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Cytochrome P450 genes expression in human prostate cancer

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ABSTRACT

CYP-dependent metabolites play a critical role in regulating the cell cycle, as well as the proliferative, invasive, and migratory activity of cancer cells. We conducted a study to analyze the relative gene expression of various *CYPs* (*CYP7B1, CYP27A1, CYP39A1, CYP51, CYP1B1, CYP3A5, CYP4F8, CYP5A1, CYP4F2, CYP2J2, CYP2E1, CYP2R1, CYP27B1, CYP24A1*) in 41 pairs of prostate samples (tumor and conventional normal tissues) using qPCR. Our analysis determined significant individual variability in the expression levels of all studied *CYPs,* both in the tumor and in conventionally normal groups. However, when we performed a paired test between the tumor and normal groups, we found no significant difference in the expression of the studied genes. We did observe a tendency to increase the level of *CYP1B1* expression in the tumor group. We also did not find any significant difference between the levels of the studied *CYPs* in the tumor and conventional normal groups at different stages of prostate cancer and pathomorphological indicators. Correlation analysis revealed the presence of a positive relationship between the expressions of some cholesterol-metabolizing *CYP* genes, as well as between genes responsible for vitamin D biosynthesis and cholesterol biosynthesis. We observed significant correlative relationships between the expression of *CYPs* and some prostate cancer-related genes (*CDH2, MMP9, SCHLAP1, GCR, CYP17A1, ACTA2, CXCL14, FAP, CCL17, MSMB, IRF1, VDR*). Therefore, the expression of *CYPs* is not directly associated with prostate cancer but is largely determined by genetic, epigenetic factors, as well as endogenous substrates and xenobiotics. The significant correlative relationship between *CYPs* and genes associated with cancer may indicate common regulatory pathways that may have a synergistic effect on the tumor, ensuring the survival of cancer cells.

1. Introduction

Cytochrome P450 (CYP) family is a group of around 60 enzyme genes that use molecular oxygen along with NADPH to catalyze the hydroxylation of compounds. These enzymes metabolize a wide range of endogenous and exogenous compounds and are involved in signaling pathways as well as environmental carcinogenesis [1,2]. Specifically, cytochrome P450 plays a crucial role in lipid metabolism, including the metabolism of cholesterol and fatty acids, which serve as precursors to hormones and vitamins. Additionally, CYP-dependent oxidation is a key step in the biosynthesis and metabolism of important signaling molecules like androgens, vitamin D, and more [3,4]. These CYP-dependent metabolites have been shown to regulate cell cycle, proliferation, and pro-apoptotic processes. The dysregulation of such processes is a critical factor in carcinogenesis [5].

Prostate cancer is a prevalent type of cancer worldwide. It is known that impaired regulation of cellular differentiation, proliferation, and apoptosis can initiate and significantly contribute to prostate carcinogenesis. These processes are directly linked to changes in lipid metabolism in cells. Additionally, changes in lipid metabolism are crucial in

Abbreviations: CYPs (*CYPs*), proteins (genes) of Cytochrome P450 superfamily; *CDH2*, the gene encodes Cadherin 2; *MMP9*, the gene encodes Matrix Metallopeptidase 9; *SCHLAP1*, the long noncoding RNA SCHLAP1; *GCR*, the gene encodes Glucocorticoid Receptor; *CYP17A1*, the gene encodes Cytochrome P450 17A1; *ACTA2*, the gene encodes Smooth Muscle Alpha-Actin; *CXCL14*, the gene encodes Chemokine (C-X-C motif) ligand 14; *FAP*, the gene encodes Fibroblast Activation Protein Alpha; *CCL17*, the gene encodes C-C motif Chemokine ligand 17; *MSMB*, the gene encodes Microseminoprotein beta; *IRF1*, the gene encodes *Interferon Regulatory Factor 1*; *VDR*, the gene encodes Vitamin D Receptor; *TBP*, the gene encodes TATA-Box Binding Protein; *FDR*, false discovery rate.

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providing energy and macromolecules for biomembrane synthesis. These changes also affect membrane functioning, such as membrane permeability and receptor functioning, which consequently aids the survival of cancer cells [6].

Several studies have shown that *CYPs* are highly expressed in the prostate gland, implying that these enzymes play a significant role in the metabolism of intracellular signaling molecules. Furthermore, CYPs are involved in the local metabolism of xenobiotics, which can affect the intracellular response to carcinogens and modulate the therapeutic effect in the prostate gland. In our previous work, we reviewed the accumulated data on changes in the expression of certain CYPs and their possible involvement in prostate carcinogenesis [7,8].

It is well established that exposure to xenobiotics can cause cancer, primarily by altering the expression of oncogenes and antioncogenes and activating carcinogens. Xenobiotics can also cause changes in the expression of enzymes that are involved in the metabolism of anticancer drugs and endogenous compounds, which are critical to the development of cancer. A study found that enzymes belonging to the cytochrome P450 family may have a significant role in the initiation, progression, and development of prostate cancer [9].

