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# In Vitro Anti-Mutagenic Effects of Vitamin E by Comet and Ames Assays on Male Nurses in Oncology Wards

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## ABSTRACT

***Objective:*** *The aim of this study is to determine the antimutagenic effects of vitamin E among the male nurses of oncology hospital exposed to chemotherapy drugs. Several studies have demonstrated that nurses occupationally expose to cytostatic drugs. In the present study the antimutagenicity effect of vitamin-E on urine samples of male nurses from oncology and non-oncology hospitals were investigated and compared by using the Ames and Comet assays.*

***Material and Methods:*** *A total of 70 nurses from oncology and non- oncology hospitals participated in the study. All urine samples of nurses before and after vitamin E consumption (200 mg/day) were evaluated by Ames and comet assays. In all steps the collected urine samples extracts were prepared using amberlit XAD-2 resins. Both mutagenicity and comet assays were studied by considering Salmonella typhimurium TA98 and DNA damage respectively. The data were analyzed with Anova one way by using t-test statistical and software of CASP.*

***Results:*** *In the present study 30% of oncology nursing staff had both apoptosis and DNA breaking in nucleus of their urine epithelial cells. However, oral consumption of vitamin E had been significant antimutagenic effects in recovery of DNA damage and able to decrease the nucleus length in urine epithelial cells.*

***Discussion:*** *It was appeared that after vitamin E consumption there was significantly depletion of urinary mutagenic activity in urine extracts among the exposed nursing personnel.*

***Conclusion:*** *We conclude that mild effects of vitamin E against poor safety and significant adverse events among men nurses handling cytotoxic drugs. There is, therefore, a need to improve the safety of the work environment, make available protective equipment, develop standard practice guidelines for oncology nurses and higher therapeutic doses of vitamin E may be a promising compound for reducing mutagenic effects of antineoplastic drugs among oncology hospital nurses.*

***Keywords:*** *Vitamin E, Ames assay, Comet Assay, Nurses, Urine extracts.*

## Introduction

Several studies have performed on biological samples to detect genotoxic effects in humans in connection to their jobs or environment. It is of increasing concern that professional personnel usually expose to anti-neoplastic drugs during preparation and administration [1]. It has been reported that multiple professional workers from clinical, pathology laboratories, farmers and welders are exposing to carcinogenic compounds [2-4]. However, the identification of substances capable of inducing mutations has become an important procedure in safety assessment. Urine mutagenicity is recognized as a marker of internal dose for detecting recent exposure to mutagens in bio monitoring studies of populations exposed to environmental and/or workplace-generated complex mixtures [5-9].

Thereby, in vitro studies have essential roles for the evaluation of urinary mutagenicity test by using Salmonella typhimurium indicator strains to monitor populations of occupationally or environmentally exposed to genotoxic compounds [10]. Genotoxic effects of handling chemotherapeutic agents in a population of nurses have been reported [11, 12].

Also recent our investigation indicates that handling of chemotherapeutic agents among female nurses play a significant role in the onset of Genotoxic effects [13, 14]. The purpose of this study was determine the anti-mutagenic effects of Vitamin E on oncology and non-oncology hospital nurses by Ames and Comet assays. Thus, in the constant quest for new therapeutic natural products have been tested for their antioxidant and antigenotoxic effects [15, 16].

In animal model, Vitamin E has been shown to inhibit completely peroxidative injury by restoring renal tissue antioxidants and glutathione redox balance of hyperoxaluria-induced renal injury [17]. Also it has been shown that Vitamin E ameliorates both the cardiac damage and carcinogenicity of the quinones adriamycin and daunomycin, which are mutagenic and carcinogenic [18]. In the course of these studies, we specifically evaluated the anti-mutagenic effects of Vitamin-E in hospital nurses that is associated with anti-neoplastic drugs exposure.

