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Original Article

Effect of Cigarette versus Electronic Cigarette on the Expression of TERT, FGFR3, PTEN, P53, and VEGF in Rat Bladder

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HIGHLIGHTS

- To assess and compare the effect of cigarettes and e-cigarettes on the expression of TERT, FGFR3, PTEN, P53, and VEGF in rat bladder.
- The e-cigarette is not an excellent alternative to cigarettes.
- No significant differences were found between cigarette and e-cigarettes.

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ABSTRACT

Introduction
This investigation aims to assess and compare the effect of cigarettes and e-cigarettes on the expression of TERT, FGFR3, PTEN, P53, and VEGF in rat bladder.

Methods
60 Wistar rats were classified into three groups (10): Group A (Control), Group B: case (cigarette smoke), and Group C: case (E-cigarette smoke). The rats were exposed to cigarettes or e-cigarettes for 10 minutes. These 10 minutes were performed three times a day, and in total, the samples were exposed to cigarettes or e-cigarettes for 40 minutes a day with 1 hour rest for 16 weeks.

Results
Histopathological findings showed cigarette-induced hyperplasia and e-cigarette-induced hyperemia and infiltration of inflammatory cells. The expression of FGFR3, TERT, and VEGF genes significantly increased and the expression of the PTEN gene significantly decreased in both cigarette and e-cigarette groups in both male and female rats compared to the control group but these changes were not significant between the two groups. The expression of P53 decreased in both groups, but the female rat in the e-cigarette significantly increased.

Conclusions
We found that both groups changed the expression of genes involved in the development of BC, but no differences were found two groups. Therefore, the e-cigarette is not an excellent alternative to cigarettes.

Keywords: Bladder Cancer; E-cigarettes; Rat; Gene Expression

Introduction

Bladder cancer is the 10th most common cancer worldwide and can be classified as non-muscle-invasive and muscle-invasive bladder cancer. In 2018, approximately more than half a million new bladder cancer cases were diagnosed globally, and 200,000 died from this cancer (1). Cigarette is the greatest risk factor for bladder cancer, explaining almost 50–65% of new items every year. Smoking is indicated to raise the chance of bladder cancer by three to four times (2). Recently, significant smokers have switched to electronic cigarettes (e-cigarettes), and approximately 3.6 million youths use e-cigarettes (3). E-cigarettes are aggressively advertised as smoking cessation or reduction aid and a cheaper, more ecological, socially acceptable, and healthier alternative to conventional cigarettes. Numerous studies assessed the effects of cigarette chemicals on genetic and epigenetic pathways that contribute to inflammation or change the cell cycle (4), while the effect of e-cigarettes on these pathways is unclear.

Several novel molecular technologies are considered to detect diagnostic biomarkers of bladder tumors (5, 6). Mutations drive bladder cancer in different sets of genetic pathways. Studies indicated the high rate of telomerase reverse transcriptase (TERT) and fibroblast growth factor receptor 3 (FGFR3) promotor mutations in bladder cancer that play critical roles in the tumorigenesis and pathogenesis of bladder cancer (5, 7-9). TERT mutation is the most common somatic genetic alteration in non-muscle-invasive and muscle-invasive urothelial cell carcinoma. Moreover, FGFR3 mutation is a common genetic event in non-muscle-invasive bladder neoplasm (10). Also, the vascular endothelial growth factor (VEGF) gene has a crucial effect on angiogenesis and tumor growth. VEGF gene polymorphisms and bladder cancer risk have been investigated broadly. (11). On the other hand, tumor suppressor genes, including P53 and PTEN, are the most commonly implicated genes in human cancer and have been the most frequently studied in bladder cancer over the past decade (12, 13).

Previous studies assessed the effect of cigarettes and their main ingredients on the mutation of critical genes involved in the development of bladder cancer. Still, very few studies investigated the impact of smoking on the expression of these genes. On the other hand, the pattern of smoking has changed, and most smokers switch to e-cigarettes, and the impact of e-cigarettes is not clear on the expression of these genes. According to our knowledge, no study evaluated and compared the impacts of cigarettes and e-cigarettes on the expression of critical genes involved in bladder cancer.

