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Integrated Pharmacogenetic Signature for the Prediction of Prostatic Neoplasms in Men With Metabolic Disorders

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Abstract

Background/Aim: Oncogenic processes are delineated by metabolic dysregulation. Drug likeness is pharmacokinetically tested through the CYP450 enzymatic system, whose genetic aberrations under epigenetic stress could shift male organisms into prostate cancer pathways. Our objective was to predict the susceptibility to prostate neoplasia, focused on benign prostatic hyperplasia (BPH) and prostate cancer (PCa), based on the pharmacoepigenetic and the metabolic profile of Caucasians.

Materials and Methods: Two independent cohorts of 47,389 individuals in total were assessed to find risk associations of CYP450 genes with prostatic neoplasia. The metabolic profile of the first cohort was statistically evaluated and frequencies of absorption-distribution-metabolism-excretion-toxicity (ADMET) properties were calculated. Prediction of miRNA pharmacoepigenetic targeting was performed.

Results: We found that prostate cancer and benign prostatic hyperplasia patients of the first cohort shared common cardiometabolic trends. Drug classes C08CA, C09AA, C09CA, C10AA, C10AX of the cardiovascular, and G04CA, G04CB of the genitourinary systems, were associated with increased prostate cancer risk, while C03CA and N06AB of the cardiovascular and nervous systems were associated with low-risk for PCa. CYP3A4*1B was the most related pharmacogenetic polymorphism associated with prostate cancer susceptibility. miRNA-200c-3p and miRNA-27b-3p seem to be associated with CYP3A4 targeting and prostate cancer predisposition. Metabolomic analysis indicated

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that 11β-OHT, 2β-OHT, 15β-OHT, 2α-OHT and 6β-OHT had a high risk, and 16α-OHT, and 16β-OHT had an intermediate disease-risk.

Conclusion: These findings constitute a novel integrated signature for prostate cancer susceptibility. Further studies are required to assess their predictive value more fully.

Keywords: Pharmacogenetics, epigenetics, metabolomics, prostatic neoplasia, PCa, BPH, diabetes, dislipidemia, hypertension, steroid hormone pathway, FoxO signaling pathway, p53 signaling pathway, estrogen signaling pathway, CYP3A4, miRNAs.

Introduction

Normal changes of the aging process seem to concern prostatic diseases such as prostatitis, benign prostate hyperplasia (BPH) and prostate cancer (PCa). PCa is a polygenic disease and the second male-leading cause of cancer-related death globally. Since the first prostate gland autopsy in the 1950s, it has been revealed that there is a link between BPH and PCa (1). However, BPH cannot be considered the first step of PCa progression due to controversies in risk factors. Many factors, including an increase in the aging population and the widespread screening for the biomarker prostate-specific antigen (PSA), resulted in a substantive rise in the diagnoses of early-stage prostate tumors. The genetic spectrum of PCa comprises aggressive and indolent varieties (2, 3). The pathophysiological threshold beyond which a predisposition of the organism to prostate cancer, turns into a real risk has not yet been adequately illustrated (4).

Central to the xenobiotic response system is the system of cytochrome CYP450 hemoenzymes (5), which may also play a prominent role in the metabolism of endobiotics (6). They mostly catalyze the oxidation of substrates and reduction reactions (7). CYPs play a dual role in carcinogenesis as they are implicated in the bioactivation and inactivation of carcinogens and anticancer drugs (8). CYPs are involved in the activation of different environmental carcinogenic chemicals inducing oncogenic mutations (9). There are two classes of xenobiotic-metabolizing CYP enzymes: Class I (CYP1A1, CYP1A2, CYP2E1, and CYP3A4) which are involved in the metabolism of procarcinogens and drugs (10) and Class II comprising CYP2B6, CYP2C9, CYP2C19, and CYP2D6 which are active in the metabolism of drugs, but not of procarcinogens (8).

The WHO Anatomical Therapeutic Chemical (ATC) classification system organizes drug-active substances into five levels according to organs or systems (11). There are fourteen principal anatomical/pharmacological groups or 1st levels with further branching into 2nd levels for pharmacological and therapeutic groups. The 3rd, and 4th levels represent chemical, pharmacological, or therapeutic subgroups and the 5th level specifies the chemical ingredient (12, 13). The molecular interplay between the genome, epigenome, and transcriptome heavily affects the complex regulation of absorption-distribution-metabolism-excretion-toxicity (ADMET) properties and drug efficacy through molecular mechanisms such as DNA methylation, post-translational histone modifications, and non-coding RNAs especially microRNAs which are encoded by the genome (14).

microRNAs are short non-coding regulatory RNA molecules, containing 18-25 nucleotides that bind genes and silence their expression (15, 16). They down-regulate gene expression by inhibiting translation (17) or initiating mRNA degradation. miRNA-based signatures have been described as promising biomarkers for the stratification, diagnosis, predisposition and progression of cancer, including prostate cancer (18-20). Additionally, miRNAs also have a role in ADMET-related transcripts (21). miRNAs may be candidate prognostic indicators for prostatic oncogenesis (22, 23).

Metabolic biomarkers of prostate oncogenic pathways are being studied (24), revealing that variations in the

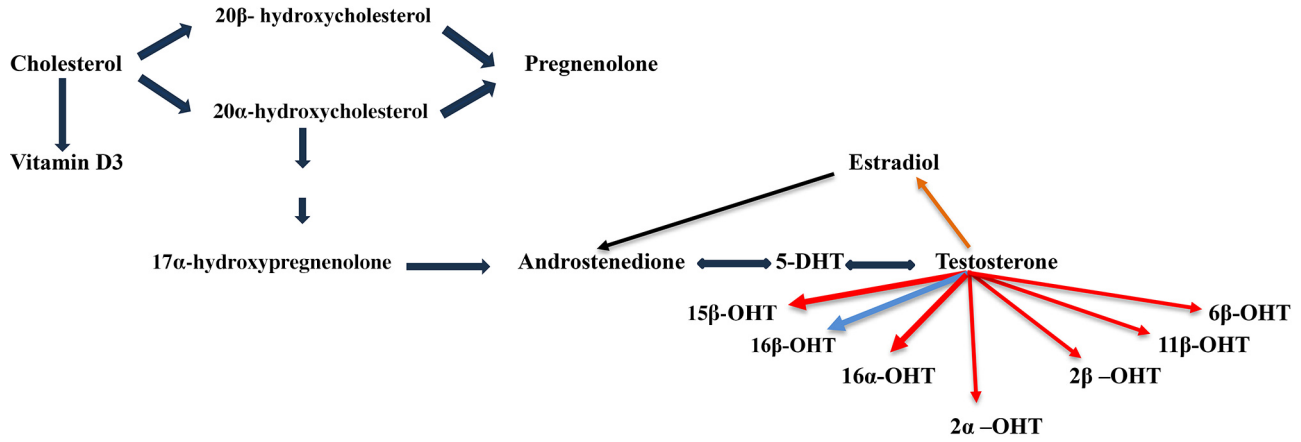

Figure 1. *Summary of the steroid hormone pathway indicating the production of testosterone hydroxylated metabolites through the enzymatic activity of CYP450s involved in the synthesis and the metabolism of testosterone in humans. Red arrows: CYP3A4; Blue Arrow: CYP2B6; 2C9, 2C19, 3A4; Brown Arrow: CYP19A1 (aromatase).*

metabolic pathways of androgens, specifically of testosterone products, can affect prostate cancer susceptibility through the enzymatic activity of CYP450 members and many other enzymes, such as SRD5A1, HSD11B1 (Figure 1).

