THERAPEUTIC ADVANCES in
Medical Oncology

Review

Ther Adv Med Oncol

2023, Vol. 15: 1–30

DOI: 10.1177/
17588359231152839

Targeting lipid metabolism in metastatic prostate cancer

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***Abstract*:** Despite key advances in the treatment of prostate cancer (PCa), a proportion of men have *de novo* resistance, and all will develop resistance to current therapeutics over time. Aberrant lipid metabolism has long been associated with prostate carcinogenesis and progression, but more recently there has been an explosion of preclinical and clinical data which is informing new clinical trials. This review explores the epidemiological links between obesity and metabolic syndrome and PCa, the evidence for altered circulating lipids in PCa and their potential role as biomarkers, as well as novel therapeutic strategies for targeting lipids in men with PCa, including therapies widely used in cardiovascular disease such as statins, metformin and lifestyle modification, as well as novel targeted agents such as sphingosine kinase inhibitors, DES1 inhibitors and agents targeting FASN and beta oxidation.

Keywords: prostate cancer, lipids, targeted therapy, high-fat diet

Received: 25 August 2022; revised manuscript accepted: 5 January 2023.

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Introduction

Prostate cancer (PCa) is the second most commonly diagnosed cancer worldwide.[1] Although localized PCa is frequently curable, 350,000 men globally die from PCa each year.[1] Despite key advances in the treatment of metastatic PCa, a proportion of men have *de novo* resistance, and all will develop resistance to therapeutics over time. Longer-term control of metastatic PCa requires approaches that target multiple hallmarks of cancer that incorporate the neoplastic epithelium, the tumour microenvironment and systemic metabolic factors including lipid metabolism.[2]

The precision-oncology era focuses on the development of treatment paradigms based on the adage, the right drug to the right patient at the right time. The development of specific biomarkers are crucial to delivering treatment to those who will benefit most, sparing non-responders the cost and side-effects of treatment.[3] Much of the research into novel personalized PCa treatments has focused on genomic changes to the cancer, including the use of PARP inhibitors for men with mutations in *BRCA1/2* or *ATM*.[4,5] However, <30% of PCas harbour these mutations, and there is significant scope for other personalized medicine approaches. One novel therapeutic target is lipid metabolism, where there has recently been an explosion in preclinical and clinical data, which is informing new clinical trials.

There are epidemiological links between obesity and metabolic syndrome and prostate carcinogenesis and progression. Obesity is associated with increased incidence of PCa, higher rates of biochemical recurrence, and increased PCa-specific mortality (PCSM).[6–8] Three meta-analyses have found a positive association between obesity and PCa incidence, with relative risks (RR) ranging from 1.01 [95% confidence interval (CI) 1.0–1.02] per 1 kg/m^2 increase in body mass index (BMI)[9] to 1.05 (95% CI 1.01–1.08)[10] and 1.03 (95% CI 1.0–1.07)[11] per 5 kg/m^2 increase.

Obesity is also associated with increased PCSM and biochemical recurrence. A meta-analysis of prospective cohort studies found that in initially cancer-free men, a 5 kg/m^2 increment in BMI was

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associated with increased risk of PCSM (RR 1.15, 95% CI 1.06–1.25) and increased risk of biochemical recurrence (RR 1.21, 95% CI 1.11–1.31). The association with biochemical recurrence remained significant when evaluating within treatment subgroups (radical prostatectomy: RR 1.25, 95% CI 1.12–1.40; radiation therapy: RR 1.15, 95% CI 1.03–1.28).[12] Other studies have also found this association between higher BMI and increased risk of PCSM among obese healthy adults[13–17] and PCa patients,[18–21] as well as higher rates of biochemical recurrence.[22–24]

Obesity also increases the risk of advanced PCa. This was assessed in dose-response meta-analyses with increases in BMI and waist circumference increasing the risk of advanced disease (BMI: RR 1.08 (95% CI 1.04–1.12) per 5 kg/m^2 BMI; waist circumference: RR 1.12 (95% CI 1.04–1.21) for each 10 cm increase in waist circumference; waist-hip ratio: RR 1.15 (95% CI 1.03–1.28) for each 0.1 unit increase).[25]

BMI trajectories during adulthood that result in obesity are also associated with an elevated risk of fatal PCa. The risk of lethal PCa is increased in men who had a normal BMI [hazard ratio (HR) 1.95, 95% CI 1.21–3.12] or who were overweight [HR 2.65, 95% CI 1.35–5.18] at age 20, but developed obesity by diagnosis, compared with men who maintained a normal BMI.[26]

Metabolic syndrome, characterized by insulin resistance plus hypertension, excess body weight with central obesity and dyslipidaemia,[27] includes metabolic and hormonal changes that may influence cancer biology. The presence of metabolic syndrome worsens PCa outcomes. Two studies found that men with metabolic syndrome were more likely to develop PCa than those without.[28,29] The time to develop castration resistant prostate cancer (CRPC) in men with metabolic syndrome prior to initiation of androgen deprivation therapy (ADT) is reduced compared to those without metabolic syndrome (16 months *versus* 36 months, $p=0.003$). The median overall survival (OS) for patients with metabolic syndrome after commencing ADT was also reduced compared to those without metabolic syndrome (37 months *versus* 47 months, $p=0.061$).[30]

Of particular concern is that many of the side effects of long-term ADT are metabolic, including insulin resistance, dyslipidaemia, sarcopenic obesity and metabolic syndrome.[31]

This review describes the preclinical and clinical evidence for targeting lipid metabolism in prostate cancer and describes novel therapeutic agents targeting lipid metabolism in prostate cancer.

The role of circulating lipids in prostate cancer

Advances in mass spectrometry technology have allowed the accurate measurement of hundreds of individual lipid species in large cohorts, achieved with high-throughput using small volumes of serum or plasma.[32] Lipidomic risk scores are well-validated in patients with Type 2 diabetes and cardiovascular disease,[33,34] including a commercially available assay.[35,36] An ever-growing number of studies measuring circulating lipids in patients with cancer have been undertaken, with promising advances.[37]

Circulating lipids associated with prostate cancer risk

Numerous large case control and cross-sectional studies identified lipids associated with PCa risk, with samples obtained up to 20 years prior to cancer diagnosis (Table 1). These studies identified several lipids associated with increased risk of PCa diagnosis including 1-stearoylglycerol,[38] glycerosphingolipids,[39] acylcarnitine species[40] and lipids involved in phospholipid metabolism.[40] Lipids were also associated with increased risk of advanced PCa, including phosphatidylcholines and lysophosphatidylcholines,[41,42] hydroxysphingomyelins[41] or acylcarnitines.[41] Similar trends were seen with aggressive disease and death.[41]

These studies were unable to reproduce each other's findings, as it is difficult to compare across trials due to differences in study methodology, assays and metabolites examined. Overall, these studies demonstrate that there are changes in the metabolome that pre-date cancer development by many years.