Therefore, a comprehensive analysis of potential alterations in the expression of particular *CYPs* in prostate tumors is necessary to enhance the comprehension of the molecular mechanisms of carcinogenesis and discover novel molecular targets for therapy.

Our research aimed to examine how certain *CYP* genes that are responsible for metabolizing lipids, polyunsaturated fatty acids, androgens, vitamin D, and xenobiotics are expressed in pairs of adenocarcinoma and surrounding conditionally normal prostate tissue samples from patients who have been diagnosed with prostate cancer. Additionally, we wanted to determine if there is a correlation between the expression levels of these genes and certain clinical and pathological data of the patients.

2. Materials and methods

2.1. Obtaining samples of prostate tissues

Surgically extracted material from both adenocarcinoma (tumor group) and conventionally normal tissues (conventional normal group) of the human prostate gland was used for this study. The study analyzed 41 pairs of tumor and conventionally normal tissue samples (T/CNT), as well as two unpaired prostate tumor samples (Table A.1). All samples were obtained from the National Cancer Institute (Kyiv, Ukraine). The prostate tissue samples were collected from 43 patients aged between 48 and 72 years, following The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

2.2. Total RNA isolation and cDNA synthesis

The total RNA was isolated from prostate tissues using the GeneJET RNA purification kit (ThermoSci, USA) following the manufacturer's protocol. The RNA samples were treated with DNAaseI (ThermoSci, Lithuania) according to the manufacturer's instructions. For cDNA synthesis, the Maxima H Minus cDNA synthesis master mix (ThermoSci, Lithuania) reagents were used as per the manufacturer's protocol. The cDNA samples were stored at −70 °C until used.

2.3. Quantitative RT-PCR for determining the levels of relative gene expression

The iCycler iQ5 Multicolor Detection System (Bio-Rad, USA) amplifier was used to perform real-time quantitative PCR (qPCR). A set of Hot FirePol EvaGreeen qPCR Supermix (Solis Biodynes, Estonia) reagents was used according to the manufacturer's protocol. The qPCR conditions were 12 min at 95 °C followed by 40 cycles of 15 s at 95 °C, 20 s at 60 °C, and 20 s at 72 °C. The primers used for qPCR can be found in Table A.2. Relative gene expression levels were normalized by the *TBP* reference gene. The 2-ΔCt method was used to calculate the levels of relative gene expression, as described earlier [10–12].

2.4. Statistical data processing

The results of relative expression studies were analyzed using STATISTICA 10 software. To determine the normality of the distribution of relative gene expression levels, we used the Kolmogorov-Smirnov and Lilliefors tests. The Wilcoxon paired test was used to evaluate the differences between adenocarcinomas and their matched conditionally normal tissues according to the 2-ΔCt model. The Benjamini-Hochberg procedure with FDR = 0.1–0.25 was used to correct for multiple comparisons for these tests.

Kruskal-Wallis and Dunn-Bonferroni tests for multiple comparisons were performed to determine differences in relative expression between all sample groups [10–12].

Statistical significance was determined for all types of analysis using a p-value of <0.05. To identify correlations between gene expression and clinical and pathological characteristics of the samples, as well as correlations between gene expression levels, Spearman's rank correlation test was employed.

3. Results

3.1. Relative levels of CYP genes expression in pairs of tumor and conventionally normal tissue samples (T/CNT) of prostate

We examined the levels of 14 *CYP* genes' relative expression in 41 pairs of prostate cancer (T) and conventionally normal tissue samples (CNT), as well as two unpaired prostate tumor samples (numbers 40 and 43). Table A.1 displays the clinical and pathological characteristics of the tissue samples and some patient anamnesis data.

The study found that all of the *CYP* genes investigated were expressed in the prostate gland in both cancer and CNT groups (Figs. 1–3). However, there was a significant variation in the relative gene expression data among individual samples of all the studied genes in both the prostate tumor and CNT sample groups (Figs. 1–3).

We observed high levels of *CYP1B1, CYP4F2*, and *CYP3A5* gene expression in some patients with a history of long-term smoking (Figs. 1, 2, Table A.1). However, there were no differences in the expression levels of *CYP* genes responsible for xenobiotic metabolism in these samples.

3.2. Statistical analysis of the levels of relative gene expression of CYP genes in the prostate cancer and CNT groups

We conducted a comparative analysis of the expression levels of CYP genes between pairs of tumor samples and CNT, as well as between groups of tumor samples and CNT. The study revealed that the available sample of expression levels for most of the studied *CYP* genes did not follow a normal distribution. Therefore, we utilized descriptive statistics and non-parametric statistical data analysis (Table 1).

We used the Wilcoxon Matched Pairs Test to analyze paired T/CNT samples and found that there were no significant differences in the expression of almost all the studied genes between the conditional normal and tumor groups. However, we did observe a slight increase in the expression level of the *CYP1B1* gene in the tumor group compared to the conditional norm, although the p-value (0.059) was not statistically significant.