Materials and Methods

Study design. We studied two distinct Caucasian cohorts of participants: A Greek cohort, defined as Cohort A, was compared with a Swedish cohort previously studied by Patel and colleagues (25). For our study, we limited our research to testing only the shared classes of drugs that were taken from the Swedish group of participants who developed long-term prostate cancer in comparison to the medications received from patients of the Greek cohort and we verified the most frequent health condition among all subjects belonging to the cohort A.

Cohort A: Retrospective Trial. Ethics statement of cohort A. In the Greek cohort, the protocol complied with the Declaration of Helsinki and its subsequent revisions. It was approved by the Research and Ethics Committee of the University Hospital of Patras (protocol approval number: 308/7-6-2023). Informed consent was obtained for all individuals involved.

Observational study design and data collection in cohort A. The study population of cohort A included 11 patients with benign hyperplasia (BPH) and 43 patients with prostate cancer (PCa) aged >18. The BPH patients underwent transurethral prostatectomy (TUR-P) and the PCa patients underwent open or laparoscopic radical prostatectomy. The participant eligibility requirements were established; Inclusion criteria: patients undergoing a prostate biopsy and surgery (according to common criteria). Exclusion criteria: patients refusing to take part in the study or mentally disordered patients unable to provide informed consent.

Cohort A: Medical history and treatment registration. Demographic, diagnosis, clinical and pathological data were extracted from the electronic medical records, (EMR), and retrospectively obtained from the University Hospital of Patras after informed consent, according to the ICH-GCP and e-CRF procedures. All participants, self-reported in the research questionnaire designed for the study the existing chronic conditions, and, if any, the related treatment regimens before the BPH/PCa surgery,

as well as their family history of prostate cancer and/or benign hyperplasia.

Electronic health record (EHR) extraction of the Swedish cohort. The clinical data of PCa patients from the Swedish cohort was extrapolated from the registry of the Centre for Primary Health Care Research at Lund University in Malmö, Sweden (25). Drug information was coded according to the ATC classification system (13). All drug therapy data could be used without further processing. Previously reported statistically significant ATC codes associated with PCa (25) were programmatically extracted using the PHP scripting language (https://www.php.net/).

ATC pharmaceutical indexing of all drugs. The medicinal active substances of both cohorts were recorded according to their chemical, therapeutic, and pharmacological subgroups, as characterized by the ATC classification system. The ATC classification of drugs with the measurement at the fourth level was extracted from DrugBank 5.0 (26) for the first cohort and from Patel *et al.* (25) for the second cohort, respectively.

Statistical methodology. Comparative descriptive statistics of cohorts. Using the self-report questionnaire, the relative frequencies of the underlying conditions and their respective medications in patients diagnosed with prostatic neoplasms were calculated using Excel 2016 (Microsoft, Redmond, WA, USA). The demographic distribution of the pharmacogenetic profile was represented and plotted as ring charts and bar plots. Each condition of cohort A was matched to its respective ATC code up to the fourth level.

In both cohorts, the ATC indexing up to the fourth level was evaluated as a key parameter that could associate the use of certain medications with the risk of neoplasmatic prostate disease development. The statistical significance of the findings of cohort A was calculated relatively to cohort B, for all PCa patients recruited, considering excluded other cancer cases, through programmatical data extraction using PHP scripts from the author's data (25). This was performed to confirm the linkage between prescribed medicines and longitudinal neoplasmatic prostate risk, for specific ATC codes. In addition, subgroup analysis by comparative statistics was carried out for the identification of the metabolic profile of patients belonging to cohort A, according to the following 3 states of prostatic neoplasia: i) BPH patients only, ii) prostate cancer patients only, with previous BPH diagnosis, and iii) prostate cancer patients only, without previous BPH diagnosis.

ADMET prediction of all drugs. Absorption-distribution-metabolism-excretion-toxicity (ADMET) frequency was measured in the first cohort. The drug categories were extracted using DrugBank 5.0 "advanced search" (26). Their relative and absolute frequencies were calculated using R (27) and plotted as histograms using ggplot2 (28).

Hypergeometric distribution analysis of CYP-related drug categories. In addition, for all ATC codes up to the 4th level, hypergeometric distribution analyses were performed to determine the predominant drug categories associated with CYP enzymes of the drugs of the first and second cohorts, respectively. For both cohorts, all ATC codes were included in cohort B. 14,665 drugs of DrugBank were used as a pool of drug categories. The resulting *p*-values for both cohorts were FDR-adjusted for multiple hypotheses, using a 0.01 significance cutoff and over-represented drug categories were ranked by their adjusted *p*-values.

Bioinformatic predictions. Aggregated miRNA: mRNA binding discovery. miRNA binding to complementary mRNA biomarker sequences for the regulation of gene expression, was predicted using the miRabel (29) web tool. Experimentally validated miRNA bindings were identified using miRTarBase (v.9.0) (30).

KEGG pathway Enrichment analysis for miRNAs and miRNA maximum coverage analysis for gene targeting. We searched for significantly enriched KEGG pathways, where previously extracted bottleneck miRNAs that were reported from the

Table I. *Anatomical therapeutic chemical (ATC) classification of drug category-level associations for prostate cancer (PCa) risk development.*

	ATC code	Medication class
High risk	C08CA, C09AA, C09CA, C10AA, C10AX, G04CA, GO4CB	Dihydropyridine derivatives, ACE inhibitors plain, Angiotensin II antagonists plain, HMG CoA reductase inhibitors, other lipid modifying agents, Alpha-adrenoreceptor antagonists, Testosterone-5-alpha reductase inhibitors
Low risk	C03CA, N06AB	Sulfonamides plain, Selective serotonin reuptake inhibitors
Not statistically significant	A10BA, A10BB, A10BG, B01AC, B01AE, C02CA, C03AA, C07AB, C08DA, L02BX	Biguanides, Sulfonylureas, Thiazolidinediones, Platelet aggregation inhibitors excl. heparin, Direct thrombin inhibitors, Alpha-adrenoreceptor antagonists, Thiazides plain, Beta blocking agents selective, Phenylalkylamine derivatives, Other hormone antagonists and related agents

identification of the best candidate pharmacogenetic biomarker targets, were uploaded in miRPathDB 2.0 (31). An interactive heatmap was produced based on the strong experimental evidence level that was set as default, for hsa-miRNA target gene sets (experimentally validated and predicted) and for the provided biochemical pathways and categories in miRPathDB 2.0. Subsequently, maximum targetome analysis was performed in silico for k=1 to find the "best" miRNAs that sufficiently regulate the candidate gene according to literature. A list of miRNAs that were significantly enriched in the "Prostate Cancer" KEGG pathway with "Strong" experimental evidence was also procured through miRPathDB 2.0 and only the common CYP-related miRNAs predicted through miRabel were retained.

Literature search for the identification of pharmacogenetic polymorphisms and metabolic patterns related to prostate cancer susceptibility. The most well-studied polymorphisms referred to the above pharmacogenetic prediction implicated in prostate cancer development were searched through literature and the linking clinical parameters between disease evolution, metabolome and genotype were identified (24, 32, 33).

Results

Demographic description of cohort A. Systematic scan of ATC prescriptions. In cohort A, we registered 33 drugs corresponding to 19 ATC codes (Supplementary Table I). Respectively, other types of drugs, including those from cohort A, were registered in cohort B, which corresponded to 552 ATC codes of the Sweden Prescribed Drug Register (25). Information on prescriptions of different types of drugs as classified by the ATC classification system were collected from Drugbank and Patel *et al.* (25).

