic effects are generally mediated through binding to cellular targets involved in DNA and protein synthesis, producing a variety of potential effects in both normal and cancer cells, including cell death; mutation; DNA damage that may be repaired, misrepaired, or not repaired; and cell transformation. The consequences of these events are variable and may range from no discernible effect to drug-induced cancers, a consequence of genetic damage to healthy cells [8,9]. The International Agency for Research on Cancer currently lists some two dozen antineoplastic drugs as known or suspected human carcinogens based on laboratory animal and patient studies [10]. Many of these drugs also have adverse reproductive effects, both in patients treated with them and workers exposed to them [11–13].

Surface contamination of the workplace with antineoplastic drugs has been documented in healthcare facilities worldwide [14–26] including detectable levels of antineoplastic drugs in the air and on employees' clothing and skin [23,27–29]. Uptake of the drugs has been confirmed by the detection of the parent molecules and/or their metabolites in the urine of exposed workers [30–32]. These surveillance studies typically focus on only a small sample of the more than 100 antineoplastic drugs currently in use. Therefore, contamination and exposure data are lacking on the great majority of these drugs, which are often prepared and administered in combination. These combination drug regimens often include non-antineoplastic drugs that meet one or more of the NIOSH criteria for Hazardous Drugs (carcinogenic, genotoxic, teratogenic, reproductive toxicant, and organ toxicity at low doses) [33,34].

Biomarkers of exposure have been used extensively for monitoring healthcare professionals who work with antineoplastic drugs [30,35–37]. In general, these biomarkers are based on the mutagenic or clastogenic properties of these genotoxic drugs. Since most of the first-generation antineoplastic drugs were genotoxic, these endpoints were ideal candidates for use in monitoring exposed worker populations. However, these endpoints are typically non-specific in nature and can be induced by exposures to any genotoxic compound present in the environment including drugs other than antineoplastics [38,39], as well as ionizing radiation [40], and possibly viral infections [41–43]. Therefore, studies using biomarkers of genotoxicity to monitor worker populations must be carefully designed and controlled in

order to eliminate confounding factors; detailed demographic questionnaires should be administered to collect information on smoking history, diet, age, illnesses, x-ray exposures, and other variables that may compromise test results [44]. Nevertheless, more than half of the 100-plus published studies in the literature have reported a statistically significant association between exposure to antineoplastic drugs and the endpoint of genotoxicity being investigated. The majority of these studies have been conducted in hospitals and pharmacies outside the United States [30,45,46], often in countries where safety precautions may not be as rigorous as those mandated in the U.S.

The first use of a biomarker for genotoxicity in healthcare workers was reported by Falck et al. [47] who employed a bacterial assay to demonstrate mutagenicity of urine samples obtained from oncology nurses; in this study, mutagenic activity increased during the course of the work week, suggesting cumulative exposure and effect. In addition to urinary mutagenicity, early cytogenetic surveillance studies in healthcare workers focused on analysis of chromosomal aberrations and sister chromatid exchanges (SCEs) [48–51], two of the endpoints that were used extensively at that time for evaluating cytogenetic abnormalities in humans as well as in animal model systems [52,53]. However, reflecting advances in methods for monitoring DNA and chromosomal damage, more recent approaches have shown greater reliance on evaluation of micronuclei and primary DNA damage, specifically the comet assay for the latter endpoint [54–56]. For submissions to regulatory agencies, tests measuring chromosomal aberrations, micronuclei, and DNA damage are accepted as standard measures of genotoxicity [57]. Use of the micronucleus test has, to a great extent, replaced the chromosomal aberration test in recent years because it requires less training to score slides, less time to complete a study, is suitable for automated scoring using flow cytometry, and it captures both structural and numerical chromosomal changes, while the chromosomal aberration test only can reliably measure structural chromosomal damage [53]. The test for measuring increases in SCEs is no longer employed outside of the basic research community due to the absence of a clear association between elevated SCEs and adverse human health effects [58], as well as a lack of understanding of the mechanisms underlying the induction of SCEs [52].

Recent well-designed and robust meta-analyses of comet assay [45] and micronuclei [46] data in healthcare workers have demonstrated a significant association between elevated DNA damage demonstrated by the comet assay and increased frequencies of micronuclei and occupational exposure to antineoplastic drugs. The present study examined the association between occupational exposure to antineoplastic drugs and frequency of chromosomal aberrations in healthcare workers.

The frequency of chromosomal abnormalities in peripheral blood lymphocytes within healthy human populations has been shown not only to be a useful biomarker of exposure-associated genetic damage (e.g., in populations residing in heavily polluted environments) but also has been demonstrated to be predictive (vs significantly associated) of increased future cancer risk and mortality (all types combined) [59–64]. A significant association between exposure to antineoplastic drugs and elevated biomarkers of chromosomal damage has been well documented in patients [54,65–70] as well as in mammalian cell systems in vitro and in vivo [71,72]. Although exposure of healthcare workers to these genotoxic agents

in the workplace is likely, since workplace contamination and worker exposure have been documented [30], results reported in the literature concerning genotoxic damage are mixed. A careful assessment of the strength of the evidence for increased genetic damage in personnel working with antineoplastic drugs is needed, and if such an association is confirmed, it may provide the evidence needed to strengthen regulations involving the safe handling of these genotoxic drugs.