Therefore, the present study aimed to assess the impact of cigarettes and e-cigarettes on the expression of central genes involved in the development of bladder cancer.

Methods

This experimental study has been performed performed in the Urology Research Center's Animal Laboratory of Tehran Medical University, Tehran, Iran, between September 2021 and April 2022 and was approved by the Ethics Research Committee of Tehran University of Medical Sciences (IR.TUMS.SINAHOSPITAL.REC.1399.019). Ethical principles of working with animals were evaluated in all stages of the study.

Animal Caring

60 Wistar rats, 30 male rats, and 30 female rats (6 weeks, weighing 218±22 g), ten rats in every group, from Pasteur Institute, Tehran, Iran (standard place for breeding laboratory animals) were prepared. The rats were housed in six clean plastic cages (18 x 22 x 30 cm), sterilized, and sanitized every 2 days. Special diets have been given to all rats containing protein and fat prepared by the Royan Institute, Iran, as a commercial feed for laboratory animals, and tap water was accessible for all rats freely. Rats were kept for two weeks before the start of the study at the Urology Research Center Animal laboratory to adjust to the environment and reduce the rats' stress. The room temperature of rats was about (22±2°C) with humidity (55±5%), and 12 hours of light and 12 hours of darkness. At the start and end of the study, rats' weights were recorded, and the male and female rats were kept separately in cages.

Exposure of Rats to the smoke of cigarette

Rats were divided into 3 groups (n=10): Group A (Control), Group B: Case-1 (Cigarette), and Group C: Case-2 (E-cigarette). Subsequently, the smoke of cigarettes or e-cigarette goes the plastic cages through a designed suction device. The rats were exposed to the smoke of cigarettes and e-cigarette three times a day for 40 minutes with a one-hour interval (1.8 mg nicotine/day) for 16 weeks. Each used cigarette includes 0.6 mg of nicotine, equivalent to 24µL of nicotine liquid from the e-cigarette used in this research. Every month of a mouse's lifespan is almost 2.5 - 3 human years (14, 15). Thus, 4 months of rats' exposure to cigarettes and e-cigarette equals 10 to 12 years of smoking in human beings.

Investigation of serum parameters and bladder pathology examination

In both research initiation and termination, blood sampling was done. A complete blood count (CBC) was performed with automated hematology and an ESR analyzer (Nihon kohden MEK-1305 Celltac α+). The urinary bladders were taken away from the rats and put in 10% neutral-buffered formalin. The specimens were sent to the comparative pathology laboratory after fixation time. Histological studies were performed

in the pathology department of the Tehran Medicine University, Urology Research Center. An automated autotechnicon tissue processor processed the samples. After molding, different slice sections (5-micron thick) were prepared from blocks of embedded tissues by a microtome machine. Then, all slides were marked based on the H & E (hematoxylin and eosin) standard protocol and observed under an Olympus light microscope.

RNA isolation and Real-Time PCR

A High Pure RNA Isolation Kit was used to extract Total RNA from bladder tissue. (Cat. No. 11 828 665 001). Quality and quantity of extracted RNA were assessed by Nanodrop ND-1,000 (Technologies, Wilmington, DE). Then, cDNAs were synthesized from the Prime-Script RT reagent Takara Kit (Bio Inc, Otsu, Japan, Cat. #RR014A/B). QIAGEN's real-time PCR cycler calculated the relative expression via the $2^{-\Delta\Delta CT}$ approach. For normalizing the gene expression levels utilized, B2M is the housekeeping gene. All steps were performed according to the factory instructions. The information on the primers used along with their product lengths is presented in Table 1.

Statistical analysis

Data were evaluated by Graph Pad prism 9. Two tests, a One-way analysis of variance used for CBC analysis and a T-test used for gene relative expression, were accomplished for statistical analysis. The range of statistical significance was demarcated at *P-value <0.05, **P-value<0.01, and ***P-value<0.001.

Results

At the end of the investigation, WBC, MCV, MCH, and RDW rised in male rats in both cigarettes groups. Significantly, PLT increased in both groups, and WBC rose just in the cigarette group (Table 2). In the female rat, PLT increased significantly in both groups, and WBC increased in the e-cigarette group (Table 3).