Comparative description of drug categories (active ingredients) of cohort A and B. It was found that some of the above ATC codes were nominally significant for increased cancer risk. Of the 33 agents provided from cohort A, 4 were on alpha-adrenoreceptor antagonists, 3 were on dihydropyridine derivates, 3 were on beta blocking agents selective, 1 was on selective serotonin reuptake inhibitors, 1 on platelet aggregation inhibitors excl. heparin, 2 on other lipid modifying agents, 2 on testosterone-5-alpha reductase inhibitors, 1 on sulfonamides, plain, 1 on sulfonylureas, 1 on thiazides plain, 4 on angiotensin II receptor blockers (ARBs), plain, 1 on direct thrombin inhibitors, 1 on thiazolidinediones, 2 on ACE inhibitors, plain, 1 on phenylalkylamine derivatives, 1 on other hormone antagonists and related agents, 3 on HMG CoA reductase inhibitors, and 1 on blood glucose lowering drugs, excluding insulins, biguanides (Table I).

In cohort A, it was also observed that a trend emerged, composed of three prevalent comorbidities recorded. These were i) hypertension if the patient was receiving some form of antihypertensive medication (*i.e.*, diuretic, β-adrenoceptor antagonist, Ca^{+2} entry blocker, converting enzyme inhibitor) (34), ii) an irregular insulin profile

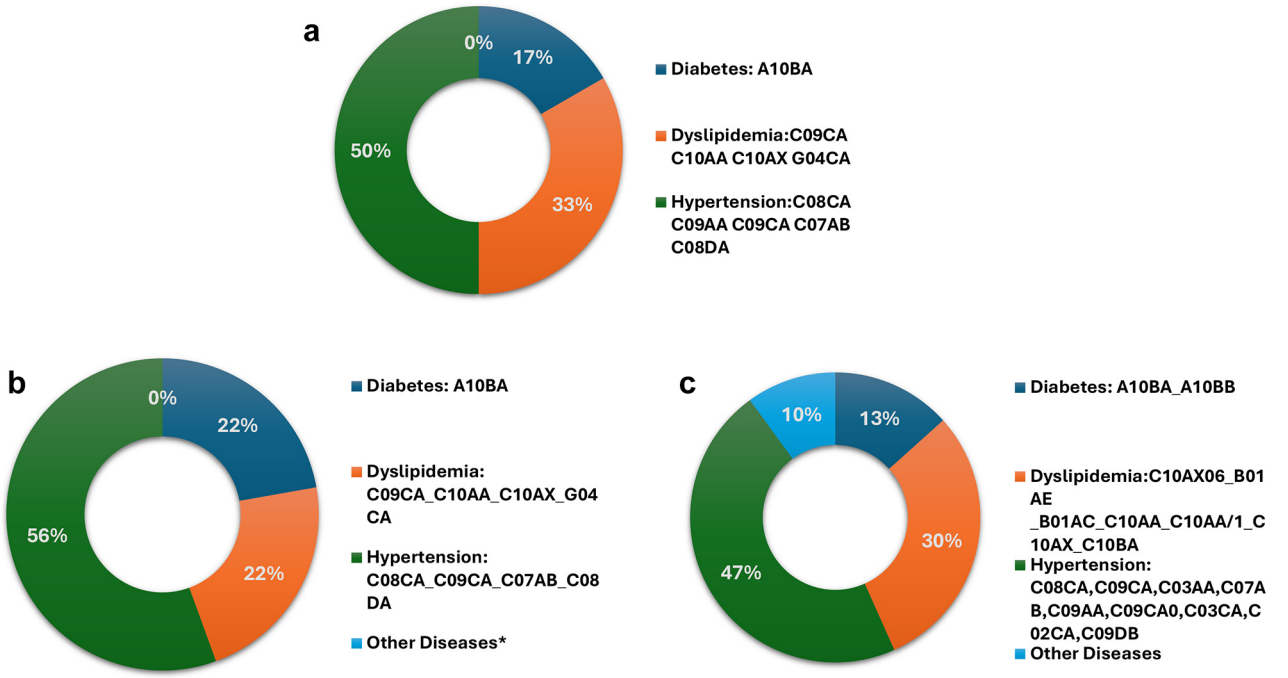

Figure 2. *Ring charts of metabolic profiles in: (a) Benign prostatic hyperplasia (BPH) subjects; (b) BPH in prostate cancer (PCa) subjects; (c) PCa*. The asterisk means that BPH in PCa subjects is excluded.*

under prescribed medications such as antidiabetic agents or nutritional precautions (35), and iii) treated hypercholesterolemia and/or hypertriglyceridemia (36). Additionally, other medical conditions, unrelated to metabolic syndrome (MetS), such as hormone-therapy and depression, were also recorded and presented with the term "other diseases".

Subsequently, the demographic description of cohort A, and the distribution of underlying health conditions were distributed into 3 sub-groups: BPH neoplasia, BPH to PCa neoplasia, and PCa neoplasia for the subgroup of patients with no previous record of BPH (Figure 2). From the overall analysis of the cohort A data, a dysmetabolic profile was depicted based on the covariates investigated. It was observed that most men had more than two cardiometabolic diseases, with hypertension and dyslipidemia being the most prevalent (Figure 3). According to the above data, among the 11 BPH subjects, 50% were hypertensive, 33% were dyslipidemic, and 17% were diabetic. Similarly, among the group of 8 subjects defined as "BPH to PCa", 56% were hypertensive, 22% were dyslipidemic and 22% were diabetic. In addition, from the group of 35 patients with prostate cancer status and no previous record of BPH, 47% were hypertensive, 30% were diabetic, 13% were dyslipidemic, and 10% suffered from other diseases. Additionally, the subgroups of "BPH" and "BPH to PCA" patients were free of prescribed medications for other diseases (Figure 3). Respectively for the Swedish cohort, drugs were categorized as shown in Patel *et al.* (25).

Category-level associations in PCa risk development from both cohorts. The exploitation of the ATC hierarchy took place to estimate category-level associations in prostate cancer following exposure to any of the drugs in each category and to verify the differences between the category-level association and possible drug-level associations. Out of all categories, 7 of them, C08CA (dihydropyridine derivatives), C09AA (ACE inhibitors, plain), C09CA

