DOI:10.31557/APJCB.2025.10.3.623

RESEARCH ARTICLE

Comparative Efficacy of Prostate Tumor Induction Methods in Wistar Rats

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Abstract

Objectives: This study aims to evaluate and compare the efficacy of three methods for inducing prostate tumors in male Wistar rats: hormonal induction using testosterone propionate, chemical induction with cadmium chloride, and a combination of both agents. The research seeks to enhance understanding of the interactions between environmental and hormonal factors in prostate cancer development. **Materials and Methods:** Twenty-five male Wistar rats (180-220 grams) were randomly assigned to five groups: a control group (no induction), a low-dose cadmium chloride group (1 mg/kg), a high-dose cadmium chloride group (2 mg/kg), a testosterone propionate group (5 mg/kg), and a combination group (1 mg/kg cadmium chloride + 5 mg/kg testosterone). Each treatment was administered over four weeks, followed by a four-week observation period. Histopathological analyses were conducted on prostate tissues using Hematoxylin and Eosin (H&E) staining to assess tumor characteristics and progression. **Results:** Histopathological examination revealed that the control group exhibited normal prostate architecture. The low-dose cadmium chloride group showed mild hyperplasia, while the high-dose group displayed significant dysplastic changes. The testosterone propionate group demonstrated hyperplastic and pleomorphic epithelium, indicative of early tumorigenesis. The combination group exhibited the most aggressive tumors, characterized by severely dysplastic epithelium and stromal invasion. Survival rates were notably lower in the combination group, indicating increased health risks associated with dual exposure. **Conclusions:** The study concludes that the combination of cadmium chloride and testosterone propionate results in a more aggressive tumor phenotype compared to either agent alone, suggesting a synergistic effect in prostate carcinogenesis. These findings underscore the importance of using combined hormonal and chemical induction models to better replicate human prostate cancer for experimental research. Further studies are recommended to explore molecular mechanisms and optimize induction protocols for improved translational relevance in prostate cancer research.

Keywords: Prostate cancer- Wistar rats- cadmium chloride- testosterone propionate- tumor induction- histopathology

Asian Pac J Cancer Biol, **10 (3)**, 623-628 Submission Date: 03/17/2025 Acceptance Date: 05/22/2025

Introduction

Prostate cancer is a major public health concern and ranks as one of the leading causes of cancer-related morbidity and mortality among men globally. Recent statistics indicate that it is the second most frequently diagnosed cancer in men, with significant challenges remaining in early detection and effective treatment

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strategies [1]. Understanding the pathogenesis of prostate cancer is crucial for developing innovative therapeutic approaches, and animal models, particularly rodent models, have proven invaluable in this research.

Cadmium, a heavy metal classified as a human carcinogen, has been linked to prostate carcinogenesis through mechanisms such as oxidative stress, DNA damage, and disruption of androgen signaling pathways [2]. The multifactorial nature of prostate cancer pathogenesis involves complex interactions between genetic, hormonal, environmental, and lifestyle factors, necessitating a comprehensive understanding to develop effective therapeutic strategies [3]. Animal models, particularly the Wistar rat, have proven invaluable in cancer research due to their genetic similarities to humans and their well-characterized prostate anatomy, which allows for the exploration of tumor initiation, progression, and response to treatments [4].

Among the various methods employed to induce prostate tumors in experimental models, hormonal induction using testosterone propionate and chemical induction with cadmium chloride are widely recognized. Testosterone propionate, a synthetic androgen, has been shown to promote cell proliferation in the prostate, increasing susceptibility to neoplastic transformation [5]. Conversely, cadmium chloride, classified as a human carcinogen, induces oxidative stress and DNA damage, contributing to prostate carcinogenesis [2]. While both agents have been studied independently, their combined effects on prostate tumor induction remain inadequately explored, highlighting the need for further investigation.