Circulating lipids as biomarkers for prostate cancer diagnosis

Several case-control studies have included lipids in metabolomics panels investigating biomarkers for PCa diagnosis (Table 1). In particular, phosphatidylcholine and lysophosphatidylcholines were implicated in several studies.[43–47] Other lipids associated with PCa diagnosis include fatty acids,[44] phosphatidylethanolamine,[46] sphingomyelins,[47]

Table 1. Circulating lipids in prostate cancer.

Study details and case numbers (*n*)	Study type	Outcome measures	Main observations	Reference
Lipids associated with prostate cancer risk				
Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) *n* = 74 (PCa) *n* = 74 (controls)	Case-control	Risk of developing PCa	**1-stearoylglycerol** inversely associated with PCa (OR 0.34, 95% CI 0.20–0.58)	Mondul *et al.*[38]
ATBC study *n* = 100 (aggressive PCa) *n* = 100 (non-aggressive PCa) *n* = 200 (controls)	Case-control	Risk of developing PCa Risk of developing aggressive PCa	Lipid metabolites inversely associated with risk of aggressive PCa, particularly **inositol-1-phosphate** and **glycerosphingolipids**. None reach statistical significance after correcting for multiple testing ($p < 0.00008$). Findings of Mondul *et al.* (2014) not replicated.	Mondul *et al.*[39]
Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening *n* = 380 (PCa) *n* = 380 (controls)	Nested case-control	Risk of developing PCa	27 metabolites associated with PCa ($p < 0.05$) including **acylcarnitine species** and lipids involved in **phospholipid** metabolism	Huang *et al.*[40]
European Prospective Investigation into Cancer and Nutrition (EPIC) *n* = 3057 (PCa) *n* = 3057 (controls)	Case-control	Risk of developing advanced or aggressive PCa Risk of PCa death	Higher concentrations of **phosphatidylcholine**s or **hydroxysphingomyelins** (OR 0.77, 95% CI 0.66–0.89, $p = 0.0007$), **acylcarnitines C18:1 and C18:2**, **glutamate**, **ornithine** and **taurine** (OR 0.72, 95% CI 0.57–0.90, $p = 0.005$) or **lysophosphatidylcholines** (OR 0.81, 95% CI 0.69–0.95, $p = 0.009$) associated with lower risk of advanced PCa. Similar trends seen with the risk of aggressive disease and death.	Schmidt *et al.*[41]
EPIC-Heidelberg *n* = 310 (PCa)	Case-cohort	Risk of developing PCa	Lower levels of **lysophosphatidylcholines** and higher levels of **phosphatidylcholines** associated with increased risk of PCa	Kühn *et al.*[42]
Lipids as biomarkers for prostate cancer diagnosis				
Austrian Prostate cancer biobank *n* = 206 (localized PCa) *n* = 114 (control)	Case-control	Presence of PCa	Two **phosphatidylcholines (16:0 and 18:0)** and two **saturated lysophosphatodylcholines (chain length 18 and 16)** can discriminate between men with PCa and healthy controls	Osl *et al.*[43]
Prospective study in Atlanta, Georgia. *n* = 64 (PCa) *n* = 50 (controls)	Case-control	Presence of PCa	Numerous metabolites were discriminant between PCa cases and controls including **fatty acids**, **lysophospholipids**	Zang *et al.*[44]
n = 77 (PCs) *n* = 77 (controls)	Case-control	Presence of PCa	Levels of **phosphatidylcholine**, **egg phosphatidylcholine** and **egg phosphatidylethanolamine** can predict for the presence of PCa	Patel *et al.*[45]

(Continued)

Table 1. (Continued)

Study details and case numbers (*n*)	Study type	Outcome measures	Main observations	Reference
n = 57 (localized PCa) *n* = 43 (controls)	Case-control	Presence of PCa	Men with PCa had significantly lower concentration of **total phospholipids** and **phospholipid fractions**. The relative concentrations of **lysophosphatidylcholine** and **phosphatidylethanolamine** were significantly lower, and **phosphatidylcholine** was significantly higher in PCa patients compared to controls.	Cvetković *et al.*[46]
n = 105 (PCa) *n* = 36 (controls)	Case-control	Presence of PCa	Identified four **lysophosphatidylcholines**, three **phosphatidylcholines**, two **ether-linked phosphatidylcholines**, and three **sphingomyelin** species that could individually serve as biomarkers for the diagnosis of PCa. Combinations of lipids increase the sensitivity, specificity and accuracy as a biomarker.	Zhou *et al.*[47]
n = 40 (stage II prostate cancer) *n* = 30 (controls)	Case-control	Presence of PCa	Alterations in the concentration of **dimethylheptanoyl carnitine** (an acylcarnitine) and **arachidonoyl amine** (a fatty amide) were diagnostic of PCa, with a ROC AUC of 0.97 and 0.86 respectively.	Lokhov *et al.*[48]
Prostate Testing for Cancer and Treatment (ProtecT) *n* = 2291 (PCa) *n* = 2661 (controls)	Case-control	Presence of PCa	Identified 35 metabolites strongly associated with PCa including lipids (**total cholesterol and ratios**, **cholesterol esters and ratios**, **free cholesterol and ratios**, **phospholipids and ratios** and **triglycerides**) and **fatty acids**.	Adams *et al.*[49]
Lipids as prognostic biomarkers in prostate cancer				
n = 96 (CRPC discovery cohort) *n* = 63 (CRPC validation cohort)	Prospective cohort	Poor prognosis in CRPC	Poor lipid profile (predominantly **sphingolipids**) associated with worse survival (HR 2.31, 95% CI 1.44–3.68). Prognostic 3-lipid signature (3LS) (**ceramide(d18:1/24:1)**, **sphingomyelin(d18:2/16:0)**, **phosphatidylcholine(16:0/16:0)** associated with shorter OS (discovery cohort: HR 4.78, 95% CI 2.06–11.1, $p < 0.001$; validation cohort: HR 2.39, 95% CI 1.63–3.51, $p < 0.001$).	Lin *et al.*[50]