2. Methods

2.1. Selection criteria

The goal of this study was to summarize and analyze in aggregate chromosomal aberrations/abnormalities in occupationally exposed healthcare workers, as reported in the peer reviewed literature. Chromosomal aberrations were utilized as biomarkers of genetic damage associated with exposure to antineoplastic drugs in the workplace (Fig. 1). A primary literature search was conducted through February 2, 2017, employing the Medline/Pubmed, Scopus, and Google Scholar search engines as well as the National Institute of Occupational Safety and Health's extensive database (http://www.cdc.gov/niosh/topics/antineoplastic/). References in all identified articles, including reviews, were cross checked in an effort to identify additional applicable publications.

Key search terms included combinations of the exposure group terms and analysis method terms, i.e., "cytogenetic damage," "chromosomal aberration," or "chromosomal abnormalities" in combination with exposure group terms including "occupational exposure," "nurse," "pharmacist/pharmacy/pharmacy technician," "healthcare worker," and genotoxic agent descriptions such as "chemotherapy," "anti-neoplastic," or "hazardous drug". The search was limited to articles available in the English language.

This study excluded data from animal studies, in vitro studies, editorials, case reports, review articles (non-primary data), and non-healthcare occupational exposures, i.e., bench research [73] and manufacturing facility exposures [48,73–76].

Articles were considered eligible for inclusion if:

1. Exposure groups were limited to occupationally exposed healthcare workers (e.g., studies of cancer patients or occupational exposures in manufacturing facilities were not included)
2. Appropriately matched cohorts consisting of non-exposed members of the general population or non-exposed healthcare workers within the same health care facility were included as controls
3. Informative questionnaires were employed to eliminate potential confounding factors such as recent x–ray exposures or exposures to other genotoxic drugs that could influence outcomes
4. Proper sample collection and culturing protocols were followed to ensure accumulation of first division metaphases for analysis of chromosomal aberrations

5. Data collection procedures met accepted criteria (e.g., sufficient description of blood collection and specimen handling, slide preparation, and scoring procedures)
6. At least 100 first division metaphases were evaluated per study subject
7. Data were presented in a manner that included the mean percentage and standard deviation of cells with chromosomal aberrations within a study group, as well as the size of the group, or in a manner that permitted the calculation of such summary statistics.
8. Correct methods of damage expression were employed:
    a. Data presented as frequency or percentage of cells with chromosomal aberrations; any alternate formats that may have been used had to allow calculation of the percentage of damaged cells within the study population or in individual subjects
    b. Chromosome and chromatid gaps were not included in the definitive analysis

Another factor considered important to interpretation of study results, but if absent was not necessarily exclusionary, was a description of available engineering controls and personal protective equipment (PPE), and information on the diligence with which PPE use was practiced among the healthcare workers who participated in the study. In some studies, where the type of engineering controls and/or work practices were described, effects on the outcomes of the chromosome damage testing were discussed by the authors.

Studies were excluded for the following reasons:

1. Duplicate data sets appearing in more than one publication were not included (i.e., the same data set was not included more than once).
2. Studies reporting chromosomal aberration frequencies in patients exposed to antineoplastic drugs were excluded, as were studies in which occupationally exposed personnel reported additional potentially genotoxic exposures (e.g., radiation, anesthetic gases, formaldehyde).
3. Studies were excluded if they did not meet the inclusion criteria listed above.

2.2. Meta-analysis of chromosomal aberrations

The purpose of this study, as with any meta-analysis, was to pool the results of a number of earlier studies. Our goal was to ascertain the impact of exposure to antineoplastic agents on chromosomal aberrations. We drew on the data presented in 16 original journal articles [50,77–91]; two studies were taken from Sessink et al. [89]. The general procedure was to obtain the mean percent of aberrant cells for both exposed and control individuals, as well as the standard deviations and sample sizes. In some instances, all of this information was present in the original journal article; in other instances, certain information had to be calculated from information presented in the article. For some articles this meant calculating the standard deviations from the standard errors and sample sizes [50,81–83,85,87,91]. For

some, the weighted mean and pooled variance had to be calculated [83,84]. In the Tompa et al. [91] study, the exposed subjects were further classified into subgroups dependent on protective measures employed in their workplace, creating well-protected and less well-protected groups. All subjects receiving any exposure, even those judged to have had good personal protection, were categorized as exposed subjects. Finally, in the Sessink et al. [89] article, the results from the Dutch and Czech cohorts were categorized as being two separate studies. Thus, a total of 17 original studies from 16 published papers were used in our analysis. The characteristics of the study populations that were used in the analysis are presented in Table 1. The general approach was to calculate for each study the standardized mean difference, namely the difference in means of frequencies of CA between exposed and control groups divided by the pooled standard deviation for the two groups. Then, an overall pooled standardized mean difference was calculated by taking a weighted average of all the individual standardized mean differences [92]. The meta-analysis was performed with the *metan* command of Stata [93] and with the software package Comprehensive Meta Analysis using Hedges' *g* [94] with a random-effects model [95] as developed by Dersimonian and Laird [96]. Hedges' *g* is a modification of the standardized mean difference of two independent groups, *d* (the difference of the two means divided by the pooled standard deviation). The drawback to *d* is that for small samples it has a slight bias and tends to overestimate δ, the population standardized mean difference. With Hedges' *g*, *d* is multiplied by a factor J to correct the bias [92]. While the number of studies in this meta-analysis was not small, neither was it large. Use of Hedges' *g* was considered preferable to the use of *d* – in order to eliminate a possible source of bias, even if that bias was likely to be small. In order to check for possible publication bias, the funnel plot [97] based on the seventeen studies was generated, using the Stata command *metafunnel* [98]. In addition, a numerical test, a modified version of Egger's test as implemented in the Stata command *metabias* was used [99]. Publication bias represents the tendency for studies showing no effect not to be published.