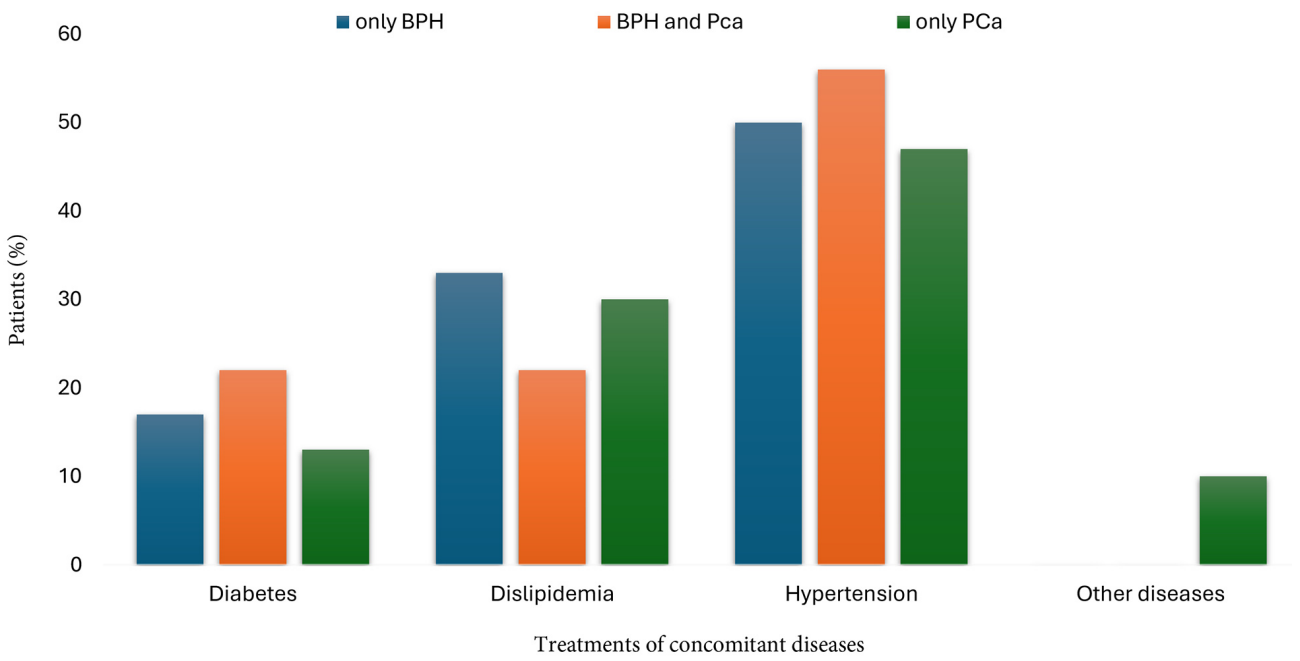

Figure 3. *Comparative health records of patients with prostatic neoplasia. The bar chart illustrates the percentage of Cohort A patients with the registered comorbidities per subgroup of neoplastic disease in examination. Colors represent each subgroup; blue: only benign hyperplasia (BPH) individuals, red: BPH in prostate cancer (PCa) individuals, green: PCa individuals without previous BPH status. The prevalence of hypertension in patients stratified by subgroup of neoplastic disease is observed.*

(angiotensin II antagonists, plain), C10AA (HMG CoA reductase inhibitors), C10AX (other lipid modifying agents) G04CA (alpha-adrenoreceptor antagonists) and G04CB (testosterone-5-alpha reductase inhibitors) were linked with higher risk of PCa. C03CA (sulfonamides, plain) and N06AB (selective serotonin reuptake inhibitors) were found to be associated with a lower risk of PCa.

The following ATC classifications were not statistically correlated with PCa: A10BA (biguanides), A10BB (sulfonylureas), A10BG (thiazolidinediones), B01AC (platelet aggregation inhibitors excl. heparin), B01AE (direct thrombin inhibitors), C02CA (alpha-adrenoreceptor antagonists), C03AA (thiazides, plain), C07AB (beta blocking agents, selective), C08DA (phenylalkylamine derivatives), and L02BX (other hormone antagonists and related agents) (Table I).

Frequency profile and over-representation analysis of CYP-ADME properties in cohorts. The overall frequency profile of Drugbank drug categories for medications prescribed to cohort A is presented in the histogram (Figure 4), where, out of 312 ADMET entities produced with R and ggplot2 (37), the CYP-ADMET categories CYP3A4, CYP2C8, and CYP3A5 are the most frequent.

The hypergeometric distribution analysis of cohort A showed that out of the categories related to cytochrome P-450, cytochrome P-450 CYP2C8 inhibitors (p-value=1.7×10^{13}) were shown as the top overrepresented, followed by cytochrome P-450 CYP3A5 substrates (p-value=2.1×10^{-10}), cytochrome P-450 CYP3A4 substrates (p-value=4.1×10^{-10}), cytochrome P-450 CYP2C8 inhibitors-strength unknown (p-value=2.5×10^{-9}), and cytochrome P-450 CYP2C9 inhibitors (p-value=1.7×10^{-8}) (Table II).

Similarly, for cohort B, hypergeometric distribution analysis showed that out of the categories related to cytochrome P-450, cytochrome P-450 CYP3A4 substrates (p-value=4.5×10^{-261}), cytochrome P-450 CYP2D6 substrates (p-value=7.7×10^{-122}), cytochrome P-450 CYP2D6 inhibitors

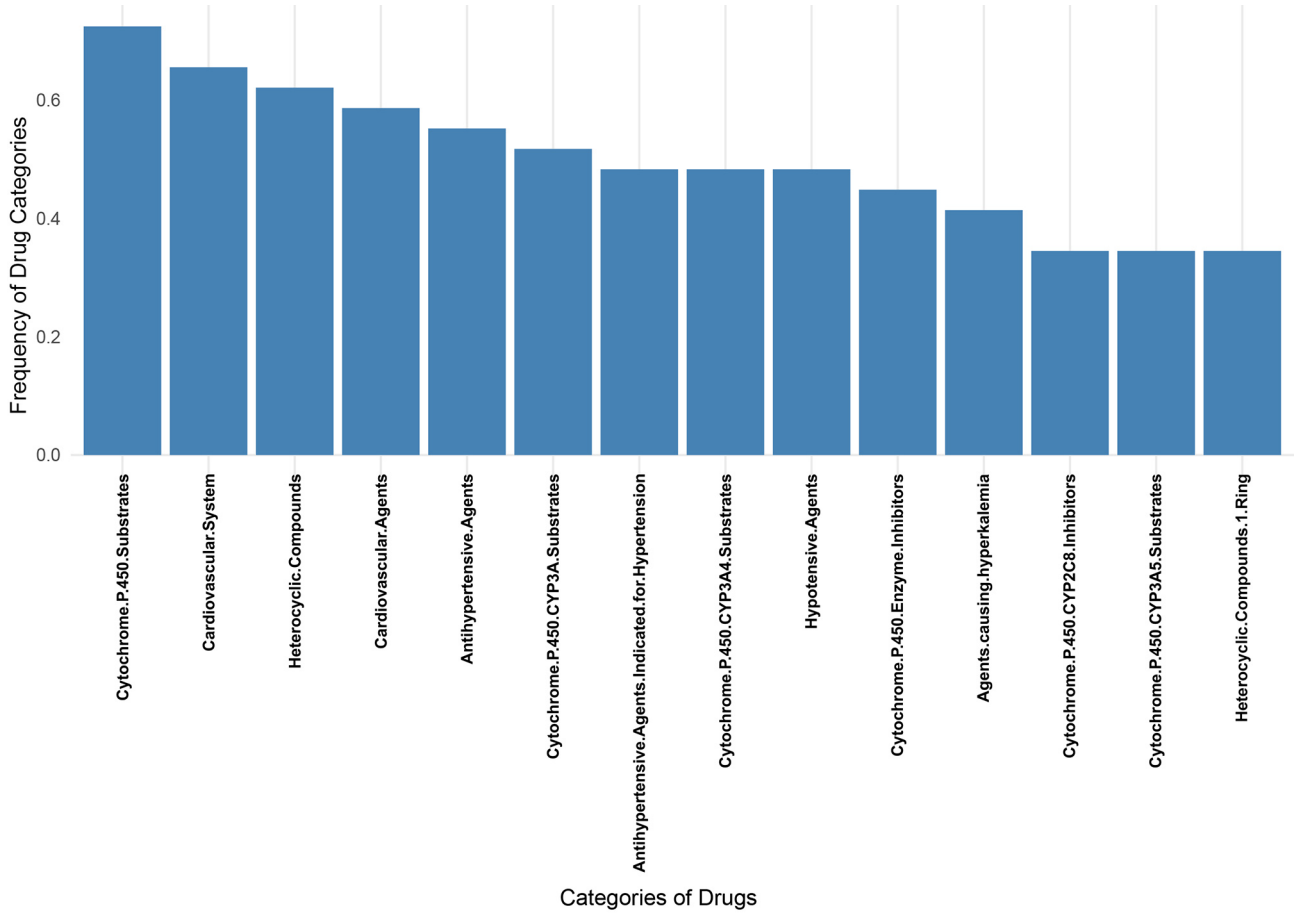

Figure 4. *Most frequent ADMET categories observed in the 33 drugs of cohort A (Greek cohort). The relative frequency of each category is displayed on the vertical axis, while the ADMET category name is shown on the horizontal axis.*

(p-value=4.0×10^{-96}), cytochrome P-450 CYP2C9 substrates (p-value=1.7×10^{-91}) and cytochrome P-450 CYP3A4 inhibitors (p-value=3.2×10^{-91}) were the most over-represented (Table III).