Histopathological finding

In the case groups compared to control, pathological findings according to the proliferation of transitional cells indicate possible tissue cancer. Transitional cell hyperplasia was observed in the cigarette and electronic cigarette groups with an approximate 2: 1 in the two case groups. The growth and proliferation of bladder tissue cells were also observed in female rats of the same groups. The occurrence of vascular reactions, especially inflammation caused by active hyperemia and inflammatory infiltration of lymphocytes, was observed as a pre-neoplastic stage in male rats.

We demonstrated increased transitional cell hyperplasia in female cigarette rats (++) and e-cigarette female rats (+) (in a 2:1 ratio, approximately). Also, we indicated an incidence of hyperemia and inflammatory cell infiltration in e-cigarette male rats (+) (Figures 1 and 2, Table 4).

The impacts of cigarette smoke on the expression of tumor suppressor gene and angiogenesis pathway

Through upregulating FGFR3, VEGF, and TERT and downregulating PTEN and P53, e-cigarette smoke might contribute to bladder cancer, although further studies are required to substantiate this proposal.

FGFR3 gene was remarkably went up in cigarette (6.82 fold; P-value<0.0001) and e-cigarette groups (2.28 fold; P-value<0.0001) in comparision to the control group in the male rats. In contrast, these changes were not noticeable in male rats between the two case groups. Gene expression of FGFR3 was significantly increased in both cigarette (1.37 fold; P-value<0.0001) and e-cigarette groups (2.71 fold; P-value<0.0001) compared to the control group. In contrast, between the two cigarette and e-cigarette groups, these changes were not remarkable in female rats. Gene expression of TERT notably rised in cigarette and e-cigarette groups in male groups compared to the control no cigarettes exposed group (P-value<0.0001). The same result was observed in female groups but not significantly different.

VEGF notably rised in both cigarette (2.80 fold; P-value< 0.0001) and e-cigarette (3.30 fold; P-value<0.0001) groups in male rats, and there was a significant difference between the two cigarette and e-cigarette groups (P-value=0.0055). In female rats, the expression of VEGF increased in the e-cigarette group compared to the control (2.12-fold; P-value<0.0001), and there was a significant difference between the cigarette and e-cigarette groups (P-value<0.0001).

Table 1. Primers used for Real-Time PCR

Gene	Forward	Reverse	Amplicon length (bp)
TERT	CAAGGCCAAGTCCACAAGTC	ACAAAGCGCAGGAAGAAGTG	191
FGFR3	AGGCTTCAAGTGCTAAACGC	TGAGGACGGAGCATCTGTTAC	117
VEGF	CAGCTATTGCCGTCCAATTGA	CCAGGGCTTCATCATTGCA	131
PTEN	GGAAAGGACGGACTGGTGTAA	AGTGCCACTGGTCTGTAATCC	199
P53	GTGGCCTCTGTCATCTTCCG	CCGTCACCATCAGAGCAACG	291
B2M	TACGTGTCTCAGTTCCACCC	TTGATTACATGTCTCGGTCCCA	229

Table 2. Hematologic parameters in cigarette and e-cigarette groups in male rats

CBC	Male- Before intervention	Male- after intervention (cigarette)	P-value	Male- after intervention (e-cigarette)	P-value
WBC×103/UL	5.5	13.2	0.0168 *	6.1	0.4563
RBC×106/UL	8.19	9.21	0.1482	8.67	0.6197
HGB g/dl	13.3	13.8	0.3751	14.2	0.8270
HCT%	38	39	0.7471	39.4	0.9646
MCV fL	46.4	52.7	0.2795	47.4	0.4707
MCH pg	16.2	19.7	0.3894	16.4	0.2619
MCHC g/dl	35	38	0.724	36	0.4880
PLT×103/UL	937	960	0.0347 *	981	0.0275 *
RDW%	10.4	10.8	0.2589	10.8	0.6745

*statistically significant with a range of P-value <0.05

Table 3. Hematologic parameters in cigarette and e-cigarette groups in female rats