Our study aimed to investigate whether there are any changes in the expression of *CYP* genes in tumor samples compared to conditionally normal tissue, based on the stage of the disease and/or the Gleason score (GS). We used the Dunn-Bonferroni post-hoc test for multiple comparisons, and our findings revealed that there was no significant difference in the expression levels of the studied genes between the cancer groups

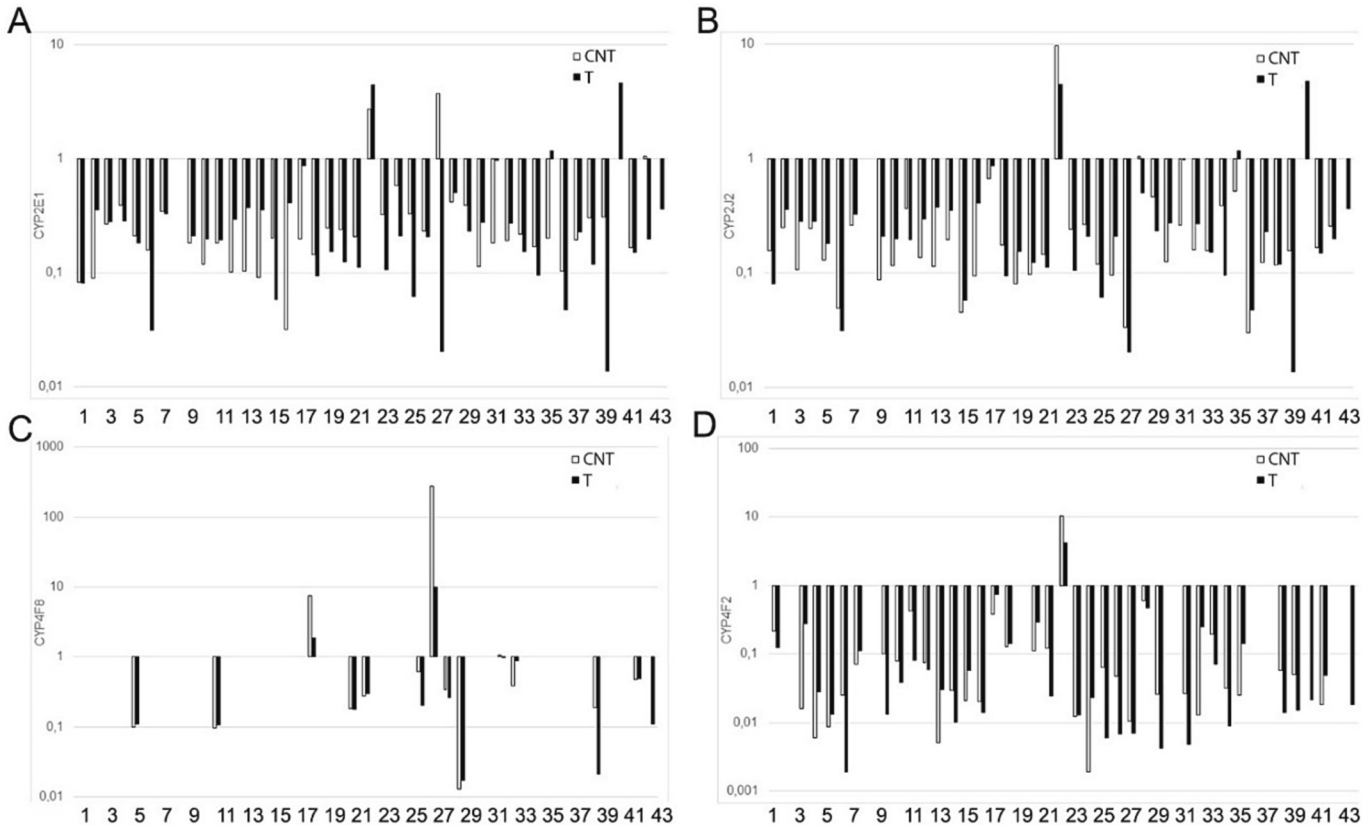

Fig. 1. The relative expression levels of *CYP* genes involved in the metabolism of polyunsaturated fatty acids in pairs of tissue samples of the human prostate gland. (A) *CYP2E1*, (B) *CYP2J2*, (C) *CYP4F8,* (D) *CYP4F2*. The horizontal axis represents the number of tissue sample pairs (T/CNT). T – tumor, CNT – conventionally normal tissue samples.

and CNT at different stages and GS indices. However, we did observe a tendency to increase the expression of *CYP2E1* in prostate tumor samples at late stages compared to the norm ($p = 0.054$) in the group of samples with SG 6. Additionally, we noticed a tendency to increase the level of *CYP2E1* expression in the cancer group samples relative to the CNT ($p = 0.059$) at the 2nd and 3rd stages of the disease.

We did not observe a significant difference in the levels of relative expression of *CYP* genes between the cancer and CNT groups. Therefore, we combined all expression values into a single group and examined potential alterations in gene expression based on the stage of the disease and/or GS.