3. Results

3.1. Data acquisition

Data collection included sample sizes for the antineoplastic-exposed populations and the control populations and the mean percent aberrant cells and the standard deviations for both groups.

3.2. Meta-analysis of chromosomal aberrations

The results of the statistical analysis had bearing on the choice of model as well as on the main question of interest – whether exposure to antineoplastic agents in occupational settings increased the level of chromosomal aberrations. The fact that I^2, the proportion of total variation in estimates of treatment effect attributable to heterogeneity [100], was high (93.2%) provided evidence for the use of a random effects model over the fixed effect model. The result of the overall test (H_0: standardized mean difference = 0) was highly significant (pooled standardized mean difference = 1.006, z = 4.25, $p < 0.001$). The estimate of between-study variance, τ^2, was 0.8393. The forest plot of the meta-analysis is shown in Fig. 2. Thus, while 8 of the 17 studies did not show a significant impact from exposure to

antineoplastic drugs, all but one of the studies showed a positive standardized mean difference, and the overall meta-analysis showed a highly significant effect due to exposure to antineoplastic drugs. The funnel plot does not appear to provide substantial evidence for publication bias. This lack of evidence is based on the authors' subjective impression of a lack of clear asymmetry for studies with less precision, i.e. larger standard errors. The result of the modified Egger's test was $p = 0.406$. In other words, the test did not reject the null hypothesis of no small study effects, thus providing no evidence for publication bias. The fact that the funnel plot was not exactly funnel-shaped could be due to the real heterogeneity of the effects. This is especially plausible given the many different factors, which can induce chromosomal aberrations (Fig. 3).

4. Discussion

Workplace contamination with antineoplastic drugs continues to be reported in hospital facilities around the world [14–25,86,101,102]. Occupational exposure to these drugs can occur in healthcare workers and non-drug handling personnel wherever the drugs are prepared and administered to patients as evidenced by detection of drugs on employees' hands and in employees' urine samples [23,31,32]. However, occupational exposure is not limited to just these groups of workers. Environmental services, shipping and receiving, maintenance, transportation, and laundry personnel may be exposed, in addition to research laboratory workers and personnel employed in veterinary practices where these drugs are used [23,28,103]. Although beyond the scope of this paper, exposure of family members of patients receiving antineoplastics has been shown to occur through contamination of various home surfaces and detection of antineoplastic drugs and metabolites in the urine of caregivers. [104,105].

In the U.S., government and professional organizations have published and updated guidelines and recommendations for protecting healthcare workers from exposure to antineoplastic and other hazardous drugs since the early 1980s [4,6,7,106,107]. However, even when such recommendations are followed, and engineering controls, personnel protective equipment, and other controls are in place, as stated above, measurable workplace contamination and worker exposures are still being reported. Due to the hands-on nature of drug preparation and especially administration, incidental exposure cannot be totally eliminated, given current practices.

There is ample evidence in patient populations that exposure to antineoplastic drugs may result in elevated levels of chromosomal aberrations and carries a known risk for secondary, therapy-induced cancers, particularly leukemias [108–112]. Ten to 20% of myeloid neoplasms are therapy-related, prompting the World Health Organization to classify "hematopoietic stem cell disorders related to previous exposure to chemotherapy and or radiation" as a separate disease category in 2008 [113–115]. Secondary cancer risk is dependent on the type of therapy administered, as well as dose, and specific treatments are linked to characteristic chromosomal aberrations. For example, alkylating agents (such as cyclophosphamide, carmustine, and temozolomide) are associated with unbalanced cytogenetic abnormalities, such as partial loss or deletions of chromosomes 5 and 7, and often have a latency period of five to ten years; secondary cancers associated with exposure

to these agents more frequently present as treatment-related myelodysplastic syndrome (t-MDS) rather than treatment-related acute myeloid leukemia (t-AML) [8,116]. Topoisomerase II inhibitors (such as etoposide and doxorubicin) are associated with translocations on chromosome 11 (11q23), loss or deletion of chromosome 7, and many other balanced translocations. Treatment with topoisomerase II inhibitors are generally associated with a shorter latency period of one to three years and secondary cancers associated with these agents more often present as t-AML. [8,116]. Latency periods in patients are variable, but the specific cytogenetic alterations associated with certain classes of antineoplastics have provided investigators biomarkers for use in evaluating occupational effects from these work place contaminants [84,117].

One of the primary driving forces for concern in healthcare worker exposure to antineoplastics and other hazardous drugs is the potential for cancer, similar to the risk noted in chemotherapy treated patients, as many of these life-saving medications are known carcinogens. U.S. epidemiological data are lacking in this area and could be improved through the creation of a single national tumor registry that includes occupation histories, rather than the current collection of state registries that vary in content. One large U.S. cancer mortality study evaluated female healthcare workers in 24 states and detected a 30 percent increase in mortality in nurses due to myeloid leukemia, liver, and ovarian cancers [118]. Mortality among female pharmacists from myeloid leukemia was increased two-fold over the general population, and increases in mortality associated with breast (OR = 1.5) and ovarian (OR = 2.4) cancers were also noted [118]. Similarly, a study evaluating data from Iowa and Minnesota on occupation and risk for leukemia, identified an increased risk of leukemia in nurses and healthcare workers [119]. An analysis of a Canadian cancer registry of over 56,000 female nurses revealed an increased risk of breast cancer (RR = 1.83; CI = 1.03–3.23) associated with working in a cancer center or oncology nursing unit, and nurses with the highest weighted durations of exposure to antineoplastic drugs had an increased risk of rectal cancer (RR = 1.87, CI = 1.07–3.29) [120]. No significant increases in risks of leukemia or other cancers were noted in this study. In a large population-based study in Denmark that relied on detailed records of occupation and health, the increased risk of leukemia in a small sample of physicians who had at least six months of exposure to antineoplastic drugs did not reach statistical significance, although an RR of 2.85 was reported [121], but a significantly increased risk of leukemia was identified in oncology nurses [122].