## Methods

### Study population

The study included 70 male nurses working in oncology and non-oncology hospitals located at Tabriz/Iran, between September 2022 to May 2023 and their duration of employment was (range 1–28 years). The first group consisted of 37 nurses working in a specialized oncology hospital, who had regular contact with anti-neoplastic drugs daily (preparation of solutions and syringes for infusion, administering of anti-neoplastic drugs and handling of body fluids of patients undergoing chemotherapy). The most frequently used chemotherapeutic drugs were doxorubicin, bleomycin, vinblastine, dacarbazine, methotrexate, fluorouracil, prednisone, epirubicin, irinotecan, leucoverin, prednisone, 6-mercaptopurine, procarbazine, lomustine, cisplatin, etoposide, 6-thioguanine and Cyclophosphamide. The handling time varied from 1 to 6 h/day. The second control group 33 nurses were selected from non-oncology general hospital with no history of occupational exposure to anti-neoplastic agents.

The exclusion and inclusion criteria of research population and selection criteria of study persons were based on a questionnaire. All subjects were asked to complete a face-to-face questionnaire, which included standard demographic data (age, gender) as well as medical (exposure to X-rays, vaccinations, medication), lifestyle (smoking, coffee, alcohol, diet) and occupational questions (working hours per day, years of exposure, use of protective measures, etc.). It was assured that the exposed nurses and the controls did not statistically differ from each other except for anti-neoplastic drugs exposure. It was also ensured that the exposed and the control subjects had not been taking any medicines, nor had they been exposed to any kind of radiation for 12 months before sample collection.

All study groups informational questionnaires were filled accordingly study exclusion and inclusion criteria. This study was confirmed university of medical sciences ethical committee and recorded on web site: http://www.irct.ir, concern to WHO.

### Reagents

All chemicals used in this study were of analytical grade and obtained from (Merck co, Germany). Vitamin-E (dL-alpha-tocopheryl acetate) pearl 200IU purchased from (Zahravi pharmaceutical company, Tabriz, Iran).

### Collection of urine samples

After obtaining satisfactory and questionnaire forms from all the nurses, the primary morning urine samples (100 ml) all volunteers from the both groups were collected and transferred to laboratory in capped sterile beakers and labeled candidate nurses names. Then they received orally 200mg of Vitamin E daily for two weeks and at the end of 14th day second urine sample (100 ml) were also delivered to laboratory. The urine samples from the nurse volunteers were centrifuged at 3000g for 5 minutes and samples were stored at -20°C until required for extraction.

### Urine samples screening

In order to verify the presence of chemotherapeutic drugs in urine samples [Table/Fig-5], all samples were screened by thin layer chromatography and in few samples as a result of Ames assay ratio ≥2, trace amount of chemotherapeutic drugs was performed [4, 19].

### Preparation of urine extracts

Extraction columns were filled with 1g from Amberlite XAD-2 resins between two layers of cotton, the resins were washed and activated with Milli-Q water and methanol for two times, then 100ml of urine samples of every volunteer passed from columns through vacuum. The column resins were rinsed with Milli-Q water again for elimination trace amount of interaction factor such as histidine then resins were dried with vacuum aspiration. The resin absorbed substances were washed with eluted solvent with equal mixture of methanol and Acetonitrile. Then these elusion solvents were evaporated with Nitrogen gas. The residue was dissolved in DMSO and refrigerated in −80°C until required for use [20, 21].

**S-9mix preparation**

Male wistar rats weighed 250g (n=4) were selected and the homogenate of S-9mix fraction was prepared. The liver was immediately removed and kept in 1.15% sterilized KCL solution while working under strile conditions at 4°C. The known amount of liver tissue was minced and mixed with (1.15% KCL 3ml/mg). The mixure was homogenized and centrifuged at 9000g for at -20°C for 10 minutes using strile centrifuge vials. Aliquot the supernatant to strile cryo vials. The supernatants were sterilized by using the 0.2µ filter. This supernatant contain P450 microsomal sterile enzymes were stored frozen at −80°C for until use [22, 23].