According to the Kruskal-Wallis Test with Dunn-Bonferroni for multiple comparisons, some significant differences were found for certain *CYP* genes. The expression level of *CYP4F8* was found to be decreased in the group of samples from GS 8 when compared to the group from GS 7 ($p = 0.011$). Additionally, a tendency to decrease the level of *CYP2J2* was observed in the group from GS 9 when compared to SG 7 ($p = 0.065$). On the other hand, an increase in the level of *CYP7B1* expression was detected in the group of samples with stage 4 disease compared to the groups with stage 2 ($p = 0.015$) and stage 3 ($p = 0.022$). In the case of *CYP27B1*, lower expression was detected in stages 2 ($p = 0.034$) and 4 ($p = 0.034$) compared to stage 1. Furthermore, there was also a tendency to decrease the expression of *CYP51* at stage 2 when compared to stage 1 ($p = 0.057$).

3.3. Study of the correlations between the expression levels of individual CYP genes and the clinical and pathological characteristics of patients

We analyzed a group of tumor samples to determine the correlation between the expression levels of 14 individual *CYP* genes and the clinical and pathological characteristics of patients. We used Spearman Rank Order Correlation tests and found that there was no significant correlation.

A combined sample of tumor and conditionally normal tissues was subjected to correlation analysis. The results showed weak but significant correlations ($p < 0{,}050$). Firstly, there was a negative correlation between the level of *CYP24A1* expression and the index of GS ($r^s = -0.268$). Secondly, there was a negative correlation between the expression levels of certain genes (*CYP7B1, CYP5A1, CYP4F2*) and age ($r^s = -0.227$, $r^s = -0.237$, $r^s = -0.266$, respectively). Finally, a weak positive correlation was found between the level of *CYP2E1* expression and the stage of the disease ($r^s = 0.218$).

3.4. Study of the correlations between the expression levels of individual CYP genes in prostate cancer samples

A study was conducted on a group of prostate cancer samples to analyze the correlation between the expression levels of *CYP* genes. The study revealed the presence of significant positive and negative correlations between the expression levels of 13 *CYP* genes. The significant rank correlation coefficients between gene expressions are presented in Table 2. The highest correlation coefficient was found between the genes *CYP51* and *CYP3A5*.

3.5. Study of correlations between relative expression of certain CYP genes and genes associated with prostate carcinogenesis

In our previous research, we analyzed the expression levels of various genes linked with prostate cancer and prostate tumor microenvironment, in prostate tissue samples from the 43 patients (Table A.1). Our investigation focused on 12 genes, namely *CDH2, MMP9, SCHLAP1, GCR, CYP17A1, ACTA2, CXCL14, FAP, CCL17, MSMB, IRF1,* and *VDR*