In the present study, published reports of studies that utilized chromosomal aberration frequencies in peripheral blood lymphocytes as a biomarker for genotoxic damage in healthcare workers who handled antineoplastic drugs were identified and analyzed. A meta-analysis was carried out using data from 17 studies that met our selection criteria. The results of this meta-analysis show a highly significant, increased genotoxic risk for healthcare workers occupationally exposed to antineoplastic drugs compared to control populations, with a summary effect (weighted mean of standardized mean differences) of 1.01. The findings of the current study are strikingly similar to those of Villarini et al. [46] who performed a meta-analysis using lymphocyte micronucleus data on some of the same populations. Of the 24 studies they included in their assessment of antineoplastic drug-associated genomic damage, published over the same approximate time span as the studies

included in the current meta-analysis, over half reported significant increases in the frequencies of micronucleated lymphocytes in occupationally exposed subjects with an overall meta-estimate for micronuclei frequency of 1.67.

Evaluation of chromosomal aberrations is a validated method to evaluate exposure to genotoxic agents, and the association of chromosomal aberration frequencies with cancer risk has been demonstrated in several prospective studies in which cohorts were followed for up to 25 years. Several studies have shown significant associations between increased frequencies of chromosomal aberrations and micronuclei in peripheral blood lymphocytes and increased incidence of multiple cancer types in healthy human populations. The cancer types documented in these surveillance studies were similar to the distribution of cancer types in the general population [46,56,59,61–64,123–129]. Smerhovsky and colleagues [130] were able to validate this relationship through cytogenetic assessment of mine workers exposed to radon beginning in 1975 in the Czech Republic. Their data showed a strong and significant relationship between lymphocyte chromosome aberration frequencies and cancer, such that a “1% increase in chromosomal aberrations was followed by 64% increase in risk of cancer ($p < 0.000$)”.

Most exposures were described as “antineoplastics” and details related to specific drug exposures were frequently not available or easily extracted from the publications we used for our analysis. Although most facilities universally use the same top 15 or so antineoplastic drugs, based on the provided information there was not an opportunity to stratify exposures based on use of specific drugs. There were four main worker categories evaluated – nurses, pharmacists, pharmacy technicians, and physicians – but as the sample size of these studies was small, sub-stratification (with the exception of the nursing cohort) would not provide sufficient subjects to allow for meaningful statistical analyses.

A number of key studies from the meta-analysis that highlight various approaches to biomarker studies of exposure are summarized below:

The study by Grummt et al. [50] in German hospitals showed the highest standardized mean difference between exposed workers and controls (2.70) and was highly significant. This study was well-powered, including approximately 100 subjects occupationally exposed to antineoplastic drugs and 100 control subjects. No correlation was observed in this study between chromosomal aberrations and age, duration of exposure, or smoking habits. The authors attributed the workers’ exposure to the routine practice of handling antineoplastic drugs without using a “safety cover” (hood).

A 1999 study measuring chromosomal aberration frequencies in several groups of occupationally exposed workers in Hungary [83] included a group of 14 hospital nurses who prepared antineoplastic drugs in a biological safety cabinet (BSC), a practice described as representing “adequate” personal protection, and another group of 7 nurses who prepared antineoplastic drugs at the bedside without adequate personal protection. The standardized mean difference between the two groups of nurses in this study, although limited in the number of subjects, was 1.41 ($p < 0.001$).

Kopjar et al. [81] examined three endpoints of genotoxicity in Croatian healthcare workers exposed to antineoplastic drugs: chromosomal aberrations, micronucleus frequencies, and sister chromatid exchanges. The drug-exposed group and the control group each consisted of 50 subjects, 25 smokers and 25 non-smokers. The authors reported a significant 5-fold increase in total chromosomal aberrations in the exposed subjects (4.48 ± 0.33 [mean ± s.e.]) compared to controls (0.86 ± 0.09). Since these authors reported standard errors, the values were converted to standard deviations for the meta-analysis. Consistent with this observation, micronuclei and sister chromatid exchanges were also significantly higher in the exposed worker group compared with the controls. The authors reported that neither smoking status nor use of personal protective equipment had a detectable effect on chromosomal aberration levels.

In the most recently published study of genetic damage in healthcare workers exposed to antineoplastic drugs that was reviewed, Moretti et al. [86] measured both chromosomal aberrations and micronucleus frequency in exposed workers and a control group. The study included 71 occupationally exposed female nurses and 77 female controls from five Italian hospitals. Significant increases were reported in both the mean frequencies of micronucleated cells (5.30 versus 3.29) and chromosomal aberrations (3.30 verses 1.84) in exposed workers versus controls. Surface wipe sampling and absorbent pads worn on the nurses' clothes were used to measure residues of the most frequently used antineoplastic drug in the work environment, cyclophosphamide. Interestingly, although both working surfaces and nurses' clothing tested positive for presence of cyclophosphamide, no correlation was observed between the amount of cyclophosphamide contamination detected and either biomarker of genotoxicity, possibly due to the very low internal doses of cyclophosphamide detected in end-of-day analysis for un-metabolized cyclophosphamide in urine samples of the nurses, suggesting similar levels of internal doses. The authors reported that despite the fact that the nurses in this study received training in safe handling practices and reported that they complied with the current Italian guidelines for handling antineoplastic drugs, they still incurred measurable genotoxic damage. The authors concluded that additional safety measures are warranted because even with careful attention to the current accepted standards, evidence of genotoxic risk related to occupational exposure exists.