*CYP3A4*1B as prostate cancer susceptibility polymorphism.* For the studied ATC drug categories, the assessment of this comparative observational, retrospective study, demonstrated the prevalence of CYP3A4 over other CYP-ADMET genes. Over-representation analyses in both cohorts showed CYP3A4 among the 10 top over-represented CYP-ADMET properties, while also being the most frequent CYP-ADMET property in cohort A. CYP3A4*1B, (rs2740574; -392A>G) was the most studied variant related to prostate cancer risk found in the literature (38, 39). Additionally, in this research, although CYP3A5, CYP2C9, and CYP2C8 were other pharmacogenes with very close p-values, the cohort size of group A could not establish statistically significant associations that could make them candidate biomarkers.

Predictive pharmacoepigenetic signature of prostate cancer. In total, 672 miRNAs which were predicted to bind CYP3A4 mRNA, were produced using the miRabel web interface (Supplementary Table II). For this research, the visualization of an interactive heatmap for shared miRNAs

Table II. *Top 10 overrepresentations of CYP_ADMET_properties in cohort A (Greek). The "Hits" column shows the number of self-reported drugs belonging to a specific CYP-category listed in the column "Category", divided by the total number of drugs of the same category in Drugbank. The "Enrichment" column shows how many times each CYP-category is enriched in each cohort versus the drugs of Drugbank.*

Rank	Adjusted *p*-value	Hits	Enrichment	Category
5	1.5×10^{-16}	22/1101 (2.0%)	9.2	Cytochrome P-450 Substrates
7	1.7×10^{-13}	11/146 (7.5%)	34.5	Cytochrome P-450 CYP2C8 Inhibitors
10	4.4×10^{-11}	16/834 (1.9%)	8.8	Cytochrome P-450 CYP3A Substrates
13	2.1×10^{-10}	10/213 (4.7%)	21.5	Cytochrome P-450 CYP3A5 Substrates
14	4.1×10^{-10}	15/826 (1.8%)	8.3	Cytochrome P-450 CYP3A4 Substrates
15	4.1×10^{-10}	14/676 (2.1%)	9.5	Cytochrome P-450 Enzyme Inhibitors
20	2.5×10^{-9}	7/79 (8.9%)	40.6	Cytochrome P-450 CYP2C8 Inhibitors (strength unknown)
25	1.7×10^{-8}	8/173 (4.6%)	21.2	Cytochrome P-450 CYP2C9 Inhibitors
41	1.7×10^{-7}	8/245 (3.3%)	15.0	Cytochrome P-450 CYP2C9 Substrates
48	1.1×10^{-6}	6/129 (4.7%)	21.3	Cytochrome P-450 CYP2C9 Inhibitors (strength unknown)

Table III. *Top 10 Overrepresentations of CYP_ADMET_properties in cohort B (Swedish). The "Hits" column shows the number of self-reported drugs belonging to a specific CYP-category listed in the column "Category", divided by the total number of drugs of the same category in Drugbank. The "Enrichment" column shows how many times each CYP-category is enriched in each cohort versus the drugs of Drugbank.*

Rank	Adjusted *p*-value	Hits	Enrichment	Category
1	$0.0\times10^{+0}$	798/1101 (72.5%)	3.9	Cytochrome P-450 Substrates
3	4.9×10^{-264}	596/834 (71.5%)	3.9	Cytochrome P-450 CYP3A Substrates
4	4.5×10^{-261}	590/826 (71.4%)	3.9	Cytochrome P-450 CYP3A4 Substrates
6	2.6×10^{-209}	482/676 (71.3%)	3.9	Cytochrome P-450 Enzyme Inhibitors
20	7.7×10^{-122}	232/281 (82.6%)	4.5	Cytochrome P-450 CYP2D6 Substrates
30	1.0×10^{-98}	246/356 (69.1%)	3.8	Cytochrome P-450 CYP3A Inhibitors
32	4.0×10^{-96}	186/227 (81.9%)	4.5	Cytochrome P-450 CYP2D6 Inhibitors
33	1.7×10^{-91}	191/245 (78.0%)	4.2	Cytochrome P-450 CYP2C9 Substrates
34	3.2×10^{-91}	230/335 (68.7%)	3.7	Cytochrome P-450 CYP3A4 Inhibitors
35	8.2×10^{-88}	207/288 (71.9%)	3.9	Cytochrome P-450 Enzyme Inducers

that target the CYP3A4 gene was illustrated bioinformatically, on a logarithmic scale. Over-Representation Analysis (ORA) confirmed a significant enrichment in the miRNAs gene subset using miRPathDB 2.0 in order to identify enriched functional categories potentially related to cancer (31). The most enriched pathways output by the ORA analysis were "microRNAs in cancer", "pathways in cancer", and "prostate cancer" at the first, second and fifth positions, respectively, showing a cluster of miRNAs within a KEGG pathway (Figure 5a).

In addition, the list of enriched miRNAs for the "Prostate Cancer" KEGG pathway downloaded from miRPathDB 2.0 was filtered using the 672 predicted miRNAs, resulting in 150 unique SNPs that are significantly enriched in PCa. The list was further filtered for miRNAs having "strong" experimental evidence, resulting in 43 unique miRNAs (Supplementary Table III). In that list, miR-200c-3p demonstrated the highest score (2.39565) with a statistically significant p-value (0.011).

These results suggest that genes more prone to oncogenesis *via* direct targeting of CYP3A4 were those involved in cancer initiation, progression, and prostate oncogenesis. Remarkably, by performing the ORA analysis, we also found significant enrichments in biological entities such as: "FoxO", "PI3K-Akt", "p53", "mTOR", "thyroid hormone", "prolactin", "chemokine", "neurotrophin", "T cell