The primary objective of this study is to conduct a comparative analysis of three distinct methods for inducing prostate tumors in male Wistar rats: testosterone propionate administration, cadmium chloride exposure at two different doses, and their combination. By assessing histopathological changes, tumor incidence, and molecular markers of carcinogenesis, this research aims to identify the most effective and ethically feasible model for prostate cancer studies. Additionally, the findings may enhance our understanding of the interactions between environmental and hormonal factors in prostate tumor development, potentially informing future preventive and therapeutic strategies. This study addresses critical gaps in the current literature and aims to contribute to the optimization of animal models in preclinical prostate cancer research.

Materials and Methods

Experimental Design

This study employed an analytic investigational design utilizing male Wistar rats (*Rattus norvegicus*) to evaluate and compare the efficacy of three distinct methods for inducing prostate tumors: testosterone propionate (Testoviron) produced by Bayer, Lagos, Nigeria, administration, cadmium chloride exposure at two different doses, and a combination of both agents.

Duration of Study

The total duration of the study was 70 days, comprising a 14-day acclimatization period for the experimental animals, followed by 28 days of tumor induction using cadmium chloride (chemical carcinogen) and an additional 28 days of observation without treatment to assess any potential reversal of chemical effects or progression of histopathological changes.

Study Location

The research was conducted at the Experimental Animal House of the Department of Anatomy, University of Benin, Edo state, Nigeria.

Ethical Approval

Ethical clearance having a clearance approval number CMS/REC/2024/692 was obtained from the Research Ethics Committee, University of Benin (RECUNIBEN), before the commencement of the research work.

Animal Model

A total of 25 adult male Wistar rats, weighing between 180–220 grams and aged 8–10 weeks, were sourced from a reputable breeding facility. The animals were housed under standard laboratory conditions (temperature 22 ± 2°C, 12-hour light/dark cycle, and relative humidity of 50–60%) for acclimatization.

Group Allocation

The rats were randomly assigned to five experimental groups, each consisting of five rats:

- Group A (Control): No induction of testosterone propionate or cadmium chloride.
- Group B: Administered 1 mg/kg of cadmium chloride via intraperitoneal injection four times a week for four weeks [6].
- Group C: Administered 2 mg/kg of cadmium chloride via intraperitoneal injection four times a week for four weeks [6].
- Group D: Administered 5 mg/kg of testosterone propionate dissolved in olive oil via subcutaneous injection daily for four weeks [7].
- Group E: Administered a combination of 1 mg/kg cadmium chloride and 5 mg/kg testosterone propionate, following the same administration routes and frequency as the respective groups [6, 7].

Tumor Induction and Observation

The induction period lasted for four weeks, followed by a four-week observation phase without treatment to assess tumor progression and health impact. At the end of each phase, two rats from each group were euthanized, and their prostate tissues were harvested for histopathological analysis.

Histological Analysis

Prostate tissues were fixed in 10% Neutral Buffered Formalin (NBF) to preserve cellular structure. The fixed tissues underwent a series of processing steps: dehydration in increasing concentrations of alcohol, clearing in xylene, and embedding in paraffin wax. Sections of 3 µm thickness were cut using a rotary microtome and stained

with Hematoxylin and Eosin (H&E) for histopathological examination [8]. The stained sections were analyzed under a light microscope at magnifications of 10X and 40X, with photomicrographs taken at 100X and 400X magnification.

Health Assessment

Weight measurements were recorded at three phases: pre-exposure, during exposure, and post-exposure. The overall health impact was assessed based on survival rates and observable symptoms of toxicity, including weight loss and lethargy.

Data Analysis

Histopathological changes were assessed under light microscopy, focusing on architectural and cellular alterations, tumor incidence, and overall health impacts. The data collected were statistically analyzed to determine the effectiveness of each induction method in generating prostate tumors.

This methodology provides a comprehensive framework for evaluating the tumor-inducing potential of different agents in a controlled experimental setting, contributing to the understanding of prostate cancer development and the optimization of animal models for future research.

Results and Discussion

The study evaluated the efficacy of three methods for inducing prostate tumors in male Wistar rats: testosterone propionate administration, cadmium chloride exposure at two different doses, and a combination of both agents. A total of 25 rats were divided into five groups, each subjected to specific treatments over 70 days.