**Media preparation**

Glucose minimum agar content 10% glucose, Top agar content 0.5mM Biotin-Histidine, nutrient broth were prepared according to Mortelmans & Ziger [23] and were stored frozen for until use.

**Ames assay**

The samples of concentrated urine were assayed for mutagenicity with the Ames test as described by Mortelmans and Zeiger [23], by using S typhimorium tester strains in overnight cultures of TA100 S typhimorium tester strains with and without 10% S-9 mix fraction. For this strain, the spontaneous background number of the revertant was approximately 75-200 of colonies, TA100 S typhimorium tester strains with and without the 10% S-9mix fraction. In this study, Sodium azide (2.5µg/plate) was used as a positive control without using the S-9mix and the 2-aminoanthracene (0.5µg/plate) as a positive control with the S-9mix. DMSO and distilled water were considered as negative controls.

## Comet Assay

**Preparation of urothelial cell suspension**

The urine samples from the nurse volunteers were centrifuged at 2 000 g for 5 min at 4 °C in a refrigerated centrifuge. The upper sections of urines were taken for mutagenic compounds extraction and were kept in refrigerator. To obtain pure and healthy urothelial cells suspension, the urine sediments were washed and centrifuged with phosphate buff er solution 3 times. 100 µl TRED (Trypsin 0.005 % + EDTA) and 100 µl FFP (Fresh Frozen Plasma) were added to urothelial cells suspension then they were incubated at 37 °C for overnight [24]. The comet assay was performed under alkaline conditions [25, 26]. The transparent plastic slides pitted were initially prepared. Every slide pit was belonging to comet assay evaluation of urothelial cells of one nurse volunteer. 100 µl NMA (normal melting agaros) was added to every pit and was coated with 100 µl LMA (low melting agaros) at 37 °C. Then 20 µl urothelial cells were spreaded, the cells fi nally were coated with 100 µl NMA at 37 °C. Then the prepared slides were kept in refrigerator at 4 °C for 10 min. For lysing the cytoplasm of cells, the slides were kept in the ice-cold container with soluble cold, freshly made lysing solution (DMSO and Triton X) for 40 min and kept in dark to avoid from false positive results. The slides were put in electrophoresis tank and electrophoresed in alkaline solution (PH = 13), an ambient temperature of 4 °C for 20 min at an electrical field strength of 25 V. The slides were taken out and surface layer were neutralized by alkaline Tris buffer (PH = 7.4) repeated thrice for 6 min [ 27], then the slides were coated with 100 µl etidium bromide and washed with distilled water and covered with cover slips by using cytology glue and lamel. The comets were studied with 50X fluorescence Olympus microscope equipped with digital camera.

## Positive control

The positive control evaluation of the urine epithelial cell suspension of selected healthy students were exposed to hydrogen peroxide 10 % v/v and incubated for 4 h at 37 °C [28]. The nuclear of these cells were processed to comet assay. Finally the photography of all nuclear were prepared by Olympus 50X fl uorescence microscopes equipped with digital camera and the nuclear tail length of images were calculated by using the CASP software analysis. The microscope was adjusted as: Objective: 100X, sensitivity: ISO 1 600, Resolution: Live/movie: 1360 × 1 024, snap: 4 140 × 3 096 (Pixel shift), exposure time: 2.5–15, dark room. Then slides were studied and photographed zigzag in the margins under microscope, and ideal nuclear of urothelial were selected in slides. Red cells nuclear were often visible in the core were diagonal form [29].

**Image analysis**

Calculation of urinary epithelial cells nuclear elongation Minimum of 50 images of urinary tract epithelial cells for each participant of nurses were prepared. Each image adjusted and saved with picture manager software then these images were loaded in CASP software. Using graph pad prism software mean of 50 stretched urinary epithelial cells nuclear was calculated for each participant of nurses [30, 31]. Accordingly the Figure 1 shows DNA breakage in epithelial cells and calculation of epithelial cells nucleus elongation with CASP software in oncology hospital nurse.