(Continued)

Table 1. (Continued)

Study details and case numbers (*n*)	Study type	Outcome measures	Main observations	Reference
n = 389 (localized PCa) *n* = 44 (metastatic HSPC) *n* = 137 (metastatic CRPC)	Prospective cohort	Poor prognosis in localized PCa, metastatic HSPC and metastatic CRPC	Lipidomic profiles at treatment initiation associated with metastatic relapse in localized PCa (HR 5.80, 95% CI 3.04–11.1, $p < 0.001$), earlier ADT failure in metastatic HSPC (HR 3.70, 95% CI 1.37–10.0, $p = 0.01$), shorter OS in mCRPC commencing docetaxel (HR 2.54, 95% CI 1.73–3.72). The prognostic 3LS derived above was verified in the mCRPC cohort (HR 2.39, 95% CI 1.3–3.51).	Lin *et al.*[51]
n = 132 (mCRPC, commencing abiraterone or enzalutamide)	Prospective cohort	Poor prognosis in mCRPC	Men with elevated **ceramides** had shorter rPFS and OS (rPFS HR 2.3, 95% CI 1.5–3.6; OS HR 2.3, 95% CI 1.4–36). The combined effect of *AR* gene aberrations with elevated circulating **ceramides** or genetic aberrations of **sphingolipid** metabolism was associated with poorer ARSI responses in mCRPC.	Lin *et al.*[52]
n = 106 (mCRPC discovery cohort) *n* = 94 (mCRPC validation cohort)	Prospective cohort	Poor prognosis in mCRPC	The 3LS derived in Lin *et al.* (2017) was associated with shorter OS in the discovery cohort (HR 2.15, 95% CI 1.4–3.3) and validation cohorts (HR 2.32, 95% CI 1.59–3.38). Elevated **sphingolipids** were associated with *AR, TP53, RB1* and *PI3K* aberrations. Men with both the 3LS and aberrations in these genes had shorter OS than men with neither.	Mak *et al.*[53]
North Carolina-Louisiana PCa Project *n* = 159 (treatment naïve PCa)	Longitudinal exploratory study	Metabolites associated with aggressive PCa	**Sphingolipids**, especially **sphingomyelins** and **glycosphingolipids** associated with PCa aggressiveness.	Snider *et al.*[54]
n = 88 (PCa all stages) *n* = 110 (men with BPH) *n* = 20 (healthy young men)	Prospective cohort	Presence of PCa Poor prognosis in localized PCa/HSPC PCa death	Circulating levels of **sphingosine-1-phosphate** (**S1P**) (a downstream metabolite of ceramide) were significantly lower in patients with PCa compared to healthy controls, and lower **S1P** levels were an early marker of progression to CRPC and correlated with PSA levels and PCa death.	Nunes *et al.*[55]
n = 491 (localized PCa on active surveillance)	Prospective cohort	Disease progression for men on active surveillance	A prognostic plasma lipid signature (consisting of plasma **sphingolipids**, particularly **sphingomyelins** and **glycosphingolipids** and **caveolin-1**) predicts for disease progression.	Vykoukal *et al.*[56]

AUC, area under the curve; BPH, benign prostate hyperplasia; CI, confidence interval; CRPC, castration resistant prostate cancer; HR, hazard ratio; HSPC, hormone sensitive prostate cancer; OR, odds ratio; OS, overall survival; PCa, prostate cancer; ROC, receiver operating characteristic; rPFS, radiographic progression free survival.
Bold text was included to highlight the lipids that were mentioned in the different articles.

acyl carnitines and fatty amides,[48] total phospholipids and phospholipid fractions,[46] total cholesterol and ratios, cholesterol esters and ratios, free cholesterol and ratios, phospholipids and ratios and triglycerides.[49] However these lipids all appear in single studies. Combinations of lipids increased biomarker sensitivity, specificity and accuracy.[47]

In one study, a biomarker comprising dimethylheptanoyl carnitine (an acylcarnitine) and arachidonoyl amine (a fatty amide) was diagnostic of PCa, with a receiver operating characteristic (ROC) area under the curve (AUC) of 0.97 and 0.86 respectively.[48] Notably, within this cohort PSA predicted PCa diagnosis with a ROC AUC of only 0.59.[48]

PSA is an imperfect diagnostic tool for PCa, particularly in identifying aggressive/clinically actionable PCa[57] and alternative tools to assist in screening for PCa are required. Although further validation is required, lipid biomarkers could meet this need.

Circulating lipids as prognostic biomarkers in prostate cancer

In a series of studies, Lin *et al.* examined circulating lipids in men with PCa, and their association with prognosis and resistance to therapy. Elevated circulating sphingolipids, including ceramides, were associated with poorer outcomes across the natural history of PCa.[50,51] Lipidomic profiles at treatment initiation were associated with an increased rate of metastatic relapse in localized PCa, earlier ADT failure in metastatic hormone-sensitive PCa (HSPC), shorter OS in metastatic CRPC (mCRPC) commencing docetaxel chemotherapy and shorter radiographic progression free survival (rPFS) and OS in men with mCRPC receiving androgen receptor signalling inhibitors (ARSI).[50–52] They derived and validated a poor prognostic 3-lipid signature (3LS) consisting of ceramide(d18:1/24:1), sphingomyelin(d18:2/16:0) and phosphatidylcholine(16:0/16:0). This 3LS was associated with shorter OS in men with mCRPC commencing docetaxel or ARSI and has been validated in internal and external independent cohorts.[50–52,58] The combined effect of *androgen receptor* (*AR*) gene aberrations with elevated circulating ceramides or genetic aberrations of sphingolipid metabolism was associated with poorer ARSI responses in men with mCRPC.[52] Further, elevated sphingolipids were associated with *AR, TP53, RB1* and *PI3K* aberrations. Men with both the 3LS and aberrations in these genes had shorter OS than men with neither.[53]

These findings are supported by further studies of circulating lipids in PCa which also found that circulating sphingolipids were associated with PCa aggressiveness and PCa death,[54,55] and could predict for progression in men with localized PCa undergoing active surveillance.[56]

The role of lipid biology in prostate cancer

The prognostic changes in circulating lipids in PCa patients described above likely flag an underlying tumour/host biology that could be modified pharmacologically. However, it remains unclear whether this relationship indicates a 'host' metabolic environment that promotes aggressive disease, or whether tumoural lipids contribute to the circulating lipidome. It has been known for decades that PCa cells exhibit intracellular accumulation of lipids and, notably, that this reflects enhanced lipogenesis that is directly stimulated by culture with androgens.[59] Moreover, with recent advances in analytical technologies we now know that clinical prostate tumours also exhibit higher concentrations of fatty acids as well as an altered 'lipidome', both of which are correlated with disease stage.[60,61] A compelling body of evidence suggests that this is not an epiphenomenon, but instead signifies the strong dependence of cancer cells on lipids for energy production, membrane production, intracellular signalling and other processes. Detailed profiling of the composition of the clinical tissue lipidome has revealed robust tumour- and androgen-related changes in lipid composition,[60,62] which exposed potential biomarkers and metabolic dependencies[62,63] that could underpin future therapeutic strategy development. Considering the prognostic value of the circulating lipidome, it will be critical to determine to what extent a prostate tumour lipidome reflects or influences the circulating lipidome and informs poor patient outcomes.