Macroscopic Observations

The mean body weights of the experimental animals were recorded at the beginning and end of the study. In Stage 1, Group A (control) showed an increase in mean body weight from 161 g to 199 g. In contrast, Group B (1 mg/kg cadmium chloride) experienced a significant decline in weight from 174.5 g to 133.5 g, while Group C (2 mg/kg cadmium chloride) showed a slight decrease from 174.5 g to 170 g. Group D (5 mg/kg testosterone propionate) maintained a stable weight, ending at 171.5 g, whereas Group E (combination treatment) decreased from 188 g to 168 g (Figure 1).

More so, the results of the second stage of the study, as illustrated in Figure 2, demonstrate significant variations in mean body weight among the experimental groups following the four-week observation period. Group A (Control) maintained a stable mean body weight, concluding at 199 g, indicating no adverse effects from the absence of tumor induction. In contrast, Group B (1 mg/kg cadmium chloride) exhibited a marked decline in mean body weight, decreasing from 133.5 g to 120 g, suggesting that even low-dose cadmium exposure may lead to health deterioration over time. Group C (2 mg/kg cadmium chloride) also showed a slight decrease in mean body weight, ending at 168 g, which reflects the increased severity of the induced changes compared to the control group.

Group D (5 mg/kg testosterone propionate) maintained a relatively stable weight, concluding at 171.5 g, indicating that testosterone alone may not significantly impact overall health during the observation period. However, Group E (combination treatment) experienced a notable decline in mean body weight from 168 g to 150 g, reinforcing the hypothesis that the combination of cadmium chloride and testosterone propionate exacerbates health issues, likely due to the synergistic effects of both agents on the prostate and overall physiology. These findings highlight the detrimental impact of the combination treatment on the health of the rats, suggesting that the dual exposure to both agents leads to more pronounced systemic toxicity.

Finally, Figure 3 illustrates the survival rates of the experimental animals across both stages of the study. In Stage 1, all rats in Group A (Control) survived, reflecting the absence of tumor induction. However, the survival rates began to diverge significantly in the treatment groups. Group B (1 mg/kg cadmium chloride) exhibited a survival rate of 80%, indicating that while some rats were affected by the treatment, a majority remained viable. Group C (2 mg/kg cadmium chloride) had a slightly lower survival rate of 60%, suggesting that the higher dose of cadmium chloride increased mortality risk.

In Stage 2, the survival rates further declined, particularly in Group E (combination treatment), which recorded a survival rate of only 40%. This stark reduction

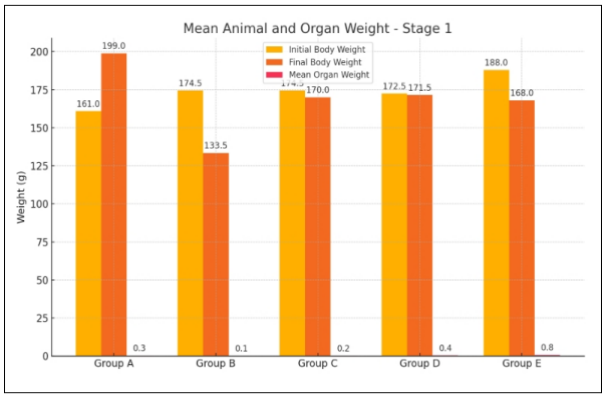

Figure 1. Bar Chart Showing Mean Animal Weight of Experimental Animals in Stage 1

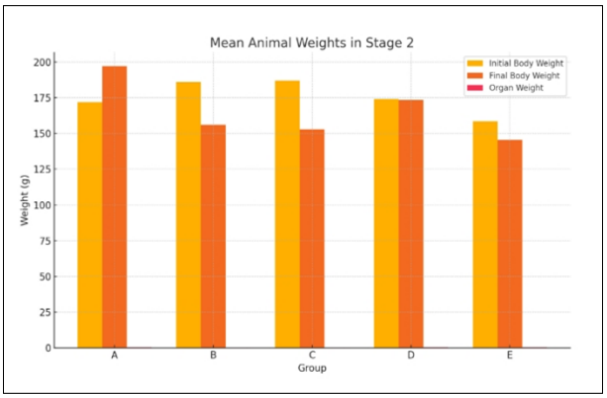

Figure 2. Bar Chart Showing Mean Animal Weight of Experimental Animals in Stage 2