CBC	Female- Before intervention	Female - after intervention (cigarette)	P-value	Female - after intervention (e-cigarette)	P-value
WBC×103/UL	5.8	6.2	0.4269	8.5	0.0257 *
RBC×106/UL	7.82	7.90	0.4400	8.28	0.3539
HGB g/dl	13.7	14.5	0.5701	13.8	0.5029
HCT%	35.3	35.6	0.9775	38.2	0.3602
MCV fL	58.3	58.4	0.1725	58.9	0.4805
MCH pg	17.6	17.8	0.2625	17.85	0.7672
MCHC g/dl	36	36.1	0.8257	37.3	0.8366
PLT×103/UL	895	1192	0.0314 *	946	0.0483 *
RDW%	12.5	13.4	0.2504	12.9	0.1372

*statistically significant with a range of P-value <0.05

P53 expression significantly decreased in female rats in the cigarette group (0.51-fold; P-value=0.0373). Still, in the e-cigarette group, the expression of P53 increased significantly (1.25-fold; P-value=0.0013), and a noticeable difference was observed between the two cigarette and e-cigarette groups (P-value<0.0001). In the male rat, expression of the P53 decreased significantly in cigarette (0.04-fold; P-value=0.0316) and non-significantly in e-cigarette (0.13-fold; P-value=0.9148) groups, and a significant difference was not found between the two cigarette and e-cigarette groups (P-value=0.1700).

PTEN was declined in cigarette (0.14-fold) and e-cigarette (1.15-fold) groups in male rats in comparision to the control group, while between the two cigarette and e-cigarette groups, these changes were not significant (P-value >0.05). PTEN was notably reduced in the female rat in the cigarette group (0.02-fold; P-value=0.0148), while this gene was decreased no significantly in the e-cigarette group (0.151-fold) in comparision with the control group and between two cigarette and e-cigarette groups (Figures 3 and 4).

Discussion

In this research, the impact of cigarettes and e-cigarettes were evaluated on the expression of primary genes included in the development of bladder cancer. Overall, the study's findings showed that both types of cigarettes induced hematologic changes, histopathological changes, and gene disturbance in rat bladder. At first, we evaluated the hematologic parameters, and the changes in blood cells approved that the rats were exposed to cigarette smoking and the previous studies showed that the white blood cell increased in smokers (16, 17). Histopathological findings showed cigarette-induced hyperplasia and e-cigarette-induced hyperemia and infiltration of inflammatory cells. Our results were consistent with previous studies (18, 19). The present study's findings showed that both cigarettes and e-cigarettes promoted tumorigenesis by upregulating the expression of VEGF, FGFR3, and TERT and downregulating the expression of tumor suppressor genes, including tumor suppression P53 and PTEN. Consequently, both cigarettes and e-cigarettes might have contributed to the development of bladder cancer, but no significant differences existed between the two kinds of cigarettes, and both types of cigarettes have the same risk of changing genes related to bladder cancer.

TERT recreates a critical function in cancer formation, providing chromosomal stability by preserving telomere length and permitting cells to prevent senescence (20). This is the first study focused on the effect of cigarettes and e-cigarettes on the TERT expression in rat bladder, and no study assessed the effect of smoking on the expression of

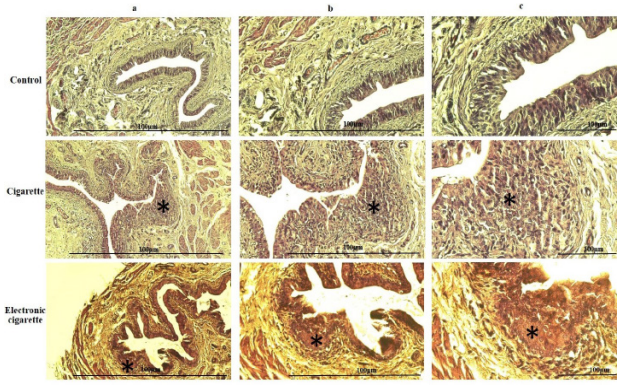

Figure 1. Histopathological sections of the urinary bladder, female rats, H&E staining. Panel c (× 400) shows a higher magnification of photomicrographs than panel b (× 200), and this panel is higher than panel an (x 100). Stars demonstrate transitional cell hyperplasia.