Tumour microenvironment

The vast majority of research into cancer metabolism, including that of PCa, has been undertaken in artificial laboratory models that poorly mimic the nutrient-deficient and hypoxic clinical tumour microenvironment (TME).[64] Prostate tumours are heterogeneous and multifocal, which likely promotes plasticity in fuel utilization by cancer cells and influences response to metabolic agents.[65,66] Moreover, while an active area of research in other cancers, very little research focus has been given to tumour-TME metabolic crosstalk in PCa.

These challenges have underpinned the increasing use of spatial analytical techniques to study the diverse metabolic profiles of the cancer and non-cancer cell types that make up the prostate TME.[60,67,68] Mass spectrometry imaging for example now has the capability to identify lipid species that are selectively associated with tumour cells, but also lipid fingerprints for stromal and immune cell populations.[69,70] Given the TME has a profound influence on tumour cell behaviour and anti-tumour immunity, understanding cell specific- and treatment-related changes in lipid metabolism will be essential to effectively exploit any potential vulnerabilities.

Reprogramming of lipid metabolism in prostate cancer cells

Cancer cells boost intracellular lipid concentration by enhancing two processes, *de novo* lipogenesis and lipid uptake. Key oncogenic signalling pathways can drive *de novo* lipogenesis in tumour cells (Figure 1). For example, AR directly regulates the expression of factors that drive lipid synthesis, including fatty acid synthase (FASN), ACACA (acetyl-CoA carboxylase alpha) and ELOVL5.[62,71,72] Furthermore, the AR signalling axis has an indirect, but potent role in lipogenesis by enhancing the expression and activity of sterol regulatory element binding proteins (SREBPs),[62,73,74] transcription factors with a fundamental role in activating lipogenic genes. PI3K-AKT-mTOR signalling can also activate SREBP1 to enhance lipogenesis in prostate cancer cells, particularly in the context of genetic alterations that lead to sustained activation of this pathway (i.e. PTEN loss, activating mutations in PI3K subunits).[61,75]

Uptake of exogenous fatty acids relies on specialized transporters at the plasma membrane. Expression of the CD36 fatty acid transporter (FAT) is essential for efficient uptake of FAs.[76] A survey of 41 candidate FATs revealed that many are upregulated in primary tumours compared to non-malignant tissue, including a subset that are regulated by androgen treatment (i.e. GOT2, SLC27A3, SLC27A4, SLC27A5 and CD36).[77] AR can also promote the expression of lipoprotein transporters, which increases cellular cholesterol and free fatty acids.[77] Similarly, aberrant PI3K-AKT caused upregulation of low-density lipoprotein receptors via SREBP, resulting in accumulation of cholesteryl esters in prostate cancer cells.[61] In short, oncogenic signalling pathways enable prostate cancer cells to increase rates of lipid synthesis and uptake.

Elevated intracellular lipid levels in prostate tumours permits a higher rate of mitochondrial fatty acid β-oxidation (FAO) compared to non-malignant cells.[78,79] FAO is the major energy source in prostate cancer, setting it apart from many other tumour types that exhibit a 'Warburg' glycolytic phenotype.[80]

Treatment-related changes to lipid metabolism in prostate cancer

Altered lipid metabolism appears to play a major role in mediating the therapy-resistant phenotype. *De novo* lipogenesis is elevated in cell line models of CRPC compared to hormone-sensitive cells,[81] a phenomenon likely mediated by hyperactive AR and mTOR in this disease context.[82] Expression of lipid transporters is also increased in metastatic prostate cancer, including CRPC tumours, compared to primary disease.[76,77] The Butler *et al.* group demonstrated that treatment of primary tumour 'explants' with the AR antagonist enzalutamide resulted in significant changes to a subset of lipid species[60] in just 48 h, providing further evidence for therapy-mediated remodelling of the lipidome and information on acute responses to this drug. However, analysis of lipid metabolism in CRPC tumours using a multi-omics approach is yet to be performed; this gap must be surmounted in order to better understand how hormonal therapies influence lipid metabolism.

Clinically, androgen deprivation causes changes to systemic lipids. ADT use leads to significantly higher concentrations of total cholesterol, high and low density lipoproteins and triglycerides as early as 6 months after initiation.[83–85] ADT also causes increased fasting blood sugar and glycosylated haemoglobin (HbA1c) among diabetic patients.[84] ADT increases fat mass, particularly subcutaneous fat, and decreases lean body mass.[86] Taken together, men on ADT have an increased prevalence of metabolic syndrome compared to men with prostate cancer not on ADT and healthy controls.[87] Whilst it is vital to manage these metabolic side effects to minimize cardiovascular risk, it is also important to consider the effects these can have on the cancer itself.

There is epidemiological evidence that elevated cholesterol is associated with an increased risk of lymph node metastases and higher Gleason scores.[88] Elevated cholesterol and triglycerides are also associated with increased PCa recurrence.[89] The metabolic syndrome worsens PCa outcomes, with a decreased time to CRPC in men with metabolic syndrome.[30]

Altered lipid metabolism is not just a consequence of systemic prostate cancer treatment, but can actively promote therapy resistance via multiple mechanisms. As examples, altered lipid membrane composition as a consequence of enhanced lipogenesis can disrupt drug uptake[90] and elevated rates of FAO have been linked to acquisition of mesenchymal and stem-ness phenotypes that can mediate drug resistance.[91,92] Importantly, although dysregulation of lipid metabolism in prostate cancer cells is associated with therapy resistance, it could also yield new therapeutic vulnerabilities, such as sensitivity to ferroptosis.[93]

Therapeutic targeting of aberrant lipid metabolism

There are several potential therapeutic targets for modulation of lipids in prostate cancer. These include reducing cholesterol through the use of statins, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and fibrates, targeting the sphingolipid metabolism pathway, targeting transcription factors such as through Sterol Regulatory Element Binding Protein (SREBP) inhibitors, targeting lipid uptake into cells, targeting lipogenesis and lipid metabolism, targeting the metabolic syndrome itself and through adjustments to dietary intake.

