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Original Article

Comparison of Conventional Cigarette and Electronic Cigarettes on P53, PTEN, and VEGF Genes Expression in Rat Kidney

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HIGHLIGHTS

- E-cigs overexpressed VEGF and down-expressed PTEN and P53 expression than C-cigs..
- E-cigs as a higher potential for kidney carcinogenesis.
- A VARIETY OF GENETIC ALTERATIONS AND GENE EXPRESSION CHANGES ARE INVOLVED IN THE PATHOGENESIS OF KIDNEY TUMORS.

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ABSTRACT

Introduction
Various genetic alterations and gene expression changes are involved in the pathogenesis of kidney tumors. The P53, PTEN, and VEGF gene expression pattern in rat kidney tissue exposed to conventional cigarettes and electronic cigarette (E-Cigarette) was evaluated.

Methods
In the study, 60 Wistar rats were categorized into three groups (10): no smoke, C-cig smoke, and E-cig smoke. Three cigarette butts used daily with the suction device were exposed for 40 minutes. After four months, kidney tissue was removed, tissue RNA was extracted, cDNA was made, and changes in mRNA expression of genes were evaluated by real-time PCR. Moreover, kidney biopsies were assessed for histopathological changes.

Results
E-cig smoke might contribute to kidney cancer more than C-cigarette through upregulating VEGF and downregulating PTEN and P53 (P-value>0.05). The effect of E-cigarettes in female rats was more significant than in male rats. The histopathological investigation revealed decreased glomerular space in E-cig male rats, increased tubular necrosis in E-cig, Interstitial infiltration in C-cig, and Hyperemia in C-cig in female rats were reported.

Conclusions
Since E-cigarette smoke displayed overexpressed VEGF and down-expressed

PTEN and P53 expression than C-cigarette, it has a higher potential for kidney carcinogenesis.

Keywords: Cigarette Smoke; Tumor Suppressor Gene; Angiogenesis Pathway; Rat

Introduction

Rising Smoking is one of the serious global concerns. Increased risk of lung diseases and various cancers, such as mouth, larynx, lung, bladder, and kidney, caused by Smoking has led researchers to look for a safer alternative for smoke cessation (1). Electronic cigarette (E-cigs) is one of these alternatives widely used recently for smoking cessation in former smokers and even nonsmokers. E-cig Contains a liquid containing flavors, propylene glycol (PG), and vegetable glycerin (VG) in a designed battery-powered device that, when heated, delivers nicotine (2). Previous studies have established less toxicity of these E-cigs. However, there is still no conclusive evidence about the effects of their long-term use on the respiratory system and cancer of various organs (3, 4). The impacts of E-cigs in animal models have shown DNA damage in mice's hearts, bladder, and lungs (5). The kidney is one organ very prone to tobacco exposure failure.

Moreover, the risk of developing RCC in smokers is much higher than in nonsmokers, and Smoking is a proven risk factor for Renal Cancer Cell (RCC) (6, 7). In recent years, some animal studies have examined the impact of cigarette smoke on the expression of genes involved in the cell cycle and apoptosis (programmed cell death), and the results show that cigarette smoke can increase the expression of genes such as Bax, Bcl-2 and Caspase-3changed significantly (8). Due to the different functional roles of PTEN and P53 genes, additional studies are needed to determine this gene's mechanism better. This study compared cancer risk exposure to conventional cig and E-cigs. For this purpose, considering the role of P53, PTEN, and VEGF genes in the onset and progression of kidney cancer, the pattern of changes in the expression of these genes in 30 samples of rat kidney tissue exposed to conventional cigarette smoke E-cigarette smoke was evaluated by Real-Time PCR molecular method.

Methods

This experimental study was performed in the Animal Laboratory of Urology Research Center of Tehran Medicine University, Tehran, Iran, from May to September 2021. It was approved by the Ethics Research Committee of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1399.940). All ethical principles on how to work with animals were considered to conduct this research. When selecting an anesthetic protocol, the rats' age and body weights should also be considered. Ketamine+xylazine (Ket 40-90 mg/kg+Xyl 5-10mg/kg) Intraperitoneal (IP) injection to produce 30-45 minutes of anesthesia, the animal is held in a head-down position, and an insulin needle is inserted into the lower left abdominal quadrant just off the midline (9).