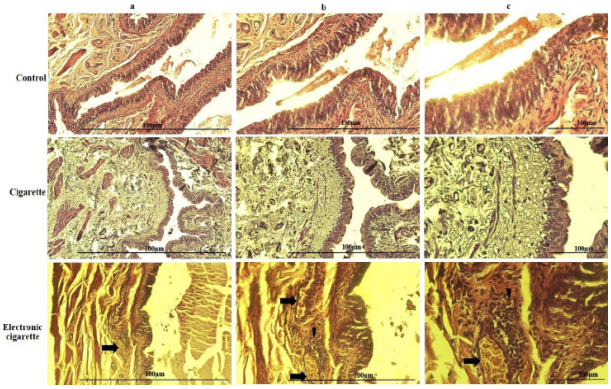

Figure 2. Histopathological sections of the urinary bladder, male rats, H&E staining. Panel c (× 400) shows a higher magnification of photomicrographs than panel b (× 200), and this panel is higher than panel an (x 100). Arrows demonstrate hyperemia, and arrowheads show lymphocytic cell infiltration.

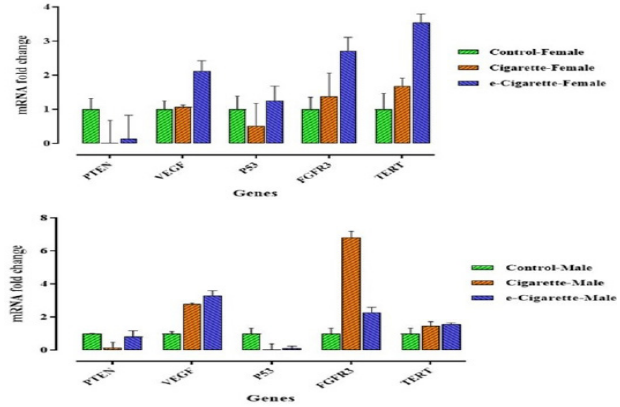

Figure 3. Results of case and control groups exposed to cigarettes and e-cigarettes on gene expression (mRNA fold change). Values are given as mean ± SD of three independent experiments.

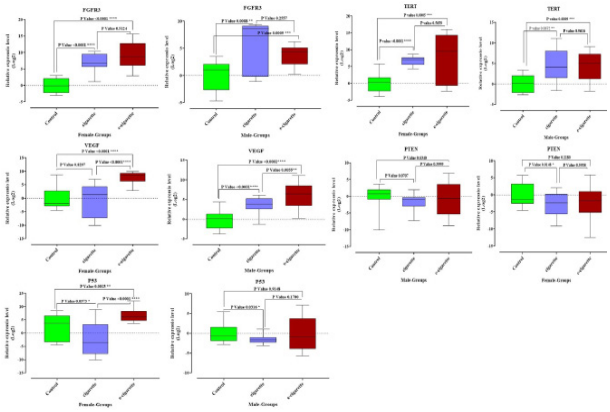

Figure 4. Results of case and control groups exposed to cigarettes and e-cigarettes on gene expression.

TERT in the bladder. The present study's findings showed that exposure to cigarettes and e-cigarettes increased the expression of TERT in rat bladder. Previously, some studies have assessed the interaction between TERT and smoking in other cancers. Capkova et al., assessed the rate of TERT expression in the bronchial mucosa of heavy smokers. The findings showed that the expression of TERT in bronchial biopsies with moderate or severe dysplasia and carcinoma was significantly higher than the normal and mild dysplasia. However, a significant association was not found between smoking status and TERT expression (21). In Lotfi et al.,'s study, there was an inverse association between smoking status and TERT expression in the skin dermis (22). Therefore, there is a lack of data on the interaction between TERT expression and smoking, and more studies are needed to conclude.