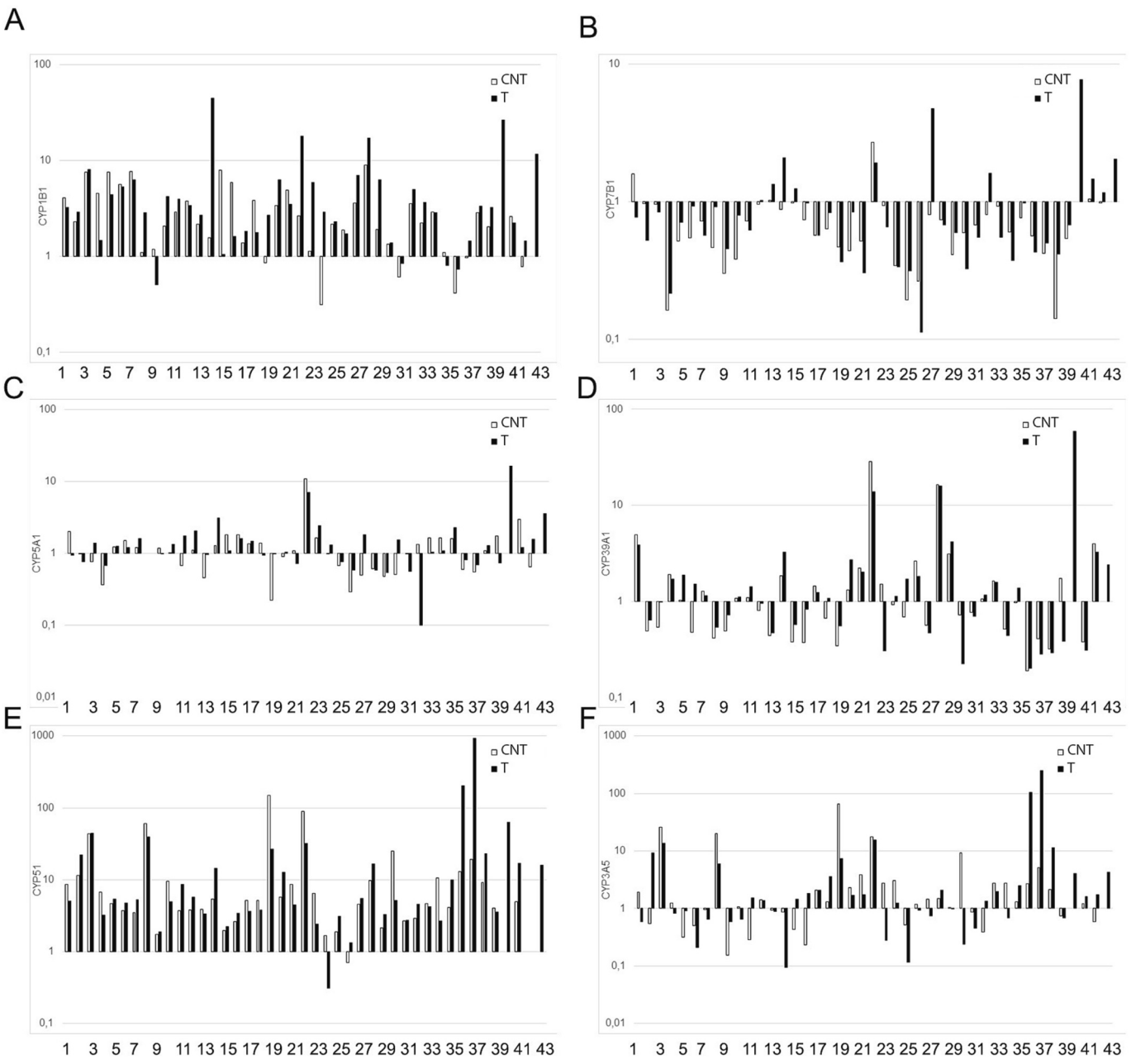

Fig. 2. The relative expression levels of *CYP* genes involved in the metabolism of cholesterol, testosterone and xenobiotics in pairs of tissue samples of the human prostate gland. (A) *CYP1B1*, (B) *CYP7B1*, (C) *CYP5A1*, (D) *CYP39A1*, (E) *CYP51*, (F) *CYP3A5*. The horizontal axis represents the number of tissue sample pairs (T/CNT). T – tumor, CNT – conventionally normal tissue samples.

[10–12]. We conducted a correlation analysis of the expression levels of these genes and *CYP* genes in prostate cancer samples, which revealed some significant positive and negative correlations between the expression levels of certain genes. The most potent positive correlation was found between *CYP24A1* and *MSMB* genes. On the other hand, the strongest negative correlation was detected between *CYP24A1* and *CCL17* genes (Table 3).

4. Discussion

It is known that certain metabolic changes in prostate cells can trigger the development of prostate cancer and contribute to its progression. Studies have shown that changes in lipid metabolism, as well as in the metabolism of hormones and vitamins, are significantly associated with prostate carcinogenesis [6–8]. Moreover, alterations in the metabolism of xenobiotics and anticancer drugs in prostate cells may also play a role in the initiation and progression of prostate cancer. These compounds are predominantly metabolized by the cytochrome P450 enzymes [7,8].

In this study, we have observed the expression of all the cytochrome P450 genes that are responsible for the metabolism of cholesterol, polyunsaturated fatty acids, androgens, vitamin D, and xenobiotics, including drugs, in samples of both prostate cancer and CNT. This suggests that cytochrome P450-dependent metabolic processes of polyunsaturated fatty acids, lipids, vitamin D, and androgens take place in prostate tissues. These processes play a vital role in regulating cell cycle, proliferation, and apoptosis [7,8]. Some of the studied *CYPs* are also involved in the metabolism of xenobiotics, which can result in the formation and activation of procarcinogens or a decrease in the effectiveness of anticancer drugs in the human prostate gland [7].