In one of the few studies conducted in the U.S., a different approach was taken by McDiarmid et al. [84] who examined structural and numerical chromosomal abnormalities involving chromosomes 5, 7, and11 in healthcare workers exposed to antineoplastic drugs and in a matched control group. This study included 63 pharmacy and nursing personnel and 46 non-exposed, matched controls. Chromosomes 5, 7, and 11 are known cytogenetic markers for therapy-related myelodysplastic syndrome and therapy-related acute myeloid leukemia [108], so their link to antineoplastic drug exposure is well documented. The healthcare workers noted all antineoplastic drug handling events (e.g. preparation, administration, disposing, etc.) in a six-week diary and blood samples were obtained on the final day of the recording period. Chromosomal abnormalities involving chromosomes 5, 7, and 11 individually, and chromosomes 5 and 7 combined, were tabulated in relation to 100 and 200 alkylating agent handling events (potential for drug exposure). A significant association for abnormalities involving chromosome 5 alone or chromosomes 5 and 7

combined was observed in the highly exposed group (153 or more handling events in a six-week period) compared with the control group, providing evidence of worker exposure despite adherence to personal protection safety measures, and a heightened risk for occupationally associated disease.

In general, it would be assumed that the use of engineering controls and PPE, in addition to proper training, would reduce and/or eliminate worker exposure to antineoplastic drugs. However, healthcare settings are complex environments with multiple interactions taking place. Theoretically, poor technique by one worker can lead to widespread contamination of surfaces in a workplace. Experience with the Ebola virus has demonstrated that improper doffing of PPE can lead to worker exposure and subsequent infection (https://www.cdc.gov/vhf/ebola/healthcare-us/ppe/guidance-clinically-stable-puis.html). Similarly, improper removal of a protective gown or gloves that are contaminated with a drug or drugs may result in contamination of the workplace and exposure of the worker as well as coworkers. Even proper use of equipment may not eliminate all potential for contamination. For example, even high quality type II BSCs do not provide 100% containment of drug residues, and BSCs and HEPA filters can and do fail, especially if not properly maintained. It has also been reported in a number of surveys of healthcare workers, that PPE may not always be available, may not be the proper type for handling these drugs, and is not utilized 100% of the time [131–134].

These are just a few of the possible scenarios that can commonly occur in healthcare settings that may result in workplace contamination with antineoplastic drugs and consequent exposure of healthcare workers. It is recommended that there be continued emphasis on appropriate education and training of healthcare workers in safe handling practices and in the potential consequences of failing to adequately follow established guidelines.

5. Conclusions

The demonstrated increases in biomarkers of chromosomal damage in healthcare workers occupationally exposed to antineoplastic drugs and the knowledge that these biomarkers are directly associated with an increased risk for cancer makes it imperative that established procedures for limiting/preventing exposure be adhered to diligently. Although measuring chromosomal aberrations or micronuclei in peripheral blood cells are effective methods for evaluating occupational exposure-related genotoxicity ([46]; the present study), neither approach is well suited to large scale population monitoring. Newer, less labor-intensive, and more sensitive monitoring procedures are needed to establish routine, on-going monitoring of healthcare workers and other worker populations potentially exposed to these genotoxic drugs in an effort to eliminate increased risk for disease.