FGFR3, a member of the transmembrane receptor kinase for the FGF family of ligands, plays a vital role in cancer cell proliferation, epithelial-to-mesenchymal transition (EMT), migration, and invasion (23). The findings of studies about the impact of cigarettes on the expression of FGFR3 are contradictory. In the present study, the expression of FGFR3 increased in rat bladder in both cigarette and e-cigarette groups. Du et al., assessed the effect of nicotine as the leading tobacco component on the expression of some miRNAs in non-small-cell lung cancer cell lines, and the findings showed that nicotine significantly increased the mRNA and protein expression FGFR3 (24). Another study reported that the FGFR3 expression level was significantly higher in urothelial carcinoma tissues than in normal tissues, and overexpression was associated with cigarette smoking (25). In contrast with previous studies, Tomlinson et al., represented no significant connection between FGFR3 expression and smoking habit in bladder cancer patients (26). So, more studies need to explore the association between FGFR3 expression and cigarettes.

VEGF, an endothelial cell-specific mitogen, is a necessary factor for inducing angiogenesis. We found the upregulating of VEGF expression after exposure to cigarettes and e-cigarettes. To assess the association between cigarettes and patterns of VEGF expression,

Table 4. The histopathology examination reports on bladder tissue in both groups of cigarettes and e-cigarettes more than the control group.

Groups (n = 5 per group)		Transitional cell hyperplasia	Hyperemia	Inflammatory cells infiltration
Female rats	Control	(-)	(-)	(-)
	Cigarette	(++)	(-)	(-)
	E-Cigarette	(+)	(-)	(-)
Male rats	Control	(-)	(-)	(-)
	Cigarette	(-)	(-)	(-)
	E-Cigarette	(-)	(+)	(+)

The plus signs indicate the presence of parameters (++ indicates a higher incidence than +). While the minus sign indicates the absence of a parameter

Rahmani has compared the patients with transitional cell carcinoma and control with inflammatory lesions of the bladder. They reported no significant association between smoking status and VEGF expression. these results might protect the hypothesis that specific carcinogens taken from cigarette smoking can induce VEGF mutations and apoptosis, that are involved in the early steps of bladder carcinogenesis (27).

PTEN is one of the most commonly mutated genes in cancer of human beings. PTEN tumor-suppressive activity regulates cell growth, proliferation, and genomic stability. The PTEN expression decreased in cigarette and e-cigarette groups in the current study. Brait et al. investigated molecular events that causes urothelial cell carcinoma, and for this purpose, they exposed the human bladder epithelial cells to 0.1% cigarette extract for four months and found a small decline in the expression of PTEN (28) that our results were consistent with this study.

The tumor-suppressor protein p53 is an impotant regulator of cell apoptosis, categorically related to the genesis of invasive urothelial carcinoma. We found a decrease in P53 expression after exposure to cigarettes and e-cigarettes; except for female rats in the e-cigarette group, the expression of P53 increases after exposure. This result showed that e-cigarette exposure induced apoptosis in the female rats in the study period, and more studies need to assess the reason for the different results between the two groups. Cheng-Hsun Wu et al. showed that cigarette smoke increased the cellular levels of phospho-p53 in rat terminal bronchioles (29).

However, another study reported that the P53 expression was unchanged after exposure to cigarette smoke extract (28).

The strength of the current study is that it is the first investigation to compare effect of cigarettes and e-cigarettes on the expression of TERT, FGFR3, PTEN, P53, and VEGF in rat bladder.

Conclusions

We found that both cigarettes and e-cigarettes changed the expression of genes included in the development of bladder cancer, but no significant differences were found between cigarettes and e-cigarettes. Therefore, the e-cigarette is not a good alternative to cigarettes and it was suggested that quitting smoking is better than replacing cigarettes with electronic cigarettes.

Authors' contributions

All authors contributed equally.

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Conflict of interest

All authors declare that there is no conflict of interest.

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Ethics statement

All animal experimentations and the study design were approved by the Ethical Committee of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1399.940).

Data availability

Data will be provided on request.

Abbreviations

CBC Complete blood count
EMT Epithelial-to-mesenchymal transition
FGFR3 Fibroblast growth factor receptor3
TERT Telomerase reverse transcriptase

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