## Statistical analysis

All calculations for Ames and Comet assays were performed by using Graph Pad Prism 5 Software and SPSS. In Ames assay the mean and Standard Deviation (SD) were analyzed for each Parameter. End point means (Mean Ames assay ratio) between oncology hospital and non-oncology hospital nurses were analyzed using Student's t-test and Anova one way. Multiple linear regression analysis was assessed between end points of independent groups. Anti-mutagenic effects of Vitamin E (exposure and age) was determined by using Student's t-test and Anova one way. The level of significance considered was ($p< 0.05$).

Graph Pad Prism 5 Software and SPSS were used for statistical analysis. The data for comet assay was tail length which calculated to oncology and non-oncology hospital nurses then statistical analysis were comparisoned between the 2 subjects. Mean and standard deviation (SD) were analyzed for each parameter. The significance of the differences between control and exposed nurses' end point means were analyzed using Student's t-test (mean DNA tail length). The anti-mutagenic effects of vitamin E (exposure and age) were assessed by Student's t-test. A p-value $< 0.05$ was considered as significant.

## Results

The effect of occupational exposure to chemotherapeutic drugs on the levels of carcinogenic compounds in exposed nurses and non-exposed control subjects were assessed by the Ames assay. [Table-1] shows the results of specific characteristics of controls reversion colony counts. [Table-2] represents the distribution of subjects with respect to age, years of exposure and duration of handling chemotherapeutic agents per day. The two groups studied had similar demographic characteristics. The mean age of the exposed group was 36±7, ranging from 21 to 60 years, and that of controls was 36±7.3, ranging from 21 to 60 years. The extent of mutagenic activity in urine extracts evaluated by Ames assay with respect to biography, work history and ages of all the study subjects are listed in [Table-3 and 4]. Table-3 and Table-4 show the results of urine mutagenic activity before and after Vitamin E consumption in exposed and non-exposed men group nurses respectively.

The extent of mutagenic activity in urine extracts evaluated by Ames assay with respect to biography, work history and ages of all the study subjects are listed in tables 3 and 4. Tables 3 shows the results of urine mutagenic activity before vitamin E consumption in exposed and non-exposed nurses. It has been shown that before vitamin E consumption approximately 25% of oncology hospital nurses excrete carcinogenic compounds in their urine. The mutagenic activity was increased by increasing the age 2.3±0.56, the observed value for non-exposed control was 1.25±0.52, T=0.11.

**Table 1.** Specific of positive and negative controls reversion colony counts.

| Controls value of salmonella Typhimorium tester strain TA100 | µg or µl /Plate | -S-9Mix | +S-9Mix |
|---|---|---|---|
| 2-Amino antheracene | 0.5 | - | 2010 |
| DMSO | 50 | 222 | 254 |
| NaN3(Sodium aside) | 2.5 | 1509 | - |
| D.W(Diluted water) | 50 | 178 | 243 |
| Spontaneous value | - | 204 | 226 |

TA100 colony counts per plates with and without S-9Mix adding.

**Table 2.** Demographic characteristics of non- exposed (control) and exposed men group nurses involved in the study.

| Parameters | Non-exposed urses (n = 33) | Exposed nurses (n = 37) | P-value (t-test) |
|---|---|---|---|
| Age (years) (mean ± SD) | 33.1±7.4 | 32±6.2 | P=0.27 |
| Years of exposure (mean ± SD) | 10.12±6.1 | 12.4±8.1 | P =0.34 |
| Per day exposure (hours)(mean ± SD) | 6.9±1.38 | 7.02±0.57 | P =0.13 |

t-test, $p<0.05$ significant for between groups.