Acknowledgements

We thank Drs. Melissa A. McDiarmid and Grace E. Kissling for providing a careful review of the manuscript and helpful comments.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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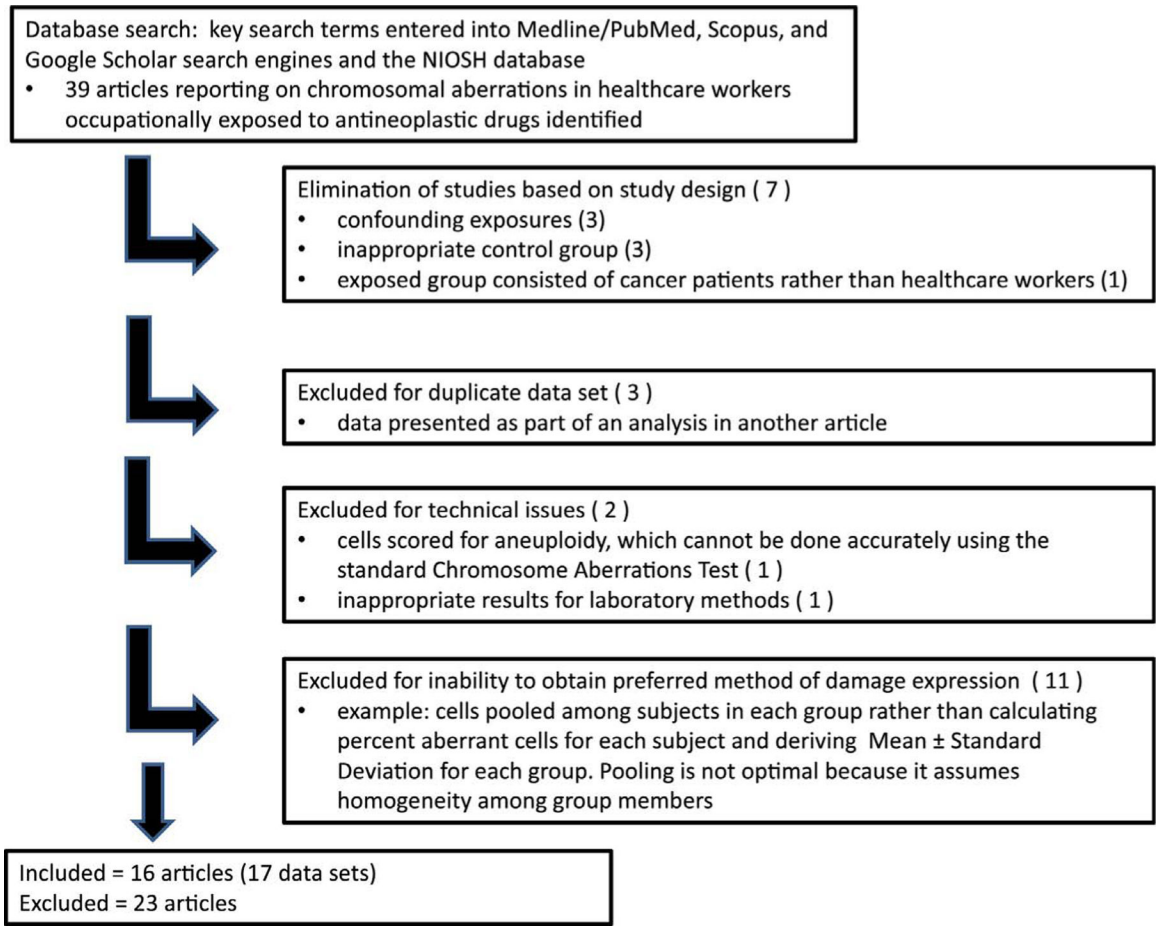

Fig. 1.

Flow chart showing identification and selection methods for studies used in the meta-analysis of chromosomal aberration frequencies in healthcare workers occupationally exposed to antineoplastic drugs.

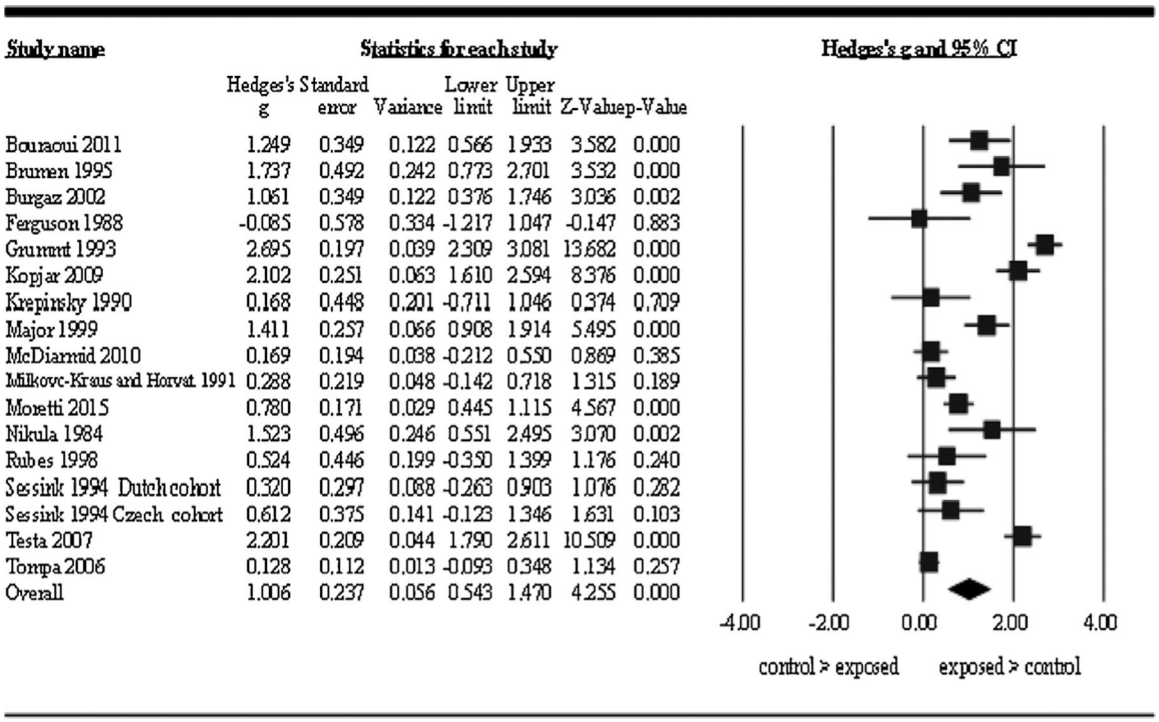

Fig. 2.

Forest plot with the treatment effects for individual studies from meta-analysis of seventeen studies in sixteen articles.