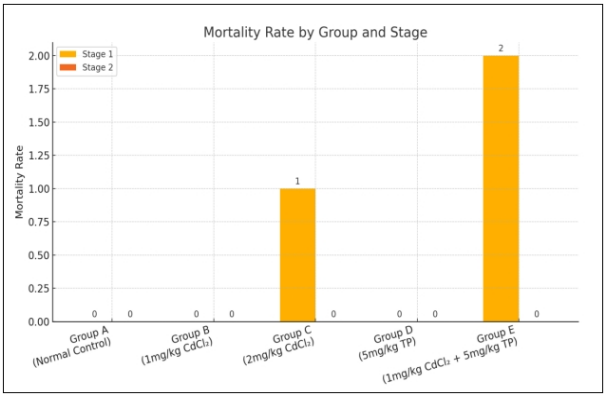

Figure 3. Bar Chart Showing the Survival Rate of Experimental Animals in Stage 1 and 2

underscores the increased health risks associated with the dual exposure to cadmium chloride and testosterone propionate, leading to a significantly higher mortality rate compared to the other groups. Group D (5 mg/kg testosterone propionate) maintained a survival rate of 60%, indicating that while testosterone alone poses some risks, it is less lethal than the combination treatment. The data presented in Figure 3 clearly demonstrate that the combination of cadmium chloride and testosterone propionate not only enhances tumor aggressiveness but also significantly compromises the overall health and survival of the experimental animals, reinforcing the need for careful consideration of combined exposure in prostate cancer research models.

Summary of Findings

The results from both figures (Figure 2 and 3) highlight the differential impacts of the various tumor induction methods on the health and survival of male Wistar rats. The combination of cadmium chloride and testosterone propionate resulted in the most severe health consequences, as evidenced by significant weight loss and reduced survival rates. These findings support the conclusion that the synergistic effects of hormonal and chemical carcinogens contribute to a more aggressive tumor phenotype and increased mortality risk, underscoring the importance of using comprehensive models to study prostate cancer development (Figure 4).

Histopathological Findings (Stage 1)

Histopathological analysis revealed distinct tumor characteristics across the treatment groups. Group A exhibited normal prostatic architecture with well-defined acini and a double-layered epithelium (PA) (a). Group B showed mild alterations, such as mild infiltrates of plasma cells (b). Group C presented more severe changes, such as cystically dilated acini (CA) (c). Group D demonstrated hyperplastic and pleomorphic epithelium (HE) (d), while Group E displayed neoplastic glands (NG) lined by severely dysplastic epithelium and evidence of stromal invasion (e) (Figure 5).

Histopathological Findings (Stage 2)

In Stage 2, the histopathological examination continued to reveal significant differences among the treatment groups, reflecting the progression of tumor characteristics over the additional 28 days of observation. Group A (Control Group): The prostate tissue maintained its normal architecture, characterized by acini lined by a double-layered epithelium (PA), with the presence of corpora amylacea (CA) in the lumen and a well-vascularized fibrous stroma (f). These findings confirm the stability of healthy prostate tissue over the study period. Group B (1 mg/kg Cadmium Chloride): The prostate tissue showed cystically dilated acini (DA)lined by focally hyperplastic epithelium and supported by thick fibrocollagenous stroma (g). These changes indicate a progression towards benign prostatic hyperplasia (BPH), although the alterations were less severe compared to higher cadmium doses. Group C (2 mg/kg Cadmium Chloride): The high-dose cadmium chloride group exhibited a more pronounced pathological progression, with prostatic acini closely packed and lined by hyperplastic dysplastic epithelium. The stroma (FS) was significantly thickened, suggesting a more aggressive transformation (h). These findings highlight the dose-dependent effects of cadmium chloride on prostate tissue. Group D (5 mg/kg Testosterone Propionate): The histopathological analysis revealed closely packed acini (PA) lined by focally hyperplastic epithelium and supported by fibrous stroma (i). This indicates that testosterone propionate continues to promote hyperplastic changes, consistent with its role as an androgenic agent in prostate cancer development. Group E (Combination Treatment): The combination of testosterone propionate and cadmium chloride resulted in the most severe histopathological changes. The prostate tissue displayed neoplastic glands lined by severely dysplastic epithelium, with notable loss of myoepithelial cells (ME) and evidence of stromal invasion (SI) (j). This aggressive phenotype underscores the synergistic effect of combining hormonal and chemical carcinogens, leading to advanced tumor characteristics that closely resemble human prostate cancer.