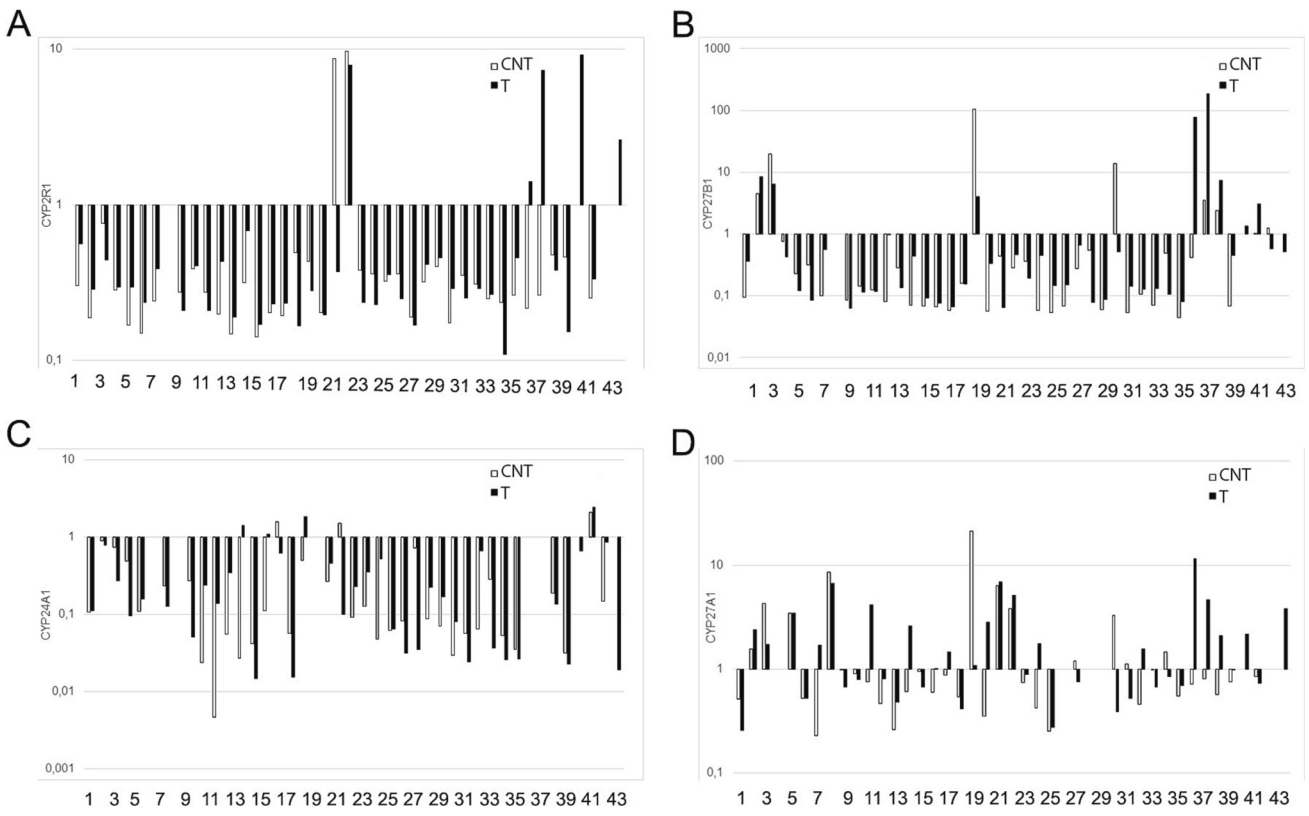

Fig. 3. The relative expression levels of *CYP* genes involved in the metabolism of vitamin D in pairs of tissue samples of the human prostate gland. (A) *CYP2R1*, (B) *CYP27B1*, (C) *CYP24A1*, (D) *CYP27A1*. The horizontal axis represents the number of tissue sample pairs (T/CNT). T – tumor, CNT – conventionally normal tissue samples.

Table 1
Descriptive statistics data of relative expression levels of *CYPs* in prostate cancer and CNT groups.

Genes	Tumor group			CNT group		
	Median	25.000	75.000	Median	25.000	75.000
CYP7B1	0.68	0.45	1.01	0.63	0.46	0.93
CYP27A1	1.05	0.67	2.62	0.79	0.53	1.33
CYP39A1	1.14	0.54	1.89	0.93	0.49	1.65
CYP51	5.10	3.34	16.56	5.05	3.58	9.61
CYP1B1	3.25	1.73	5.94	2.30	1.35	3.84
CYP3A5	1.46	0.68	3.56	1.30	0.74	2.77
CYP4F8	0.23	0.11	0.88	0.34	0.18	0.62
CYP5A1	1.14	0.77	1.59	1.08	0.63	1.55
CYP4F2	0.03	0.01	0.12	0.04	0.02	0.11
CYP2J2	0.21	0.11	0.35	0.16	0.11	0.26
CYP2E1	0.20	0.16	0.36	0.20	0.15	0.32
CYP2R1	0.29	0.23	0.43	0.28	0.20	0.38
CYP27B1	0.26	0.11	0.58	0.15	0.07	0.51
CYP24A1	0.15	0.04	0.53	0.10	0.05	0.28

Notes: 25.000 and 75.000 – Percentiles.

It is important to note that the levels of *CYP* genes expression varied significantly among the samples studied. In some cases, very high or very low expression levels were observed in paired samples from the same patient, which can be attributed to individual differences in *CYP* genes expression [13]. This may be due to individual metabolic processes or external factors such as smoking and certain medications. [13]. Cigarette smoke compounds are known to affect the expression of several *CYP* genes, including *CYP1B1, CYP3A5, CYP4F2, CYP7B1,* and *CYP2E1*, which have been linked to increased risk of carcinogenesis in respiratory tract tissues [14–18]. Long-term smoking has also been associated with prostate cancer [19]. We found that some smoking patients had relatively high levels of expression of *CYP1B1* (numbers 6, 7, 15, 28, 29, 32), *CYP3A5* (numbers 30, 33, 34, 35, 38), and *CYP4F2* (numbers 28, 32). However, due to a lack of data, we cannot assess the relationship between the expression level of these genes and prostate cancer.