Targeting cholesterol

Statins are a class of lipid-lowering medication used to treat hypercholesterolaemia. Over 30 observational studies examining the association between use of statins and PCa risk have shown mixed results (Table 2). Some population-based studies found no association between statin use and the risk of developing PCa.[94–98] While others focusing on the risk of advanced and fatal PCa demonstrated a reduced likelihood of advanced[99,100] or fatal disease.[101] A

Table 2. Association between prostate cancer and statins or metformin.

Study details and case numbers (*n*)	Study type	Outcome measures	Main observations	Reference
Statins and prostate cancer risk				
Seattle-Puget Sound Surveillance, Epidemiology and End results Programme *n* = 1001 (PCa) *n* = 942 (control)	Case control	PCa risk	No overall association was found between statin use and PCa risk, even for cases with more advanced disease.	Agalliu *et al.*[94]
Osteoporotic fractures in men *n* = 5069 (men aged 65+)	Prospective cohort	Risk of developing PCa	There was no evidence of an association between statin use and total PCa or low/high stage or grade PCa.	Chan *et al.*[95]
Cancer Prevention Study II Nutrition cohort *n* = 60,059 (men)	Prospective cohort	Risk of developing PCa	There was no association between current use of cholesterol-lowering drugs for 5 + years and PCa incidence.	Jacobs *et al.*[96]
Cancer Prevention Study II Nutrition cohort *n* = 55,454 (men)	Prospective cohort	Risk of developing PCa	There was no association between current use of cholesterol-lowering drugs overall PCa incidence, but there was an association with advanced PCa (rate ratio 0.60, 95% confidence interval 0.36 – 1.00).	Jacobs *et al.*[97]
n = 24,723 (PCa) *n* = 24,723 (control)	Case Control	PCa risk	There was an association between having ever-used a statin and elevated PCa risk (OR 1.07, 95% CI 1.00–1.16).	Murtola *et al.*[100]

(Continued)

Table 2. (Continued)

Study details and case numbers (*n*)	Study type	Outcome measures	Main observations	Reference
n = 6 (randomized clinical trials) *n* = 13 (observational studies)	Meta-analysis	PCa risk	There was no association between statin use and total PCa. In contrast, statin use was associated with lower risk of advanced PCa (RR 0.77, 95% CI 0.64–0.93).	Bonovas *et al.*[99]
Health Professionals Follow-up Study *n* = 34,989 (men)	Prospective cohort	Risk of developing advanced PCa	Current statin use was associated with lower risk of advanced PCa (RR 0.51, 95% CI 0.30–0.86) and metastatic/fatal PCa (RR 0.39, 95% CI 0.19–0.77). There was no association with overall risk of PCa.	Platz *et al.*[101]
n = 15 (cohort studies) *n* = 12 (case-control studies)	Meta-analysis	Risk of PCa	Statin use significantly reduced the risk of total PCa (RR 0.93, 95% CI 0.87–0.99) and advanced PCa (RR 0.80, 95% CI 0.70–0.90).	Bansal *et al.*[102]
Statins and risk of recurrence of localized disease				
n = 34 (observational cohort)	Meta-analysis	Risk of progression amongst men with localized disease	Statin use was associated with reduced risk of metastases and PCSM. It was associated with reduced biochemical recurrences post radiation therapy (HR 0.79, 95% CI 0.65–0.95) but not radical prostatectomy.	Raval *et al.*[103]
n = 13 (studies) including *n* = 7 (radical prostatectomy) and *n* = 6 (radiotherapy)	Meta-analysis	Risk of progression amongst men with localized disease	Statin use only improved recurrence free survival in the radiotherapy population (HR 0.68, 95% CI 0.74–1.08) but not the overall population or those treated with radical prostatectomy.	Park *et al.*[104]
Statins and risk of progression with hormone sensitive prostate cancer				
n = 926 (HSPC)	Retrospective cohort	Time to progression during androgen deprivation therapy	Men taking statins had a longer median TTP during ADT compared with nonusers (27.5 *versus* 17.4 months).	Harshman *et al.*[105]
Statins and castration resistant prostate cancer				
n = 187 (CRPC starting abiraterone)	Retrospective cohort	Overall Survival	Statin use was a significant prognostic factor for longer OS (multivariate analysis HR 0.40, 95% CI 0.27–0.59).	Di Lorenzo *et al.*[106]
COU-AA-301 and COU-AA-302 (CRPC, abiraterone *versus* placebo) *n* = 1195 (COU-AA-301) *n* = 1088 (COU-AA-302)	Randomized control trials	Overall survival	OS was prolonged among those treated with statins (pooled HR 0.78, 95% CI 0.68–0.88).	Wilson *et al.*[107]
n = 108 (mCRPC)	Prospective cohort	Progression-free and Overall survival	Use of statins did not improve PFS or OS, PSA-decline, or best clinical benefit in men with mCRPC treated with Abiraterone.	Boegemann *et al.*[108]
AFFIRM, PREVAIL, PROSPER (CRPC, enzalutamide *versus* placebo) *n* = 1184 (AFFIRM) *n* = 1699 (PREVAIL) *n* = 1394 (PROSPER)	Randomized control trials	Overall survival	OS was significantly associated with statin use for AFFIRM + PREVAIL + PROSPER (HR 0.75, 95% CI 0.66–0.85).	Joshua *et al.*[109]
STABEN study *n* = 598 (CRPC treated with second line abiraterone or enzalutamide)	Retrospective observational	Early PSA decline Overall survival Cancer-specific survival	Statin use was associated with prolonged OS (HR 0.47, 95% CI 0.35–0.63), cancer-specific survival (HR 0.43, 95% CI 0.32–0.58) and increased early >30% PSA declines (OR 1.63, 95% CI 1.03–2.60).	Gordon *et al.*[110]

(Continued)

Table 2. (Continued)