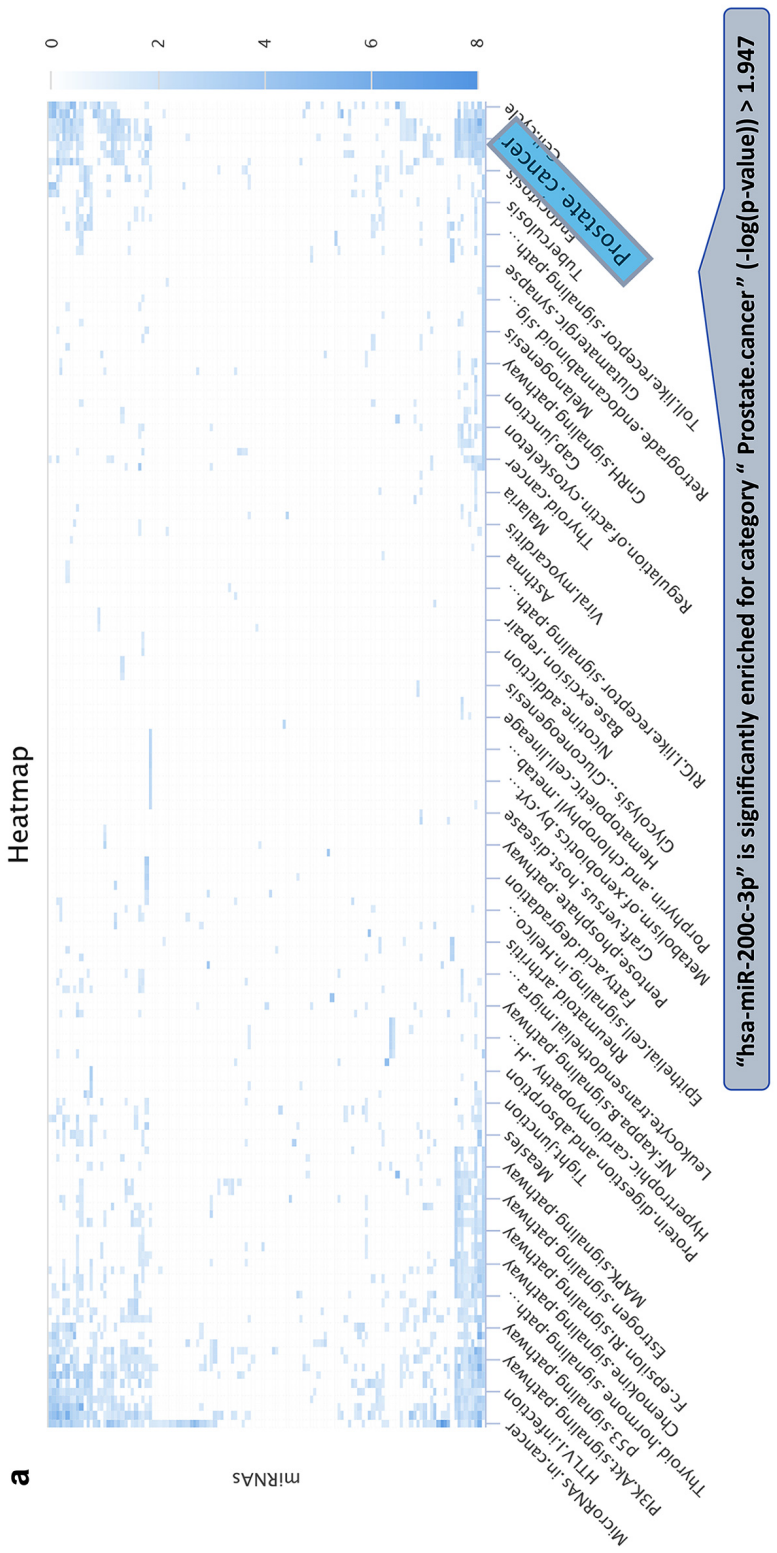

Figure 5. *Continued*

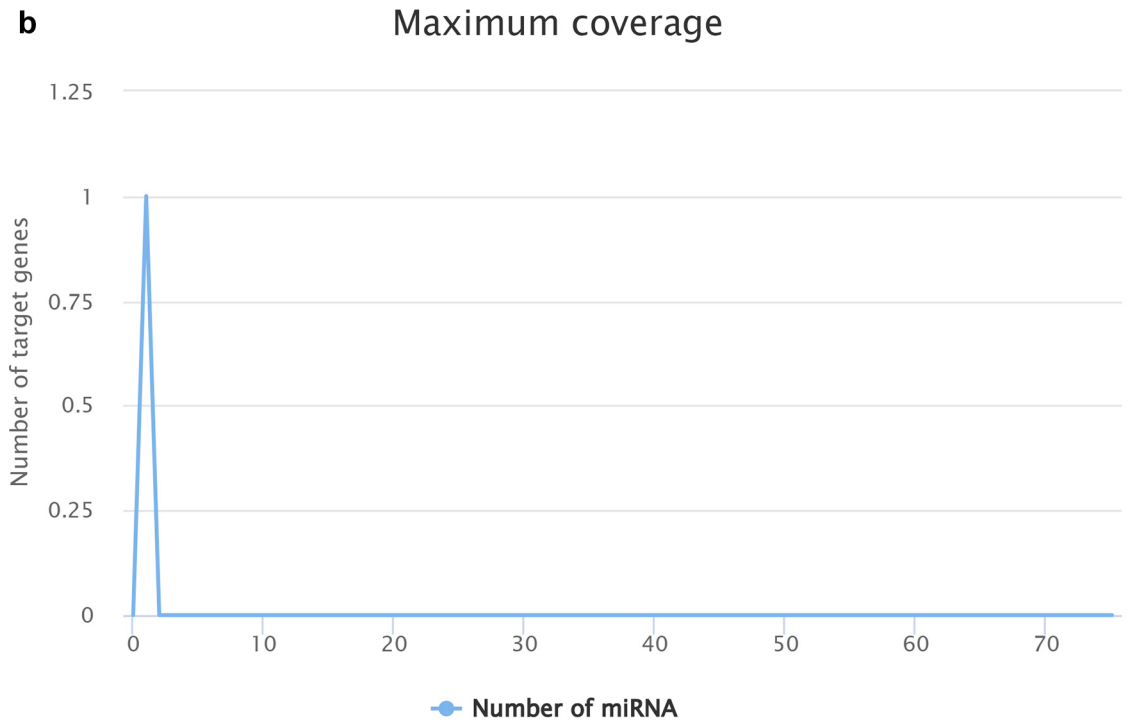

Figure 5. *(a) Over-representation analysis (ORA) based on the hypergeometric distribution showing the significantly enriched biological entities that involve the CYP metabolic enzyme targeted by miRNAs as they were identified by the use of the miRabel prediction tool. The heatmap shows that the enriched "prostate cancer entity" term has a functional significance on the CYP3A4 gene, through its epigenetic regulation by hsa-miR-200c-3p; (b) Interactive visualization of maximum-coverage analysis based on miRPathDB 2.0 tool, indicating that numerous miRNAs can target a specific gene of interest. X and Y axes show the increasing number of miRNAs and the number of covered target genes, in this case CYP3A4, which is directly regulated by hsa-miR-27b-3p. This result was further confirmed by miRTarBase.*

receptor", "VEGF", "ErbB", "Estrogen", "Rap 1", "Ras", "MAPK", "Insulin", "JakSTAT" and "Wnt" signaling pathways, as well as "proteoglycans in cancer", "transcriptional misregulation in cancer", "Natural killer cell mediated cytotoxicity", "regulation of actin cytoskeleton", "Endometrial cancer", "Non-small cell lung cancer", "Glioma", "Melanoma Bladder cancer" and "cell cycle" pathways (Figure 5a). The enrichment of these biological functions and signaling networks are important hallmarks and key players in cancer development (40). Cancer incidence data from recently published literature (41) concerning the miRNAs that are displayed in the interactive heatmap, confirmed the updated outcome.

Similarly, for each category, among the clusters of miRNAs, the hsa-miR-200c-3p was the most significantly enriched result for prostate cancer using miRPathDB 2.0 (22). Although hsa-miR-200c-3p does not directly interact with CYP3A4 mRNA, it is possible that those two molecules could be used as a predictive molecular signature for prostatic neoplasia. Instead, the reported optimal set of miRNAs for CYP3A4, based on the maximum targetome coverage analysis using miRPathDB 2.0 (31), was represented only by hsa-miR-27b-3p (Figure 5b); this was further confirmed from the literature search as well as from the miRNA–target interaction network of miRTarBase (30, 42).

Metabolic patterns integrating the Predictive pharmaco-epigenetic signature. Our literature search relied upon recent experimental evidence and focused on the

Table IV. *Panel of the studied metabolic-miRNA-PGx components for PCa risk stratification. Discrimination of urinary androgen concentrations represented by perturbed hydroxylated metabolites in three distinct patterns composing the metabolic fingerprint (metabotype) which is associated with prostate cancer risk. The regulatory mechanism via CYP3A4*1B activity is targeted in an indirect and direct modality via the epigenetic function of miRNA-200c-3p and miRNA-27b-3p, respectively.*

Candidate miRNA-PGx signature for prostate cancer susceptibility	Metabolic signature based on urinary androgen excretion patterns for prostate cancer susceptibility		
	Pattern I	Pattern II	Pattern III
CYP3A4*1B miRNA-200c-3p miRNA-27b-3p	11β-OHT 2β-OHT 15β-OHT 2α-OHT 6β-OHT	16α-OHT 16β-OHT	16β-OHT
	High risk	Intermediate risk	Low risk

measurement of androgen metabolites. It was estimated that the testosterone hydroxylated metabolites and the increased testosterone concentrations seem to be associated with a higher and/or intermediate prostate cancer risk, through the activation of biosynthetic pathways involving specific variants of CYP450 pharmacogenes (24). Subsequently, we completed the SNPs-PGx signature based on the urinary excretion patterns reflecting the metabolotype related to prostate cancer susceptibility or prostate cancer differentiation (Figure 1, Table IV).