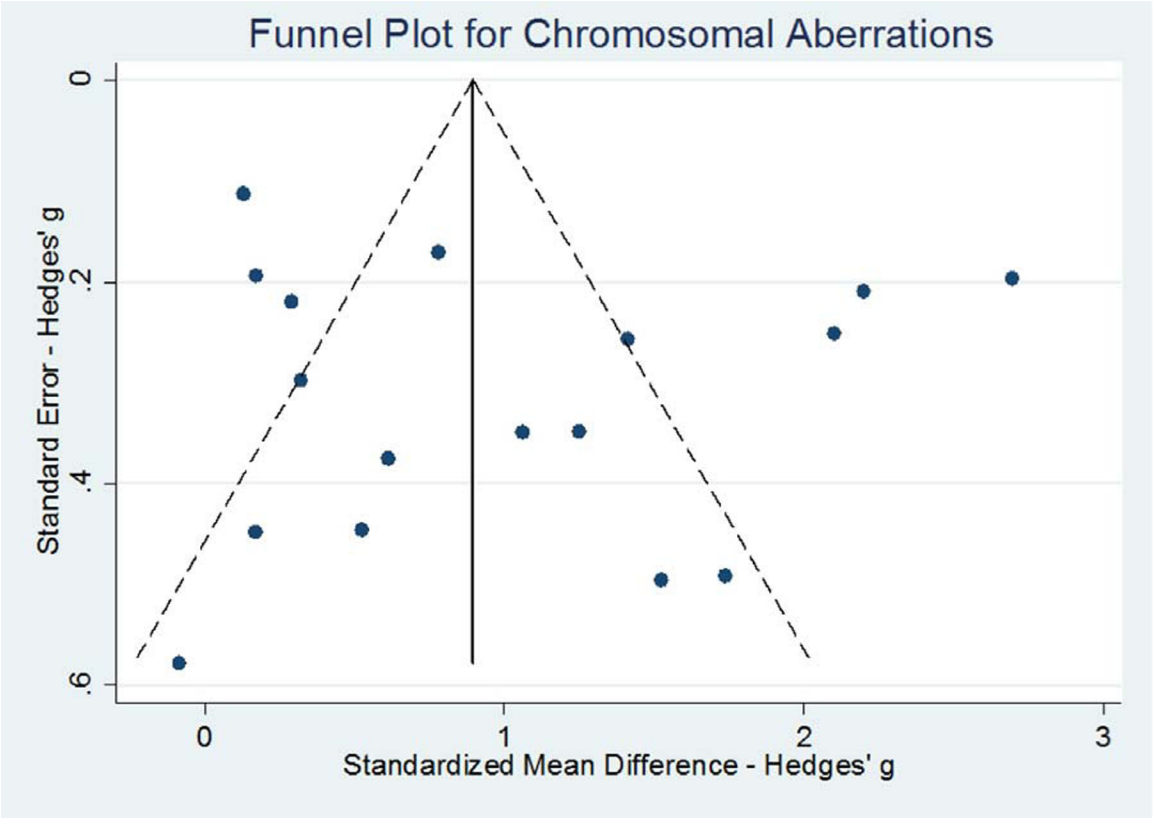

Fig. 3.

Funnel plot resulting from meta-analysis of seventeen studies in sixteen articles. Although the results are from a meta-analysis assuming a random-effects model, the center vertical line is actually from the results of the fixed-effect model, which has an overall effect of 0.895.

Table 1

Characteristics of the sample populations evaluated for chromosomal aberrations in the studies included in the meta-analysis[a].

Citation and location of study	Drug exposures as described by authors	Source of endpoints for analysis	Sample size[b]			
			Exposed (M/F) Mean ± SD	Control (M/F) Mean ± SD	Occupational category	Use of personal protective equipment (PPE)
Bouraoui et al. [77] Tunisia	Numerous antineoplastics[c] (e.g., bleomycin, melphalan, CP, cisplatin, busulfan)	Means, SDs in original article (p. 253)	20 (4/16) 1.85% ± 1.56	20 (4/16) 0.32% ± 0.67	Nurse	Some (70% gloves, 15% masks, 10% gowns); laminar flow safety hood used
Brumen et al. [78] Croatia	Numerous antineoplastics (e.g., CP, 5-FU, vincristine, cisplatin, dacarbazine); radioisotopes[d]	Means, SDs in original article (p. 873)	12 (0/12) 2.2% ± 0.9	12 (0/12) 0.92% ± 0.45	Nurse	Strict adherence to existing recommendations
Burgaz et al. [79] Turkey	Numerous antineoplastics (e.g., CP, 5-FU, cisplatin, iphosphamide, vincristine, etoposide, Adriamycin)	Means, SDs in original article (p. 131)	20 (0/20) 1.15% ± 0.65	18 (0/18) 0.49% ± 0.56	Nurse	50% used gloves and masks; Safety hoods not used
Ferguson et al. [80] New Zealand	Cytotoxic drugs	Calculated means, SDs from raw chromosome, chromatid break data (Table 1)	6 (3/3) 2.16% ± 1.6	6 (3/3) 2.33% ± 2.06	Pharmacist (6) Administrative staff as controls (6)	Double gloves and “cytoguard hood” available but frequency of compliance not provided
Grummt et al. [50] Germany (former E. Germany)	Numerous antineoplastics	SDs calculated from SEMs[e,f] and sample sizes	106 (5/101) 3.3% ± 1.03	93 (5/87) 0.6% ± 0.96	Nurse Physician	No PPE used
Kopjar et al. [81] Croatia	Numerous antineoplastics	SDs calculated from SEMs and sample sizes	50 (0/50) 4.48% ± 2.33	50 (0/50) 0.86% ± 0.64	Nurse (46) Physician (4)	Gloves, masks and laminar vertical flow hood available; 6% reported using all 3 simultaneously, 40% used gloves
Krepinsky et al. [82] Canada	16 Antineoplastics (e.g., cisplatin, 5-FU, CP, vincristine)	SDs calculated from SEMs and sample sizes	10 (0/10) 1.23% ± 0.76[g]	10 (0/10) 1.1% ± 0.73[g]	Nurse	Surgical gloves, masks, glasses, gowns available but use not monitored
Major et al. [83] Hungary	Cytostatic drugs	Weighted mean and pooled SD (as sq. root of pooled variance) had to be calculated for exposed group; SD calculated from SEM and sample size for controls	21 (0/21) 2.09% ± 1.88[g] Safety Cabinet Cohort 1.71% ± 0.46 No Safety Cabinet 2.85% 0.83	101 (22/74) 0.39% ± 1.00[g]	Nurse	14 used a safety cabinet; 7 did not use safety cabinet
McDiarmid et al. [84] USA	Alkylating agents, mitotic inhibitors, antimetabolites, topoisomerase II inhibitors, anthracyclines	Weighted mean and pooled SD (as sq. root of pooled variance) had to be calculated for exposed group; SD calculated from SEM and sample size for controls	63 (8/55) 0.21% ± 0.49[g] Low Exposure Cohort 0.11% ± 0.31	46 (12/34) 0.13% ± 0.4	Nurse Pharmacist	PPE available and encouraged; Biologic Safety Cabinet was used. A subset used closed system transfer device intermittently