Study details and case numbers (*n*)	Study type	Outcome measures	Main observations	Reference
Statins and prostate cancer specific mortality				
n = 249,986 men	Retrospective cohort	Risk of developing PCa	Statin use was associated with increased PCa incidence (HR 1.07, 95% CI 1.02–1.12), lower risk of metastatic PCa (HR 0.69, 95% CI 0.61–0.79) and PCSM (HR 0.73, 95% CI 0.66–0.81).	Van Rompay *et al.*[111]
Taiwan Cancer Registry *n* = 5749 (locally advanced and metastatic PCa)	Retrospective cohort	Prostate Cancer Specific Mortality	Statin use was associated with a reduction in PCSM (HR 0.76, 95% CI 0.68–0.86) for metastatic disease but not locally advanced disease.	Wu *et al.*[112]
Taiwan National Health Insurance Research Database *n* = 15,264 (PCa + hyperlipidaemia)	Population cohort	Prostate Cancer Specific Mortality	Statins were associated with reduced PCSM (HR 0.84, 95% CI 0.73–0.97), and risk was inversely associated with dose of simvastatin.	Chen *et al.*[113]
Danish Cancer Registry *n* = 31,790 (PCa)	Prospective cohort	Prostate Cancer Specific Mortality	Post-diagnosis statin use was associated with lower PCSM (HR 0.83, 95% CI 0.77–0.89).	Larsen *et al.*[114]
n = 11,772	Prospective cohort	Prostate Cancer Specific Mortality	Post-diagnostic use of statins was associated with decreased PCSM (HR 0.76, 95% CI 0.66–0.88), with a more pronounced effect in those that also used statins before diagnosis (HR 0.55, 95% CI 0.41–0.74).	Yu *et al.*[115]
Metformin and Prostate Cancer risk				
Danish Cancer Registry *n* = 12,226 (PCa) *n* = 122,260 (controls)	Case Control	PCa risk	Metformin users were at decreased risk of PCa compared with never-users (OR: 0.84, 95% CI 0.74–0.96). Diabetics on no medication or on other oral hypoglycemics did not have a reduced risk of PCa.	Preston *et al.*[116]
Finnish randomized study of screening for PCa *n* = 78,615 (men)	Randomized controlled trial	Risk of developing PCa	Men using antidiabetic drugs had lowered PCa risk (HR 0.85, 95% CI 0.79–0.92) but increased risk of metastatic PCa (HR 1.44, 95% CI 1.09–1.91).	Haring *et al.*[117]
n = 85,289 (men and women)	Prospective cohort	Risk of developing PCa	Use of metformin reduced the risk of developing PCa compared to sulphonylureas (HR 0.92, 95% CI 0.88–0.97).	Ruiter *et al.*[118]
SEER database *n* = 2652 (diabetes + PCa)	Observational cohort	Risk of advanced PCa	Metformin users were less likely to be diagnosed with advanced PCa compared to nonusers (4.7% *versus* 6.7%, $p < 0.03$).	Raval *et al.*[119]
n = 9486 (diabetes)	Retrospective cohort	Risk of PCa	Metformin was associated with PCa incidence, but sulphonylurea and insulin were not.	Onitilo *et al.*[120]
National Health Insurance reimbursement database *n* = 395,481 (new diabetes)	Retrospective Cohort	Risk of developing PCa	Metformin use was associated with reduced risk of developing PCa, in a time-dependent manner (HR lowest tertile 0.74 (95% CI 0.70–0.79) *versus* HR highest tertile 0.23 (0.21–0.25)).	Tseng[121]
n = 1001 (PCa) *n* = 942 (controls)	Case control	PCa risk	Metformin use was associated with lower risk of PCa (OR 0.56, 95% CI 0.32–1.00) in Caucasian but not African American men.	Wright and Stanford[122]

(Continued)

Table 2. (Continued)

Study details and case numbers (*n*)	Study type	Outcome measures	Main observations	Reference
REDUCE study $n=540$ (diabetic men post negative prostate biopsy)	Single arm surveillance trial	Risk of developing PCa, and risk of higher grade PCa	Metformin use was not significantly associated with total (OR 1.19, $p=0.5$), low (OR 1.01, $p>0.9$) or high-grade (OR 1.83, $p=0.19$) PCa diagnosis.	Feng *et al.*[123]
$n=80,001$ (men)	Retrospective cohort	Risk of PCa	There was no association between metformin and risk of PCa in Asian or non-Asian men with diabetes.	Chen *et al.*[124]
$n=76,733$ (diabetic men)	Retrospective cohort	Risk of PCa	Use of metformin alone or metformin + statins was associated with a greater PCa incidence reduction in Hispanics compared with non-Hispanic whites, but not African Americans.	Wang *et al.*[125]
$n=185,667$ (men post first PSA) $n=18,574$ (men post first prostate biopsy)	Retrospective cohort	Risk of PCa	There was no significant association between antidiabetic medication and the risk of PCa.	Nordström *et al.*[126]
FINRISK $n=23,394$ (men)	Prospective cohort	Risk of PCa	No association between antidiabetic medications and PCa risk.	But *et al.*[127]
Prostate Cancer Data Base Sweden 3.0 $n=612,846$ (men)	Prospective cohort	Risk of developing PCa	Men with >1 year of T2DM had a decreased risk of PCa compared to men without T2DM (HR 0.85, 95% CI 0.82–0.88). Use of metformin was not associated with risk of PCa (HR 0.96, 95% CI 0.77–1.19).	Häggström *et al.*[128]
Fremantle Diabetes Study $n=1426$ (people)	Prospective cohort	Risk of developing PCa	Diabetes was not associated with PCa risk (RR 0.83, 95% CI 0.59–1.14)	Magliano *et al.*[129]
$n=145,617$ (diabetic men)	Prospective cohort	Risk of developing PCa	Metformin use in the previous year was associated with increased PCa risk (HR 1.53, 95% CI 1.19–1.96). Use during the previous 2–7 years was associated with lower PCa risk (HR 0.58, 95% CI 0.37–0.93.	Freedman *et al.*[130]
Metformin and risk of recurrence of localized disease				
$n=2441$ (localized PCa treated with radiotherapy)	Prospective cohort	Biochemical recurrence free survival	Metformin users had a 50% reduction in biochemical recurrence compared to non-metformin users (HR 0.5–0.6, $p=0.03$–0.04).	Taussky *et al.*[131]
$n=2901$ (localized PCa treated with radiotherapy)	Retrospective cohort	PSA-RFS, DMFS, PCSM, OS and development of CRPC	Metformin use was associated with an improvement in PSA-RFS (HR 1.99, 95% CI 1.24–3.18), DMFS (HR 3.68, 95% CI 1.78–7.62), PCSM (HR 5.15, 95% CI 1.53–17.35) and decreased development of CRPC in patients experiencing biochemical failure.	Spratt *et al.*[132]
$n=504$ (localized PCa treated with radiotherapy)	Retrospective cohort	3-year biochemical relapse-free survival	Metformin use was associated with decreased early biochemical relapse rates ($p=0.01$).	Zannella *et al.*[133]
$n=447$ (high-risk localized PCa treated with radiotherapy + ADT)	Retrospective cohort	Biochemical and distant failure	Metformin use was not associated with biochemical failure free survival or distant failure free survival.	Cadeddu *et al.*[134]
$n=2055$ (localized PCa treated with radiotherapy)	Retrospective cohort	Biochemical failure, metastasis, PCSM and OS	Metformin was not associated with biochemical failure, time to metastasis or OS, but there was a 1.5-fold increase in PCSM in patients on metformin and ADT.	Ranasinghe *et al.*[135]