Animal Caring

60 young rats (30 males and 30 females) (4 weeks to 8 weeks, weight 200±20g) Wistar rats were purchased from Pasteur Institute Tehran-Iran. The rats were kept in four hygienic plastic cages (14×21×27cm). All of them were fed intensive diets via a commercial feed pellet for laboratory animals in Royan, Iran. To adapt to the environment, these animals were kept at the Urology Research Center animal house for one week before the start of the experiment to prevent possible environmental changes and to allow them to be held at room temperature (22±2°C) and humidity (55±5%) and adapt 12h light/12h darkness. All five homosexual rats were kept in separate cages to avoid stress in isolation or overpopulation.

Exposure of Rats to cigarette smoke

Subsequently, cigarette or E-cigarette smoke enters the box through a suction device. Also, after the smoke enters the box, it gradually escapes through a unique sponge chimney placed on it. Each period of exposure of rats to cigarette smoke or E-cigarettes lasted 10 minutes. These 10 minutes were performed 4 times a day, and in total, the samples were exposed to cigarette smoke or e-cigarettes for 40 minutes a day.

Grouping Rats

Rats were classified into three groups (10): Group A: Control (n=10, no exposure), Group B: Case-1, conventional smoking (n=10, 3 Cigarette contains 0.6 mg, 1.8mg nicotine/day), Group C: Case-2, E-cigarette (n=10, 3 Cigarette contains 24µL, 72µL nicotine/day). The rats were exposed to cigarette smoke or E-cigarette 3 times a day for 40 minutes at 1-hour intervals.

Investigation of serum parameters

Blood samples were taken six weeks after the rats were exposed to smoke. Rats were anesthetized with ether, then blood sampling was performed using the cardiac blood sampling technique. Blood samples were then stored at laboratory temperature for 15 minutes. Model Nihon kohden Celltac α cell counter device was used for CBC examination.

kidney pathology examination

For pathology, the kidney was taken away from the rats, put in 10% formalin, and sent to the laboratory. Histological studies were performed in the pathology

department of the Urology Research Center.

Preparation of tissue sections

According to the standard method in the autotechnicon machine, after molding, from the paraffin blocks of the kidney of male and female rats of both control and case groups, 5-micron microscopic incisions from different sections by microtome were prepared and stained (hematoxylin-eosin), and observations were performed by Olympus light microscope (image magnification ×200).

RNA isolation and Real-Time PCR

Total RNA was extracted from kidney tissue according to the manufacturer's instructions. cDNAs were reverse transcribed using cDNA synthesis Prime Script RT reagent Takara Kit (Bio Inc, Otsu, Japan). The cDNAs were exposed to amplification by using QIAGEN's real-time PCR cycler. The housekeeping gene (B2M) was used to normalize the expression levels, and the 2−ΔΔCT method was used for calculating the relative expression. The primers are provided in Table 1.

Statistical analysis

At the end of the study, the data obtained from the graph-pad Prism 9 software program and one-way analysis of variance and post-Schiff test were analyzed. Statistical significance was defined at *P-value<0.05, **PF-value<0.01, and ***P-value<0.001 compared to the corresponding control.

Results

Weight and serum parameters

In both C-cigarette and E-cigarette groups, male and female rats gained weight at the end of the study (Table 2). The levels of WBC, MCV, MCH, and RDW increased in cigarettes in both groups of male rats at the end of the study, In contrast, WBC in C-cig, PLT in E and C-cig, HCT in E-cig increased significantly in male rats, WBC in C and E-cig, HCT in E-cig, and PLT in C and E-cig increased significantly in female rats (P-value>0.05) at the end of the study (Tables 3 and 4).

Regarding project completion, these experiments were performed by Nihon Kohden, celtac α model device cell counter. Significance means level (P-values) for CBC at different groups in rats exposed to smoke and e-smoke. Histopathology finding.

We demonstrated a decreased glomerular space in E-cig male rats (+), Tubular necrosis in E-cig female rats (+), Hyaline cast in C-cig male rats (+), Interstitial infiltration in c-cig female rats (+), Hyperemia in E-cig male rats (+) and finally Hyperemia in C-cig female rats (++++) (Table 5) (Figures 1 and 2).

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

E-cigarette smoke might contribute to kidney cancer by upregulating VEGF and down-regulating PTEN and P53, although further investigations are applied to substantiate this proposal (P-value>0.05). VEGF gene expression significantly increased in male and female Electronic Smoke rats (Figures 3 and 4).

Discussion

Much evidence of the association between kidney cancer and Smoking (exposure to tobacco) has been reported by the International Agency for Research on Cancer. Studies have shown that even consuming very few cigarettes a day is associated with an increased risk of renal cancer. Therefore, sooner smoking cessation can reduce the risk of RCC (10, 11).