Similarly the effect of vitamin E among exposed and non-exposed nurses is represented in Table 4, as it is shown, the mutagenic activity was increased by increasing the age, so above the age of 36 the observed value was 2.3±0.94 and observed value in case of control was 1.19±0.59.

**Table 3.** The results of urine mutagenic activity before vitamin E consumption (Ames assay Ratio, without 10% microsomal S-9mix system) between Exposed nurses and non-Exposed men group nurses.

| Parameters | Exposed nurses ratio | | Non-exposed nurses ratio | |
|---|---|---|---|---|
| Age (years) | | | | |
| ≥36 | n=37 | 2.2±0.58 | n=33 | 1.31±0.43 p = 0.12 |
| <36 | n=30 | 1.62 ±0.49 | n=28 | 1.09±0.43 p = 0.05 |
| Years of exposure | | | | |
| ≥10.5 | n=32 | 1.81 ± 0.41 | n=30 | 1.21±0.53 p = 0.09 |
| <10.5 | n=32 | 1.76 ± 0.59 | n=32 | 1.18±0.45 p = 0.08 |
| Per day exposure (hours) exposure | | | | |
| ≥7.5 | n=32 | 1.68±0.0.37 | n=34 | 1.31±0.47 p = 0.08 |
| <7.5 | n=33 | 1.7±0.56 | n=32 | 1.09±0.53 p = 0.13 |

t-test, $p<0.05$ significant for between groups.

**Table 4.** The results of urine mutagenic activity after vitamin E consumption (Ames assay Ratio, without 10% microsomal S-9mix system) between exposed and non exposed men group nurses.

| Parameters | Exposed nurses ratio | | Non-exposed nurses ratio | |
|---|---|---|---|---|
| Age (years) | | | | |
| ≥36 | N=37 | 2.17±0.88 | n=33 | 1.22±0.57 p = 0.09 |
| <36 | n=37 | 1.91 ±0.71 | n=33 | 1.08±0.53 p = 0.08 |
| Years of exposure | | | | |
| ≥10.5 | n=35 | 2.32 ± 0.71 | n=31 | 1.08±0.14 p = 0.08 |
| <10.5 | n=35 | 1.93±068 | n=31 | 1.03±0.39 p = 0.07 |
| Per day exposure (hours) exposure | | | | |
| ≥7.5 | n=35 | 1.78±0.0.46 | n=31 | 1.28±0.48 p = 0.08 |
| <7.5 | n=34 | 1.69±0.57 | n=32 | 1.08±0.56 p = 0.11 |

t-test, $p<0.05$ significant for between groups.

Figure 1 shows DNA breakage in epithelial cells nucleus and calculation of epithelial cells nucleus elongation with CASP (Comet assay software) in oncology hospital nurses. Fig. 2 shows DNA breakage in epithelial cells nucleus in an oncology hospital nurse before and after 200 mg/day vitamin E treatment. As it is shown in Figure 2A. Large 'comets' were observed in cells before vitamin E. However, vitamin E treatment causes decrease in the size of the 'comet' Figure 2B.