It has been observed that some patients exhibit either extremely high or low levels of expression of *CYP* genes, which play a key role in controlling the metabolism of cholesterol, fatty acids, and vitamin D. However, due to the unavailability of individual patient data on the

Table 2
Spearman Rank Order Correlations coefficients (r^s) for *CYP* genes expression in human prostate cancer samples according to the Dunn-Bonferroni test *($p < 0.05$).*

Genes	*CYP51*	*CYP1B1*	*CYP3A5*	*CYP5A1*	*CYP4F2*	*CYP2E1*	*CYP2R1*	*CYP27B1*	*CYP24A1*
CYP7B1	–	0.420	–	0.507	–	–	–	–	–
CYP27A1	0.583	–	0.580	–	–	–	–	–	–
CYP39A1	–	0.478	–	–	–	0.539	–	–	–
CYP51	–	–	0.643	–	0.437	–	0.622	0.601	–
CYP3A5	0.643	–	–	–	0.594	–	–	–	–
CYP2J2	–	–	–	–	–	–	0.406	–	–
CYP2E1	–	–	–	–	–	–	0.430	–	−0.441

– The value of the coefficient (r^s) is either very low or statistically insignificant.

Table 3
Spearman Rank Order Correlations coefficients (r^s) for the expression of *CYP* genes and some genes associated with carcinogenesis in human prostate cancer samples according to the Dunn-Bonferroni test *($p < 0.05$)*.

Genes	*CYP7B1*	*CYP27A1*	*CYP4F2*	*CYP2E1*	*CYP27B1*	*CYP24A1*
CDH2	–	0.800	0.700	–	–	−0.317
MMP9	–	−0.600	−0.700	–	−0.283	−0.267
VDR	−0.517	–	–	−0.717	−0.817	–
SCHLAP1	–	−0.683	−0.633	–	–	–
GCR (AG)	–	0.367	–	–	–	−0.817
CYP17A1	0.733	–	−0.283	–	0.500	–
ACTA2	–	0.633	0.317	–	–	−0.667
CXCL14	–	–	−0.317	0.400	–	−0.833
FAP	−0.483	−0.267	−0.333	−0.533	−0.717	–
MSMB	0.267	–	0.433	0.483	0.350	0.833
IRF1 (T1)	−0.350	−0.300	−0.250	−0.467	−0.667	–
CCL17	–	–	−0.617	–	–	−0.850

– The value of the coefficient (r^s) is either very low or statistically insignificant.

metabolism of these compounds, it is difficult to assess the correlation between the variability in gene expression and these processes.

In our previous review of the literature, we discovered significant changes in the expression levels of certain *CYP* genes in malignant tumors, as compared to normal prostate cells.

Specifically, we found evidence of increased expression of *CYP* genes that are involved in lipid metabolism, especially *CYP1B1* [7]. It is known that *CYP1B1* catalyzes the conversion of estradiol to 4-Hydroxy-17β-estradiol and promote the development and progression of hormone-related prostate cancer [20]. In our research, we also observed an increase in the level of expression of this gene in the tumor when compared to conditionally normal tissue. CYP1B1 plays an important role in energy homeostasis, regulation proliferative activity and procarcinogen activation, so an increase in its expression may contribute to carcinogenesis [21].

In a previous study, we discovered that changes in the expression of cytochrome P450 enzymes (which are crucial in the metabolism of vitamin D, a potent anticancer agent) in a tumor compared to normal tissue, depending on their function [8]. Specifically, it was observed significant suppression of the genes *CYP27A1* and *CYP27B1*, which play a critical role in the synthesis of vitamin D, and a significant increase in the expression of *CYP24A1*, which degrades vitamin D, in prostate cancer samples [8]. However, in our study, we did not find significant changes in these *CYPs* in the tumor compared to conditionally normal tissue. Other researchers have reported significant suppression of *CYP3A5* expression, which regulates testosterone metabolism and the functioning of the androgen receptor, as well as metabolizes most drugs [8]. Nevertheless, we did not observe such changes in the tumor compared to the conditional norm in our work.

We found that there was no significant variation in the expression of the other *CYP* genes in prostate cancer tissue in comparison to the CNT samples. However, it is worth noting that different authors have employed various approaches in studying changes in relative gene expression. For instance, some studies have analyzed the expression of certain *CYP* genes in cell lines [22–24], while others have compared the expression levels of other *CYPs* in prostate cancer patients with those of the corresponding genes in normal and adenoma prostate tissues of other patients [25–27]. In our research, we compared the gene expression levels in a pair of samples taken from cancer and surrounding conventionally normal tissue without signs of carcinogenesis in each individual patient. This approach considers the individual variability of *CYPs* expression levels, which is essential in characterizing this family of enzymes.