Due to the many evidence and studies on the harms and effects of tobacco exposure in smokers, it has been essential to find a way to smoke cessation or a safer alternative for smokers. E-cigs are one of these alternatives that are safer than conventional cigarettes. Comparing the effects of C-cig and E-cig Smoking on the lungs demonstrated that it is a safer alternative to the lungs than C-cigs (4). In this study, thirty Wistar rats (male/female) were categorized into three groups. Group A: no smoke (Control), Groups B: C-cigarette smoke, and Group C: E-cigarette smoke. Group B and C were exposed to conventional and electronic cigarettes for 40 minutes, respectively. According to previous studies that proved tobacco exposure raises WBC, RBC, and Platelet levels (12, 13), After the end of the intervention phase, to ensure the effectiveness of the intervention, WBC, RBC, PLT, MCH, HCT, MCV, and HGB levels of the three groups were compared to their levels at the beginning of the study. The result showed that the levels

Table 1. Primers used for Real-Time PCR

Symbol Gene	Forward	Reverse	Product length (bp)
VEGF	CAGCTATTGCCGTCCAATTGA	CCAGGGCTTCATCATTGCA	203
PTEN	GGAAAGGACGGACTGGTGTAA	AGTGCCACTGGTCTGTAATCC	199
P53	ATTCTCACCCTTAAGATCCGTGGG	AGATCTGGCCCTTCTTGGTCT	149
B2M	TACGTGCTCTCCAGTTCCACCC	TTGATTACCATGGTCTCGGTCCCA	221

Table 2. Weight at the beginning, the end of the second month, and, the end of the fourth month

	Weight A	Weight B	Weight C
1	Control Male Group		
	191.68	215.38	261.88
2	Control Female Group		
	186.33	196.97	239.83
3	Smoke Male Group		
	217.12	238.79	264.27
4	Smoke Female Group		
	171.29	199.72	194.39
5	E-cigarette Male group		
	209.31	211.8	234.44
6	E-cigarette Female group		
	180.08	164.95	187.51

Table 3. The result of the male rat's serology testing at the end of the study

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

Table 4. The result of the female rat's serology testing at the end of the study

CBC	Female- Before intervention	Female - after intervention (Cigarette)	P-value	Female - after interven- (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

of WBC, MCV, MCH, PLT, and RDW increased in C and E-cigarette groups of female and male rats at the end of the study (P-value>0.05).

Studies on the effects of Smoking on tobacco-related cancers are underway. For instance, the study of Teresa Franco et al., on oral cancers, one of the main cancers associated with tobacco exposure, has been shown to reduce the risk of oral cancer in E-cig smokers (14).

Table 5. Microscopic rat kidney histopatology findings

Groups (n = 5 per group)		Decreased gGlomerular Space	Tubular Necrosis	Hyaline Cast	Interstitial Infiltration	Hyperemia
Female Rats	Control	-	-	-	-	-
	C-cig	-	-	-	+	++++
	E-cig	-	+	-	-	-
Male Rats	Control	-	-	-	-	-
	C-cig	-	-	+	-	-
	E-cig	+	-	-	-	+

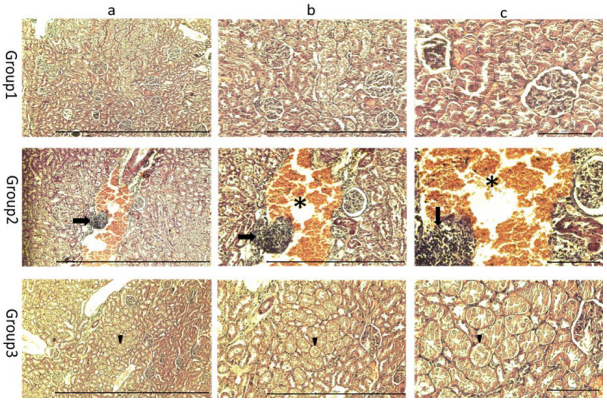

Figure 1. Histopathological sections of the kidney, female rats, H&E staining. Panel c (× 400) shows higher magnification of photomicrographs in panel b (× 200) and this panel is higher than panel a (x 100). Group1: control, Group2: c-cig, and Group3, e-cig. Arrows demonstrate mononuclear inflammatory cells infiltration. Hyperemia is shown by stars. Arrow head in photomicrographs of group 3 indicates tubular necrosis.