(Continued)

Table 2. (Continued)

Study details and case numbers (*n*)	Study type	Outcome measures	Main observations	Reference
n = 371 (localized PCa treated with radical prostatectomy)	Retrospective cohort	Time to biochemical recurrence	There were no associations between metformin use, high metformin dose or duration of use and time to biochemical recurrence.	Allott *et al.*[136]
n = 746 (localized PCa treated with radical prostatectomy)	Retrospective cohort	Time to biochemical recurrence	Metformin use was not associated with biochemical-RFS (OR 0.662, $p = 0.13$).	Lee *et al.*[137]
n = 12,052 (localized PCa treated with radical prostatectomy)	Retrospective cohort	Biochemical recurrence	Metformin use was not associated with a reduction in biochemical recurrence, systemic progression, or adverse pathological features.	Kaushik *et al.*[138]
n = 616 (localized PCa treated with radical prostatectomy)	Retrospective cohort	Biochemical recurrence	Metformin use was not significantly associated with risk of biochemical recurrence (HR 0.94, 95% CI 0.6–1.5).	Patel *et al.*[139]
n = 1314 (localized PCa treated with radical prostatectomy)	Retrospective cohort	Biochemical recurrence	Antidiabetic drug use was not significantly associated with risk of biochemical recurrence.	Joentausta *et al.* (2016)[140]
n = 767 (diabetic men with PCa treated with radical prostatectomy)	Retrospective cohort	Biochemical recurrence	Neither statin nor metformin use was associated with biochemical-recurrence free survival.	Danzig *et al.*[141]
n = 6863 (localized PCa treated with radical prostatectomy)	Retrospective cohort	Biochemical recurrence	Diabetes with or without metformin use was not associated with biochemical RFS.	Rieken *et al.*[142]
n = 8 (cohort studies in localized PCa)	Meta-analysis	Recurrence free survival	Metformin use was associated with improved RFS in men with localized PCa (HR 0.60, 95% CI 0.42–0.87).	He *et al.*[143]
Metformin and risk of progression with hormone sensitive prostate cancer				
MASNMED *n* = 124 (high-risk locally advanced or metastatic HSPC)	Randomized controlled trial	CRPC-free survival	Metformin was associated with longer time to CRPC (HR 0.5, 95% CI 0.3–0.8).	Alghandour *et al.*[144]
Metformin and castration resistant prostate cancer				
n = 2832 (CRPC)	Retrospective cohort	PCa-Specific Survival, OS	Metformin use with docetaxel did not improve PCa specific survival (HR 0.96, $p = 0.66$) or overall survival (HR 0.94, $p = 0.39$).	Mayer *et al.*[145]
COU-AA-301 and COU-AA-302 (CRPC, abiraterone *versus* placebo) *n* = 1195 (COU-AA-301) *n* = 1088 (COU-AA-302)	Randomized control trials	Overall survival	OS was prolonged among those treated with metformin (pooled HR 0.77, 95% CI 0.62–0.95).	Wilson *et al.*[107]
AFFIRM, PREVAIL, PROSPER (CRPC, enzalutamide *versus* placebo) *n* = 1184 (AFFIRM) *n* = 1699 (PREVAIL) *n* = 1394 (PROSPER)	Randomized control trials	Overall survival	Metformin use was not associated with improved OS for AFFIRM + PREVAIL + PROSPER (HR 0.83, 95% CI 0.67–1.03).	Joshua *et al.*[109]
SAKK 08/09 *n* = 44 (CRPC)	Single-arm Phase II	PCa progression	36% of patients were progression free at 12 weeks and 9% were progression-free at 24 weeks. Two men had $a \geqslant 50\%$ reduction in PSA.	Rothermundt *et al.* (2[146]

(Continued)

Table 2. (Continued)

Study details and case numbers (*n*)	Study type	Outcome measures	Main observations	Reference
MetAb-Pro *n* = 25 (CRPC progressing on abiraterone)	Single-arm Phase II	PCa progression	Men were continued on abiraterone, with metformin added. Only 3/25 men were not progressing at 12 weeks, with no meaningful clinical benefit overall.	Mark *et al.*[147]
Metformin and overall survival/prostate cancer specific mortality				
n = 233 (diabetic men with PCa)	Retrospective cohort	Overall survival	Metformin use was associated with improved OS (HR 0.55, 95% CI 0.32–0.96).	He *et al.*[148]
n = 3837 (diabetic men with PCa)	Retrospective cohort	Prostate Cancer Specific Mortality	Metformin was associated with lower PCSM in a dose dependent fashion.	Margel *et al.*[149]

ADT, androgen deprivation therapy; BMI, body mass index; CI, confidence interval; CRPC, castration-resistant prostate cancer; DMFS, distant metastases free survival; HR, hazard ratio; HSPC, hormone sensitive prostate cancer; OR: odds ratio; PCa: prostate cancer; PCSM: prostate cancer specific mortality; PFS: progression free survival; RFS; recurrence free survival; RR: relative risk; TTP: time to progression; T2DM: type 2 diabetes mellitus.

meta-analysis of 15 cohort and 12 case-control studies found statin use was associated with a reduced risk of advanced PCa (RR 0.80, 95% CI 0.70–0.90).[102]

Statin use also modifies the association between high saturated fat intake and increased PCa aggressiveness. High saturated fat intake was associated with increased PCa aggressiveness, and this was attenuated in statin users compared with non-users.[150]