Discussion

To this day, controversial issues remain concerning the origin, development, progression, and structural inter-relationships, between the two pathological conditions of the prostate gland: benign prostatic hyperplasia, which is a non-cancerous lesion (43, 44), and prostate cancer, especially because of the associations of their common risk factors, such as genetic variants implicated in the androgen metabolism (45), prostate volume polymorphisms (PV-related SNPs), and obesity (46). Factors like age, family history, and ethnicity, as well as the impact of the metabolic syndrome, suggest etiologic heterogeneity for BPH susceptibility (47) and prostate cancer risk and aggressiveness (48).

The trend of the three common comorbidities observed in cohort A, hypertension, dyslipidemia and diabetes (Figure 3), is a confirmatory outcome of prior knowledge (36, 49-51) supporting the hypothesis that these are promoters of the most common prostatic neoplasms, benign and malignant, as well as they are potential components of the metabolic syndrome (51-54). From these findings, in concordance with previous reports (55, 56), it can be stated that men with prostatic neoplasms have indeed a high burden of concurrent cardiometabolic and cardiovascular disease (CVD) risk factors (57, 58).

In our study, as hypertension was the most prominent condition in all the subjects recruited, it can be deduced that the association between BPH and/or PCa with hypertension, concerns apparently diverse disease processes that have some features in common, primarily through androgen-mediated pathways. These processes are likely to be pathophysiologically relevant, but they are unlikely to have immediate therapeutic implications (34, 59). Studies suggest an interconnection between prostate cancer and hypertension attributed to the shared androgen-mediated mechanism, although more clinical data are needed to validate whether hypertension and antihypertensive drugs may alter prostate cancer susceptibility and prognosis (55, 56).

Moreover, as a secondary outcome, considering that certain classes of treatments used for prostate cancer (60), could directly or indirectly raise the risk of hypertension (55) our data concerning the subcohort of PCa patients without previous BPH condition, were assessed for being associated with AEs or with pre-existing CVD risk factors. It was found that they were consistent with registry studies (61) for patients receiving LHRH-agonist therapy (ATC:V04CM), suggesting that GnRH agonists are associated with higher cardiovascular risk factors when compared to GnRH antagonists, such as Degarelix (ATC:L02BX) prescribed to cohorts patients (Figure 3). The interconnection between BPH neoplasia and hypertension, due to shared transcription factors and signaling pathways, becomes more prevalent and severe with age (44, 62) with great therapeutic significance since both diseases can be treated with a1-adrenoceptor antagonists (63, 64).

The concerns raised by the metabolic trends observed in the first cohort, address issues highlighted in the literature. Firstly, the mechanisms underpinning the relationship between the male dysmetabolism and prostatic neoplasms of the present study are likely to be similar, especially among middle-aged and elders (65, 66). Secondly, prolonged pathologic conditions may contribute to the risk of new-onset diseases such as prostatic neoplasia (67, 68). Research also reinforces the evidence of a diabetogenic effect caused by statin utilization, emphasizing the need for a better follow-up of patients (69, 70) especially those predisposed to diabetes and, an increased likelihood of developing metabolic syndrome (71, 72).

The independent study of cohort A lacked the statistical power to allow reliable conclusions due to small sample sizes. This limited reliable conclusions about the association of benign hyperplasia and hypertension, or prostate cancer and hypertension. However, understanding the implications of such comorbidities could provide insights into the causes and the pathophysiology of both diseases, influencing their management (73, 74). In this perspective, meta-analytic data have shown that for drugs belonging to angiotensin-converting enzyme inhibitors (ACEI) there was an increased risk of prostate cancer and (75) and users of ACE inhibitors may be marginally affected by cancer in particularly gastrointestinal and lung cancer (76, 77).

However, the evidence linking a causative association between the use of blood-pressure-lowering drugs to prostate cancer susceptibility for the categories listed in Table I, specifically for the angiotensin-converting enzyme inhibitors (ACEIs) (78, 79) and for angiotensin II antagonists (80), remains unclear. Furthermore, meta-analytic data retrieved in Taiwan estimated the composite chemopreventive effects against cancer through the use of drug combinations such as statins, aspirin, metformin, and angiotensin-converting enzyme inhibitors (ACEIs)/ angiotensin II receptor blockers (ARBs). Consequently, it was observed that for some cancer types, chemoprevention was more efficient by using combinations of two agents, whereas the use of four, in general, was ineffective (81).

Since 2018, concerns have emerged about the presence of carcinogenic nitrosamines in some medications belonging to certain angiotensin receptor blockers (ARBs) detected through patient follow-up. These impurities (NDMA, NDEA, and NMBA) have been found in valsartan, irbesartan and losartan leading to recalls of 1255 approved ARB drugs in US FDA and Canada (82, 83). In addition, some ARBs may increase oxidative stress which further increases carcinogenesis, while regulating insulin sensitivity and the maintenance of glucose concentrations, whose deregulation is linked to cancer risk (84).

An alternative class of antihypertensive drugs are HMG CoA reductase inhibitors (statins) (85), which are used for lowering the serum LDL concentrations. Their anti-inflammatory action may occasionally increase prostate oncogenesis (86, 87) limiting their beneficial properties to the hormone-sensitive phase but not to the later stages of CRPC prostate cancer therapy (88). According to Li *et al.* (70), statin prescription is associated with a decreased risk of advanced prostate cancer, but not of localized, low-grade, or high-grade disease. Unfortunately, although statins are studied as potential therapeutic option for secondary prevention in metastatic prostate cancer, their

anticancer role still remains controversial due to the undetermined potency of hydrophilic or lipophilic molecules and their limited indications (89).

Alpha1-selective adrenergic receptors, (α1-AR) antagonists, also named α-blockers or α-adrenoreceptor antagonists (63) are essential for LUTS/BPH treatment. Furthermore, 5-alpha-reductase inhibitors (Table I), have been correlated with improvements in LUTS/BPH in men with larger prostates, especially when combined with a1-AR antagonists (63). However there has been much interest in their potential influence on prostate oncogenesis with research showing (90) that the risk of high-grade prostate cancer was bigger between both 5ARI and α-blocker users compared with non-users (91). Similarly, Yang *et al.* (92) observed an increment of 13% in the risk of prostate cancer after hypertensive treatment with dihydropiridine derivates, particularly calcium channel blockers (CCBs). This was also confirmed by Copland *et al.* (93) supporting that, it cannot be entirely excluded that among the antihypertensive medications examined, CCBs, acting as potent dihydropyridine vasodilators, may be associated with prostate and skin cancer risk.

Taking into consideration that patients with BPH and metabolic syndrome (MetS) could take advantage of polypharmacy, the use of preventive pharmacogenetic tests should be recommended, especially for carriers of CYP3A4 polymorphisms, to avoid unconventional doses of medications (94, 95). As per the literature, our results shown in Table I suggest that some of the studied ATC drug classes, when metabolized by mutated and polymorphic CYP450 enzymes could result in increased risk of cancer or other diseases (96). Such risks, specifically PCa risks, are unlikely to be possible to document robustly unless very wide, clinical studies with standardized protocols are carried out (92).

The present study investigated the identification of pharmacoepigenetic patterns in silico, within a subset of metabolically unhealthy patients. This study workflow was performed with reference to the ATC classification system to search evidence of the molecular miRNA-epigenetic signature that could predict the gradual progression from healthy and/or unhealthy state to the prostatic neoplasms.