Citation and location of study	Drug exposures as described by authors	Source of endpoints for analysis	Sample size[b]		Occupational category	Use of personal protective equipment (PPE)
			Exposed (M/F) Mean ± SD	Control (M/F) Mean ± SD		
			High EXposure Cohort 0.47% 0.80			
Mikovic-Kraus and Horvat [85] Yugoslavia	Numerous antineoplastics (e.g., CP, 5-FU, cisplatin, Adriamycin)	SDs calculated from SEMs and sample sizes	42 2.11% ± 2.59[g]	42 1.56% ± 0.65[g]	Nurse	No PPE used
Moretti et al. [86] Italy	Numerous antineoplastics (most frequently used was CP, second was etoposide)	Means, SDs in original article (p. 683)	71 (0/71) 3.3% ± 2.05	77 (0/77) 1.84% ± 1.67	Nurse	Potentially variable among 5 sites; nurses instructed in use of engineering controls and PPE; wipe and pad samples detected CP (only drug tested for)
Nikula et al. [87] Finland	Cytostatic agents (e.g., 5-FU, CP, doxorubicin, vincristine)	SDs calculated from SEMs and sample sizes	11 4.0% ± 1.33[g]	11 1.9% ± 1.33[g]	Nurse (11) Hospital clerk as controls (11)	Gloves, masks, “fume cupboard and place of handling isolated” initiated 1 year prior to sampling; no PPE before that
Rubes et al. [88] Czech Republic	Numerous antineoplastics (e.g., 5-FU, CP, cisplatin, doxorubicin)	Means, SDs in original article (p. 296)	10 (3/7) 2.7% ± 2.3	11 (5/6) 1.63% ± 1.59	Nurse Physician	Not stated
Sessink et al. [89] Dutch cohort	Numerous antineoplastics (e.g., CP, cisplatin, 5-FU, doxorubicin, etoposide)	Means, SDs in original article (p. 195)	17 (0/17) 2.6% ± 1.4	35 (0/35) 2.1% ± 1.6	Nurse Pharmacy tech	Gloves, masks, special clothing and laminar down-flow hood; CP detected in urine (3/11 workers sampled)
Sessink et al., [89] Czech cohort	Numerous antineoplastics (e.g., CP, cisplatin, 5-FU, doxorubicin, etoposide)	Means, SDs in original article (p. 195)	11 (0/11) 2.7% ± 1.7	23 (3/20) 1.8% ± 1.3	Nurse Cleaning staff Lab tech	Gloves, masks, special clothing and laminar down-flow hood; CP detected in urine (8/11 workers sampled)
Testa et al. [90] Italy	Numerous antineoplastics, (e.g., 5-FU, CP, cisplatin, vincristine, bleomycin)	Means, SDs in original article (pp. 47, 49, 51)	76 (14/62) 11.2% ± 4.39	72 (29/43) 3.04% ± 2.76	Health care worker[h]	Gloves, overalls, googles, biohazard laminar flow hood available; no information on compliance
Tompa et al. [91] Hungary	Cytostatic drugs	Calculated SDs for 3 subgroups of exposed from SEMs and sample sizes; calculated pooled variance with sq. root as SD; calculated weighted mean	500 2.12% ± 3.21[g]	94 (0/94) 1.72% ± 2.42[g]	Nurse	Variable: Use of PPE: Excellent (14), good (161), none (339)

[a] Route of exposure is presumed to be through dermal absorption and/or inhalation; no specific information on exposure route was provided in any of these studies.

[b] Where no indication of the number of male and female subjects is presented, it is due to the absence of this information in the manuscript.

[c] CP, cyclophosphamide; 5-FU, 5-fluorouracil.

[d] Nurses in this study worked with antineoplastic drugs as well as radioisotopes (e.g., iodine, strontium, gold, and cesium); all nurses wore personal radiation dosimetry badges and employed strict adherence to recommended protective procedures.

[e] Standard error of the mean.

[f] Assumed to be Poisson errors.

[g] Values for SD rounded from those used in the actual analysis.

[h] Exact occupation not specified.