Overall, the histopathological findings from Stage 2 indicate that the combination treatment not only accelerates tumor progression but also enhances the aggressiveness of the tumors compared to the individual treatments. These results reinforce the importance of

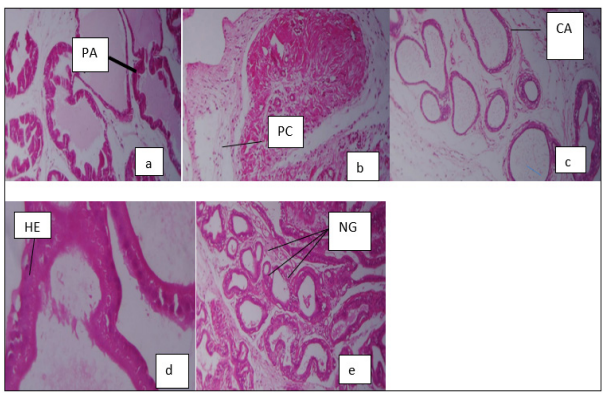

Figure 4. Showing Photomicrograph of all H & E Stained Slides in all Five Experimental Groups in Stage 1 at Magnification 100x

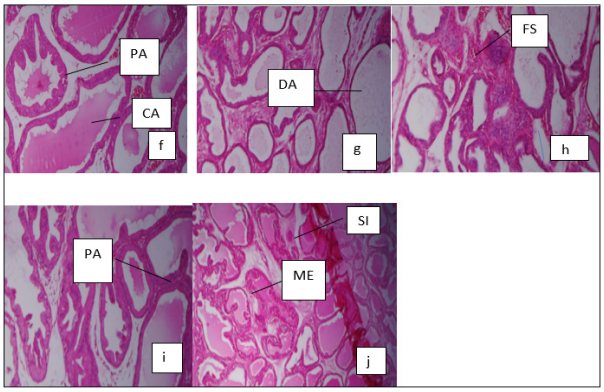

Figure 5. Showing Photomicrograph of all H& E Stained Slides in all Five Experimental Groups in Stage 2 at Magnification 100x

understanding the interactions between hormonal and environmental factors in prostate cancer development and highlight the utility of these animal models for future therapeutic research.

Discussion

The findings of this study provide significant insights into the comparative efficacy of three methods for inducing prostate tumors in male Wistar rats: testosterone propionate administration, cadmium chloride exposure, and their combination. The results demonstrate that the combination of cadmium chloride and testosterone propionate leads to the most aggressive tumor characteristics, aligning with previous research that suggests a synergistic effect between hormonal and chemical carcinogens [9]. This is particularly relevant given the multifactorial nature of prostate cancer, where both environmental and hormonal factors contribute to tumor development.

Histopathological analysis revealed that tumors induced by the combination treatment exhibited severe dysplastic features and significant stromal invasion, which are hallmarks of malignant transformation. This finding is consistent with literature indicating that cadmium chloride induces not only oxidative stress but also inflammatory responses that facilitate tumor progression [10].

The presence of immune cells within the tumor microenvironment, as observed in our study, further supports the notion that cadmium exposure exacerbates tumorigenesis through inflammatory pathways. This aligns with findings from prior studies that have highlighted the role of chronic inflammation in prostate cancer progression, suggesting that cadmium's genotoxic effects may be compounded by its ability to promote an inflammatory milieu [11].