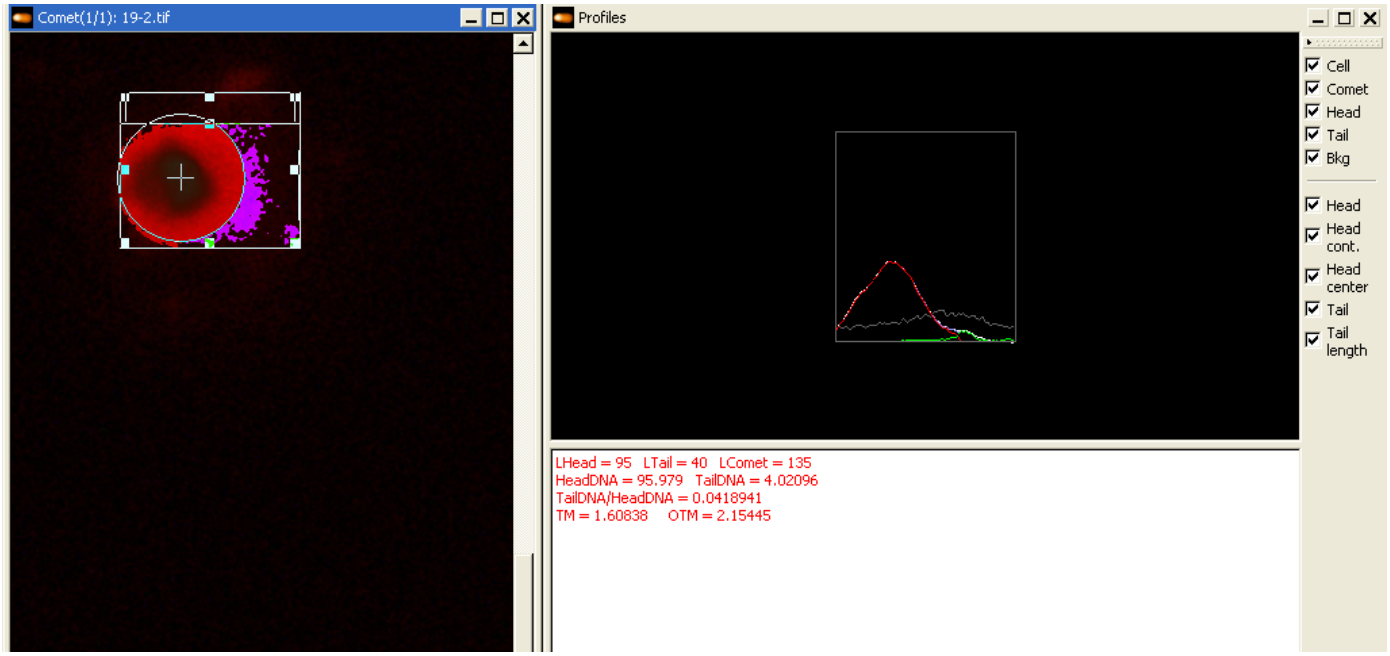


***Figure 1:*** *Show DNA breakage in epithelial cells nucleus and calculate nucleus elongation with CASP software.*

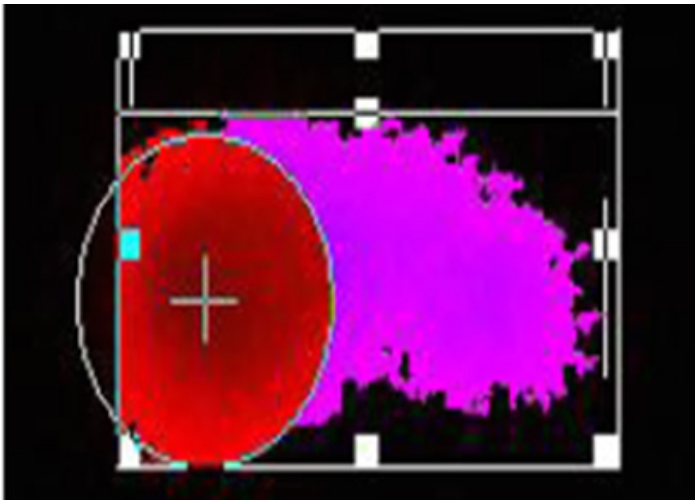

***Figure 2A:*** *Before vitamine E consumption. Tail Length=86.*

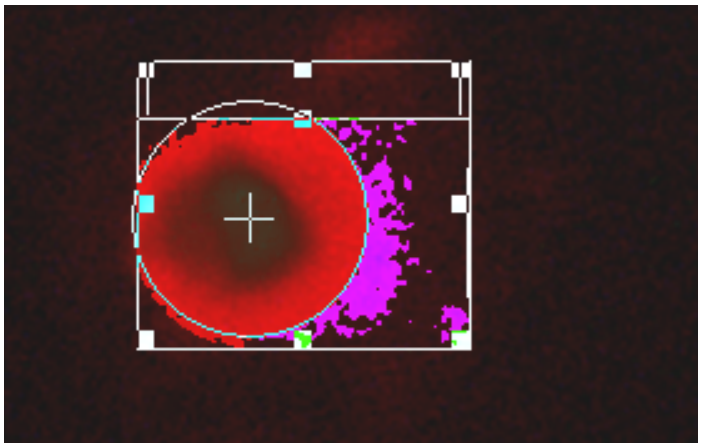

***Figure 2B:*** *After vitamine E consumption. Tail Length=40.*

## Discussion

The present study provides first evidence that Vitamin E supplementation significantly diminishes the mutagenic effects of anti-neoplastic drugs among nursing personnel. Chemotherapy agents with low therapeutic index having major role for chemical control of cancer and on this light, they induce mutagenic effects on normal cells. Studies have investigated the mutagenic potential of anti-neoplastic agents among the medical personnel chronically handling these drugs and it has been found that the excretion of mutagenic compounds in urine extracts are significantly higher than the control [32]. A study by Kosgeroglu, coworkers claimed that with regard to nursing self-protection, when the information and administration scores decrease and increase in the working period, may incur risk exposure to chemotherapeutic drugs [33]. So nursing and healthcare personnel, who admix, administer or dispose of anti-neoplastic drugs or body waste products from patients being treated with such drugs are at great risk of exposure to these agents and they need to be monitored for risks.

Several prior studies indicate that drugs congaing thiol group decrease the activity of mutagenic compounds in urine [34, 35], so

our results are in line with these studies and we tried to confirming of anti-mutagenic effect of oral Vitamin E on study population. The purpose of our study was to evaluate the anti-mutagenic effect of Vitamin E on possible mutagenic risk associated with antinoeplastic drugs. So because of ease to sampling of urine, we assessed the anti-mutagenic effects of Vitamin E of nursing urine samples. Some studies have suggested that, antioxidants especially Vitamin E, a chain-breaking lipophilic antioxidant found within biological membranes, is also physiological