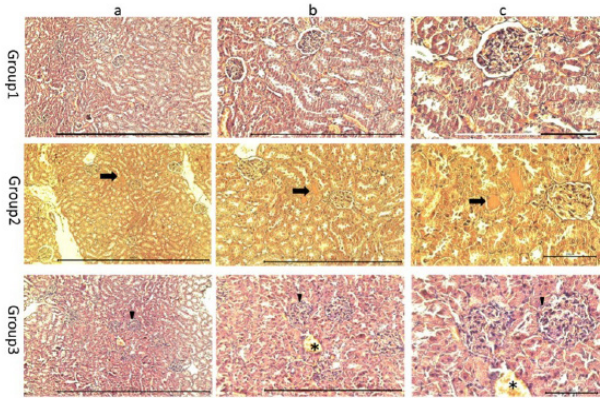

Figure 2. Histopathological sections of the kidney, male rats, H&E staining. Panel c (× 400) shows higher magnification of photomicrographs in panel b (× 200) and this panel is higher than panel a (x 100). Group1: control, Group2: c-cig, and Group3, e-cig. Arrows demonstrate hyaline casts. Hyperemia is shown by stars. Reduction of Bowman's capsular space is highlighted by arrow heads.

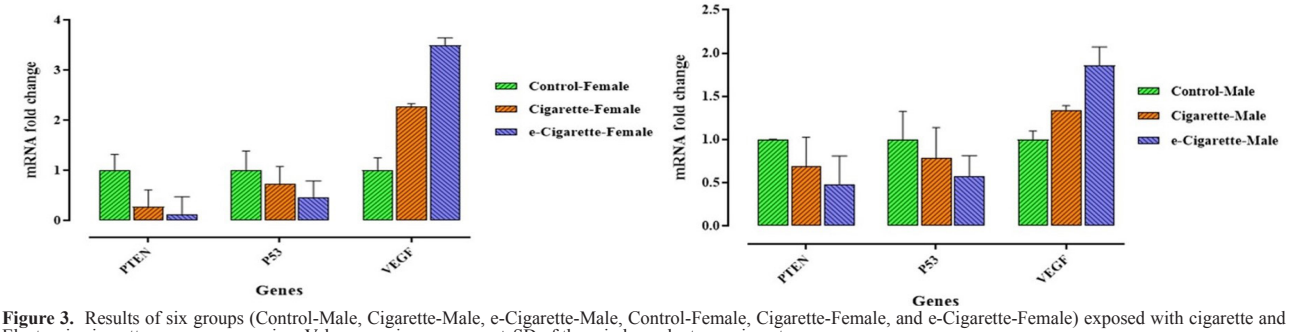

Figure 3. Results of six groups (Control-Male, Cigarette-Male, e-Cigarette-Male, Control-Female, Cigarette-Female, and e-Cigarette-Female) exposed with cigarette and Electronic cigarette on gene expression. Values are given as mean ± SD of three independent experiments.

However, evidence and studies on the cancers are not yet complete, and there is a need for further study. This research was designed to compare the risk of kidney cancer in C-cig and E-cig exposure. For this purpose, the expression of three important genes, P53, PTEN, and VEGF, with key roles in the development and progression of renal cancer in two groups of animals exposed to C-cig and E-cig, were evaluated.

P53 is one of the important genes with a key role in cell apoptosis during DNA damage in the kidney. Studies have shown that smokers are 13 times more likely to mutate this gene than nonsmokers. Genetic studies in patients with RCC have shown low expression of normal p53 gene and high risk of mutated p53 in these patients (6, 15-17). Moreover, the study of Nils Kroeger et al., evaluated and compared the results of mutated P53 gene expression in smokers, and nonsmokers and the survival of RCC patients in these two groups. The results showed a significant increase in the expression of this mutated gene (decreased gene expression without mutation) in smokers