In contrast, tumors induced by testosterone propionate alone displayed hyperplastic and pleomorphic epithelium, indicating that while this method effectively stimulates tumor growth, it may not fully replicate the aggressive nature of prostate cancer seen in human patients. The moderate tumor development observed with testosterone propionate is consistent with previous reports that indicate this method primarily leads to localized tumor growth with minimal metastatic potential [12]. This limitation underscores the importance of using combination models to better reflect the complexity of human prostate cancer, which often involves both hormonal and environmental influences.

The dose-dependent effects of cadmium chloride were also evident in our findings. The low-dose group exhibited benign prostatic hyperplasia, while the high-dose group showed significant dysplastic changes and a higher incidence of neoplastic transformation. This observation is in line with existing literature that emphasizes the critical role of dosage in determining the carcinogenic potential of chemical agents [13]. The ability of cadmium to induce both benign and malignant lesions highlights its relevance as a model for studying the progression of prostate cancer.

Furthermore, the health impact observed in the combination treatment group, characterized by significant weight loss and decreased survival rates, emphasizes the systemic toxicity associated with cadmium exposure. As shown in Figure 3, the survival rates were notably lower in the combination group compared to the other groups, corroborating earlier studies that have reported cadmium's detrimental effects on overall health and organ function, particularly in the context of cancer [14]. The combination of hormonal stimulation and chemical toxicity appears to place considerable stress on the animals, resulting in a more pronounced decline in health compared to single-agent models.

Overall, the results of this study underscore the significance of understanding the interactions between hormonal and environmental factors in prostate cancer development. By demonstrating the enhanced tumor-inducing potential of the combined treatment, this research provides a valuable framework for future studies aimed at exploring the molecular mechanisms underlying prostate carcinogenesis. The findings also support the need for standardized protocols in preclinical research to improve the reproducibility and translatability of results to human prostate cancer, ultimately contributing to the development of more effective therapeutic strategies.

In conclusion, the comparative analysis of tumor induction methods presented in this study not only advances our understanding of prostate cancer but also highlights the importance of utilizing robust animal models that accurately reflect the disease's complexity. This research lays the groundwork for future investigations into the multifaceted nature of prostate cancer and the potential for developing targeted interventions that address both hormonal and environmental risk factors.

In conclusion, this study successfully demonstrated the differential tumor-inducing potential of three methods for inducing prostate tumors in male Wistar rats: testosterone propionate administration, cadmium chloride exposure, and their combination. The findings revealed that the combination of cadmium chloride and testosterone propionate resulted in the most aggressive tumor characteristics, including severe dysplasia and significant stromal invasion, which closely mirrors the complexities of human prostate cancer.

The results underscore the importance of understanding the interactions between hormonal and environmental

factors in prostate cancer development, highlighting the need for comprehensive models that reflect the multifactorial nature of the disease. Furthermore, the study contributes to the optimization of animal models for preclinical research, providing a valuable reference for future studies aimed at improving therapeutic strategies and preventive measures against prostate cancer.

In light of the observed health impacts and survival outcomes, particularly in the combination treatment group, this research advocates for the careful consideration of ethical practices in animal experimentation, promoting the application of the 3Rs (Replacement, Reduction, and Refinement). Overall, the insights gained from this comparative analysis will enhance the validity and reproducibility of prostate cancer research, ultimately contributing to advancements in understanding and treating this prevalent malignancy.

Acknowledgments

The authors would like to express their sincere gratitude to all individuals who contributed to the successful completion of this research. We extend our heartfelt thanks to our research supervisors Prof. G.I Eze and Prof F.O Akinbo, for their invaluable guidance and support throughout the study.

We are also grateful to Mr. Samuel M. Nwangbada for his assistance in taking care of the experimental animals, ensuring their well-being during the course of the research. Their dedication and attention to detail were crucial in maintaining the integrity of the study.

Additionally, we would like to acknowledge Mr. Augustine I. Obiozor, who provided writing assistance for his help in drafting and refining this manuscript. His expertise greatly enhanced the clarity and quality of our work.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors declare no conflict of interest.

Finally, we would like to thank our families and friends for their unwavering support and encouragement throughout this research journey.

Funding

The authors of this original research article did not receive any funding to perform the present research.

Conflict of interest

Author declares no conflict of interest.

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