The systematic outcome of this research, using the miRabel, miRPathDB 2.0 and miRTaRBase platforms (31, 97) produced a gene-miRNA interaction network that interprets the pathological metabolic degradation towards the onset of prostate cancer due to xenobiotic toxicity, in particular deriving from drugs. Moreover, KEGG pathway analysis of the predominant pharmacogenes epigenetically regulated *via* the cluster of miRNAs, showed enrichment in oncogenic pathways such as prostate cancer, chemical carcinogenesis, drug metabolism, and metabolism of xenobiotics by CYP450 (Figure 5a).

According to the literature, there are more than 114 miRNAs that alter the expression levels of CYP3A4, and about 10% mediate the reduced expression, observed in healthy and cancerous tissue samples. Among them, as a member of the miR-200 family located in chromosome 12p13.31, miR-200c-3p is reported to be associated with solid tumor progression, such as ovarian, lung, endometrial and esophageal, as well as prostate cancer (22). It is shown that ZEB2 has a significant correlation with miR-200c-3p which was up-regulated in PCa tissues. Furthermore, ZEB2 expression was suppressed by the up-regulation of miR-200c-3p and was identified as a direct target of miR-200c-3p. In addition, repression of ZEB2 could restore the levels of miR-200c-3p in PCa cells, in turn, suggesting a potential negative loop between miR-200c-3p and ZEB2. miR-200c-3p also had an antitumor effect by negatively regulating ZEB2 in a xenograft mouse model (98). Furthermore, the tumor suppressor miRNA-27b-3p (located at 9q22.32) is responsible for the regulation of ADMET gene expression, through direct binding in the 3' UTR of CYP3A4 (42). miRNA-27b-3p is also found to cause down-regulation of the CYP3A4 protein in pancreatic and colon cancer cells, promotes prostatic neoplasia and activates procarcinogens that exert their genotoxic effects by targeting of CYP3A4 (99). It can distinguish between prostate cancer and benign prostatic hyperplasia subjects or normal controls (100).

The most predominant allele of the CYP3A4 gene, is the wild type CYP3A4*1A, whereas the variant CYP3A4*1B rs2740574, is present in 66%, 4%, and 0% of Afro-Americans, Europeans, and Asians, respectively (101). The complexity of the associations of CYP3A4*1B with prostate cancer risk concerning age, clinical and family history suggests that relationships with other possible endogenous parameters are required. Thus, CYP3A4*1B cannot be probably considered an independent risk factor for the onset of the disease (102). Besides, CYP3A4 shares substrate specificity with CYP3A5 due to their paralog genetic origin. Both belong to the CYP3A gene cluster. Variants of CYP3A4 and CYP3A5 such as CYP3A5 (*1/*3), or other alleles on the haplotypes, are associated with prostate cancer risk and aggressiveness, as well as hypertension having also a role in the onset of hypersensitivity to different xenobiotics (103).

The present work also delivers some secondary findings produced from the hypergeometric distribution analysis that concern the over-representations of CYP3A4 and CYP3A5 previously mentioned, as well as those of CYP2C9, CYP2C19 and CYP2D6 genes (Table II, Table III). Although not yet statistically important due to the small cohort size, our results which call for the implementation of pharmacoepigenetic testing on the above polymorphic candidate biomarkers, are quite close to other studies that have also reported the need to develop PGx tests for the genes related to phase I drug metabolism. Through the detection of CYP3A4 variants, it will be feasible to limit the incidence of adverse drug effects (ADRs), either the dose-related Type A, or the idiosyncratic reactions of Type B, as well as the harmful drug interactions (DDIs), and the drug-disease interactions (DDSIs), in which frequently, the annotated ATC system medications useful to treat one condition, may worsen another, or may cause symptoms of a new one, or may cause immune-mediated adverse drug reactions (IM-ADRs) without the implementation of personalized pharmacogenetic prescription (104).

The current work could be clinically applicable in patients with cardiometabolic risk factors favoring the optimization of therapeutic dosages that fit the patient's genetic make-up. Translating this research to clinical experimental outcomes, the novelty of the present study consists in the creation of a bio-molecular fingerprint which can be used preventively for prostatic neoplasms but not diagnostically. Following our methodology, the annotated ADME data sets produced a multiple SNPs integrated signature that consists of rs2740574 for the CYP3A4*1B; similarly of rs782249241, rs904135271, rs1466815657, rs1400433260 for hsa-miR-200c-3p, and of rs767630390, rs1198266267, rs1311621476, rs1331167542, rs192552111 for hsa-miR-27b-3p.

The present pharmacoepigenetic signature of miRNA-CYP3A4 SNPs was complemented by the involvement of the metabolome as it is the end point of genome-environmental interaction, capturing the individuals' adaptability to the external stimuli and the endogenous changes such as disease. More specifically, as testosterone is further converted by different CYP isoforms into various testosterone-hydroxylated metabolites (6β OHT, 11β-OHT, 16α-OHT, 2α-OHT, 2β-OHT, 16β-OHT, and 15β-OHT), it has been deduced that different metabolic profiles of testosterone-hydroxylated metabolites, concerning age may characterize the physiopathology of prostate cancer (105).

The limitations of the integrated pharmacogenetic signature concern that CYP3A4 variant frequency is ethnicity-related and its activity depends on co-administration of drugs as well as on other non-genetic factors such as the nutritional status (106). As most drugs metabolized by CYP3A4 are also metabolized by CYP3A5, the use of pharmacogenetic testing by polymerase chain reaction (PCR) with allelic discrimination analysis might be useful for determining therapeutic strategies only for drugs that are metabolized by CYP3A4, including atorvastatin, simvastatin, and lovastatin. Instead, this test, if not standardized, could be not useful for patients receiving other statins such as fluvastatin, rosuvastatin or pravastatin, since these drugs are not metabolized primarily by CYP3A4 (95).

In addition, a non-invasive panel of miRNAs could be more accurate and informative for prostate cancer prediction. This study proposes a polygenic integrated signature which is based on variants that cannot be

generalized to drug outcomes produced from the combined effect of polypharmacy. Defined directives based on multiple variants, made on per-gene evidence and future investigations are needed for the implementation of PGx testing. Finally, the usefulness of metabolomic urinary androgen patterns for prostate cancer sensitivity and prognosis, alone or in conjunction with epigenetic and CYP450s genotyping or expression, should be assessed in prospective large-scale studies as it is a promising tool for prostate cancer screening.

Conclusion

Despite significant achievements directed toward prostate cancer prevention, it is unclear whether certain drug classes and xenobiotics have the potential to promote malignancy progression. Current research does not provide a consistent statement on this association, and a causal relationship remains controversial. The prevailing conclusion must be that there is not a definitive signal for drug exposure related to prostate neoplasia progressing to malignancy. However, this possibility has not been completely precluded. The issue of nitrosamine impurities in certain medicinal products or the oncogenic effect of other xenobiotics requires further investigation, so the hazard may be mitigated by their elimination. Pharmacogenetic testing is an up-and-coming field of precision medicine, essential for the implementation of pharmacovigilance and pharmacoepidemiological monitoring, whereas epigenetic and metabolomic biomarkers seem to represent novel molecular phenotypes reflecting aspects of the disease.

Supplementary Material

Supplementary material is available at: https://doi.org/10.6084/m9.figshare.27960858

Conflicts of Interest

The Authors declare that they have no conflicts of interest or financial ties related to this study.

Authors' Contributions

Conception and design: M.P. Methodology: M.P., V.L.Z., I.M., G.T.T. and N.D. Sample collection: S.K., E.F. and V.Z. Manuscript writing: M.P and V.L.Z. Editing: M.P., V.L.Z., I.M., V.Z., A.T., A.M.T., G.T.T. and N.D. Supervision: I.M., A.M.T. and N.D. All Authors read and approved the final manuscript for submission.

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