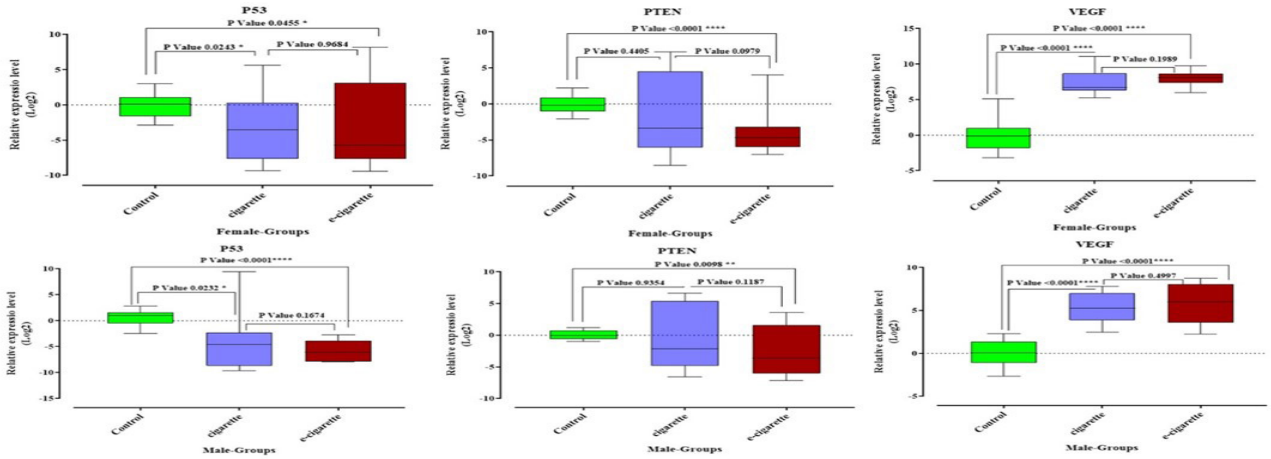

Figure 4. Detail information of relative expression level in cigarette, e-cigarette and control groups in female rats for five target genes. Values are given as mean ± S.E. of three independent experiments. Statistical significance was defined at *P<0.05, **P<0.01, and ***P<0.001 compared to the corresponding control.

compared to nonsmokers. Also, the worse pathologic characteristics of RCC in patients are associated with a lower survival rate. Additionally, the worse pathologic characteristics of RCC and lower survival were reported in smokers than in nonsmokers (1).

According to the general perception, E-cigs are expected to have less effect on P53 gene expression than C-cig smokers and, therefore, have a lower risk of renal cancer. However, the results of the present research indicated that contrary to the assumption, the expression of the P53 gene in E-cig smokers was significantly lower than in C-cig smokers.

The VEGF gene is also one of the most important genes in the development and prognosis of bladder, breast, lung, and RCC cancers. Studies have shown that high VEGF expression is directly related to an increased risk of RCC, progression, and angiogenesis (18, 19). Evidence from previous articles has also shown that tobacco exposure increases the expression of this gene compared to nonsmokers (20). Results of the study by W. Xian et al., that tobacco smoking has been shown to have a crucial part in directly increasing angiogenesis in kidney cancer. It also indirectly affects the progression of cancer by increasing the expression of the VEGF gene, which plays an essential role in angiogenesis (20, 21).

The results of the VEGF gene study in the present study in the two groups of E-cig and C-cig animal groups, contrary to expectations, indicated a significant increase in its expression in the E-cig exposure group. Another gene studied in this study was PTEN, an important tumor suppressor gene in kidney cancer. PTEN is a tumor suppressor gene located on chromosome 3.10q23. Deletion or mutation of this gene was observed in many cancers. PTEN signaling regulates cell division and can also induce cell apoptosis. Loss of PTEN leads to overactive Akt, resulting in uncontrolled cell proliferation. Decreased apoptosis and increased tumor angiogenesis are associated (6, 22, 23). Expression of this gene was significantly lower in the E-cig smoker group than in the C-cig group. Histopathologic investigation of kidney tissues in rats demonstrated lower glomerular space in males, higher Tubular necrosis and Hyperemia in female e-cig-exposed rats, and higher Hyaline cast in males, Interstitial infiltration and Hyperemia in female C-cig-exposed rats than the same sex rats in another group. It is concluded that the destructive effects of Smoking on kidney tissue were higher in female rats. To conclude, the results of the present paper stated that an E-cig is not safer than a C-cig in terms of increasing the potential risk of kidney cancer in the animal model, and it increased the potential risk of RCC more than a C-cig. These effects were more pronounced in female rats than in males. Of course, for precise and more accurate conclusions, more extensive animal studies with more genes and human studies are needed.

Conclusions

Cigarette smoke has a rather noticeable effect on angiogenesis gene expression in rats. Although further documentation, especially in humans, is required, the potential impact of Smoking on cancer progression in society should be considered in public health education.

Authors' contributions

AM: Writing original–draft, FJ, RM, PZ, LZB and ZT: Data acquisition, FG: Data analysis/interpretation, GHM, and BKP: Statistical analysis, MKH: Supervision, RR: Conceptualization

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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 the Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1399.940).

Data availability
Data will be provided on request.

Abbreviations

C-cigs	Conventional cigarette
E-cigs	Electronic cigarette
IP	Intraperitoneal
PG	Propylene glycol
RCC	Renal Cancer Cell
VG	Vegetable glycerin

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