membrane-bund free radical scavenger [36], and our earlier observation indicates that Vitamin E as an effective chemopreventive agent is associated with diminution of oxidative stress [37]. Vitamin E ameliorates both the cardiac damage and carcinogenicity of the quinones adriamycin and daunomycin, which are mutagenic, carcinogenic, cause cardiac damage, and appear to be toxic because of free radical generation [38], and its Protective effects against radiation-induced DNA damage, mutation and dimethylhydrazine-induced carcinogenesis have also been observed [39]. In addition, it has been shown that Vitamin E in both the cases, by pretreatment/treatment has essential role on epithelial cells counts [40]. It was appeared that the urinary mutagenic activity will decrease by receiving Vitamin E. However, after Vitamin E consumption there were significantly depletion of urinary mutagenic activity in urine extracts among the exposed nursing personnel. Hence, since nurses are subjected to several anti-neoplastics drugs in job setting, which has been shown to have potent carcinogenic activities and the nursing resistance may decrease and they may encounter with oxidation stress of cellular components [41].

## Conclusion

In summary the amount of mutagenic compounds in urine samples of oncology nurses depends on several factors likes protective equipment, the working period, the information and administration scores with regard to self-protection, and physiological states of a person, age and nutrition. Besides to these, a proper natural diet rich in antioxidants and anti-mutagenics such as Vitamin E should be considered. Also based on experimental evidence we propose that multiple higher therapeutic doses of Vitamin E supplements and increasing the length of treatment period will significantly diminish the level of mutagenic compounds in urine samples of oncology hospital nurses. Because of ease to sampling of urine, it can be inferred that urine sample may have essential diagnostic role among oncology nursing personnel.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.


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