Research has shown that the expression levels of certain *CYP* genes, particularly *CYP27A1* and *CYP24A1*, are associated with the degree of cell differentiation and the stage of prostate cancer. These genes may also affect the rate and prognosis of the disease [26]. In our study, we found a weak but significant negative correlation between *CYP24A1* and the index of SG. Additionally, we observed weak but significant correlations between other *CYP* genes and the stage of the disease. It is possible that a larger study could reveal new correlations between gene expression levels and clinical or pathological characteristics of patients.

Upon conducting a correlation analysis on the expression levels of *CYP* genes studied within the prostate tumor group, it was discovered that there is a positive correlation between the expression levels of individual *CYP* genes that may be functionally related. Specifically, we observed that genes responsible for metabolizing cholesterol are positively correlated with each other in the tumor group. Additionally, we found a positive correlation between the expression of genes responsible for vitamin D biosynthesis and genes that biosynthesize cholesterol, which is the precursor of all fat-soluble vitamins [7,8].

In a study of 43 prostate cancer patients (as presented in Table A.1), we investigated the correlation between the expression of certain genes associated with prostate cancer and *CYP* genes. The genes in question are *CYP17A1, MMP-9, GCR, ACTA2, SChLAP1, CXCL14, FAP, CCL17, VDR, IRF1,* and *MSMB*, which play a role in processes such as proliferation, migration, invasion, angiogenesis, apoptosis, and cell cycle control [28–39]. It was found that the expression of a number of genes of cytochrome P450 had significant correlations with the expression of these genes (Table 3).

It is known that cholesterol is a crucial structural lipid in cells, and an increase in its biosynthesis is linked to an increase in the rate of proliferative processes. Moreover, cholesterol is a precursor to hormones, particularly androgens, which are crucial for prostate carcinogenesis. CYP-dependent derivatives of omega-6 polyunsaturated fatty acids, especially arachidonic acid, regulate the migration and invasion processes of cancer cells [8,9]. We have observed a strong correlation between *CYP* genes that regulate lipid metabolism and oncogenes, as well as prostate cancer suppressor genes. We found that the expression of the *CYP7B1* gene is positively correlated with the *CYP17A1* oncogene, which is responsible for testosterone synthesis [32]. The *CDH2* oncogene, which controls the proliferative and migratory potential of prostate cancer cells [35], is positively correlated with the *CYP27A1* and *CYP4F2*. Furthermore, we observed a strong negative correlation between the expression level of *CYP2E1* and the vitamin D receptor gene, *VDR*, which is one of the tumor suppressor genes that stimulates proapoptotic processes and inhibits cell proliferation [37]. We have discovered some correlations between the *CYP* genes, which regulate vitamin D metabolism, and genes that are linked to prostate cancer. The tumor suppressor gene *CYP27B1* is negatively correlated with the oncogene *FAP*, and also negatively correlated with the tumor suppressor genes *VDR* and *IRF1*. The potential oncogene *CYP24A1* is negatively correlated with almost all the studied oncogenes and positively correlated with the tumor suppressor gene *MSMB*.

The role of these genes in causing cancer suggests that their functional relationship has a combined effect on the tumor. This promotes the survival of cancer cells and increases their carcinogenic potential.

5. Conclusion

Based on the given data, it can be assumed that changes in the expression level of CYPs in prostate tissues do not have a direct correlation with carcinogenesis in the prostate gland. Instead, it is largely due to the individual characteristics of endogenous metabolism in the tissues of this organ, along with the impact of certain exogenous factors such as smoking, drugs, etc. Further research is required to understand the effect of these factors in detail. The presence of a significant correlation between certain *CYP* genes and genes associated with prostate carcinogenesis suggests that there may be common regulatory pathways that can have a synergistic effect on the tumor, promoting the survival of cancer cells, and increasing their proliferative, invasive, and migratory potential.

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Author contributions

Conceptualization, O.M. and G.G.; methodology, V.K.; validation, O.M. and G.G.; formal analysis, O.M. and G.G.; investigation, O.M., G.G., O.K. and I.R.; resources, E.S, O.K. and A.T.; data curation, V.K.; writing original draft preparation, O.M.; review and editing, G.G. and V.K.; supervision, V.K.; project administration, V.K. All authors have read and agreed to the published version of the manuscript.

Ethical approval

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Ethics Committee of Institute of Molecular Biology and Genetics of NAS of Ukraine (protocol code 32 and date of approval 04/10/2022).

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used [Grammarly's generative AI/ https://www.grammarly.com] in order to improve readability and language. After using this tool/service, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

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CRediT authorship contribution statement

Oksana Maksymchuk: Conceptualization, Formal analysis, Funding acquisition, Investigation, Validation, Writing – original draft. **Ganna Gerashchenko:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Validation, Writing – review & editing. **Inna Rosohatska:** Investigation, Funding acquisition. **Oleksiy Kononenko:** Investigation, Resources. **Andriy Tymoshenko:** Resources. **Eduard Stakhovsky:** Resources. **Volodymyr Kashuba:** Data curation, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

The data used to support the findings of this study are included in the article. Other data that might be useful for the findings of this study will be supplied as supplementary information by the corresponding author upon request.

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