Two large meta-analyses found that statin use was associated with a reduction in disease recurrence following radiation therapy, but not radical prostatectomy.[103,104] The authors postulated that this may be explained by statin-induced radiosensitizing effects that have been demonstrated in both *in vitro* and *in vivo* models.[151,152] Statin use at the time of ADT initiation for HSPC prolonged median time to progression (statin users 27.5 months *versus* non-users 17.4 months, HR 0.83, 95% CI 0.69–0.99).[105] Concurrent statin use amongst men receiving ADT is associated with reduced overall mortality (HR 0.73, 95% CI 0.66–0.82) and reduced PCSM (HR 0.65, 95% CI 0.58–0.73).[153]

Although some studies have shown that concomitant use of statins with abiraterone in men with CRPC was associated with improved OS,[106] particularly in the post docetaxel setting (HR 0.76, 95% CI 0.63–0.93),[107] others have not shown a response.[108] A study of pooled data from three large randomized controlled trials (RCTs) of enzalutamide in CRPC found that statin use was associated with improved OS (HR 0.75, 95% CI 0.66–0.85).[109] A retrospective study of men treated with either abiraterone or enzalutamide in the post-docetaxel setting also found statin use was associated with improved OS (HR 0.57, 95% CI 0.46–0.71).[110]

Lastly, statin therapy is associated with improved PCSM.[103,111–115] This effect is most pronounced for patients who used pre-diagnosis statins in addition to post-diagnosis statins.[114,115]

The mechanisms for statins' anti-cancer effects are unclear, with two broad categories proposed: lipid-mediated and non-lipid mediated.[154] Although several large studies and a meta-analysis have found no association between total cholesterol or cholesterol fraction and total PCa risk,[155–157] they did demonstrate an association between serum cholesterol and aggressive PCa risk [odds ratio (OR) 0.61, 95% CI 0.39–0.98],[157] suggesting that lipid-lowering actions may contribute to statins' effects. However, statins have several off-target effects, including reducing systemic and local inflammation.[158–160] A trial of atorvastatin prior to radical prostatectomy found that men with high-grade PCa randomized to atorvastatin had lower histological inflammation ($p = 0.054$).[160] A gene set enrichment study of 10 statin users and 103 non-users with PCa found that T-cell receptor activation was the top differentially expressed pathway associated with statin

Table 3. Active trials targeting lipid metabolism in prostate cancer.

Intervention	Condition	Primary outcome	Trial registration	Recruitment status
PEACE-4: acetylsalicylic acid and/or atorvastatin	Castration resistant prostate cancer	Overall survival	NCT03819101	Recruiting
EST02: atorvastatin	Metastatic or recurrent prostate cancer	Time to castration resistance	NCT04026230	Recruiting
Evolocumab	Metastatic castration resistant prostate cancer	Change in circulating lipid biomarker	ANZCTRN12622001003763p	Not yet recruiting
Opaganib with enzalutamide or abiraterone	Metastatic castration resistant prostate cancer	Disease control status	NCT04207255	Recruiting
STAMPEDE: Androgen deprivation therapy + metformin	High-risk locally advanced and metastatic hormone-naïve prostate cancer	Overall survival	NCT00268476	Recruiting
Metformin	High risk localized prostate cancer following local treatment	PSA doubling time	NCT02176161	Completed, awaiting results
Metformin with enzalutamide	Castration resistant prostate cancer	Dose limiting toxicity	NCT02339168	Active, not recruiting
SAKK 08/15 PROMET – Salvage radiotherapy ± metformin	High risk localized prostate cancer after prostatectomy	Time to progression	NCT02945813	Terminated (prematurely closed by the SAKK board), awaiting follow-up
Increase omega-3 long chain fatty acids and reduce intake of saturated and trans fatty acids	Prostate Cancer on Active Surveillance	Effects on Lipid metabolism from blood and prostatic microenvironment	NCT01653925	Active, not recruiting
Low fat diet and fish oil	Prostate Cancer on Active Surveillance	Decrease in prostate cancer Decipher score	NCT02176902	Active, not recruiting
16 week exercise programme and continuous Fitbit monitoring	Prostate cancer on ADT	Improved atherosclerotic disease 10 year risk score through improvements in blood pressure, cholesterol and HDL	NCT05054296	Recruiting

use, with other pathways involved in inflammation also being significantly altered.[161] Another hypothesis is that statins may synergize with ADT by reducing intratumoural cholesterol, reducing the substrate for *de novo* androgen synthesis.[162]

There are ongoing trials of statin use in prostate cancer including the PEACE-4 and EST-02 trials (Table 3).

In addition to statins, there are other therapeutics, such as PCSK9 inhibitors, that also target cholesterol metabolism. PCSK9 modulates cholesterol metabolism by attaching to the low-density lipoprotein (LDL) receptor and reducing LDL-receptor mediated removal of LDLs from circulation.[163] There is good evidence for PCSK9 inhibitors in reducing cardiovascular disease.[164] PCSK9 is also involved in other biological processes, including cell cycle, inflammation, apoptosis, cancer cell invasion and metastases, and PCSK9 inhibitors can modulate these processes as off-target effects.[163,165]

There is also increasing evidence that there is aberrant PCSK9 expression in cancer. Cancer Genome Atlas RNA sequencing data showed differential expression of PCSK9 in cancer and matched normal samples.[165] Inhibition of PCSK9 through siRNA has a radioprotective effect in PCa cells by promoting cell viability.[166] A study of PCSK9 inhibitors in addition to anti-PD1 immunotherapy showed that PCSK9 inhibitors enhanced the efficacy of immunotherapy, albeit in a mechanism independent of cholesterol regulation.[167] There have been no trials of PCSK9 inhibitors as anti-cancer therapeutics.

Fibrates are another widely used class of medication for hypercholesterolaemia, acting to lower lipid levels.[168] Studies in PCa cell lines showed that fenofibrate inhibits the growth of androgen-independent PCa cells via apoptotic cell death, with activation of the mTOR/p70S6K survival pathway,[169] and through blockage of autophagic flux and induction of endoplasmic reticulum stress.[168] Fenofibrate also down-regulates the expressions of *AR* and *AR* target genes and induces oxidative stress.[170] Fenofibrate significantly inhibited *in vivo* growth of PCa in mice.[168] A study of fenofibrate in multiple myeloma was terminated early due to lack of accrual (NCT01965834). There have been no further clinical trials of fibrates in cancer.

Targeting sphingolipid signalling

There are numerous points in the sphingolipid metabolism pathway that may provide innovative targets for anti-cancer therapy, either alone or in conjunction with existing therapeutics.[171] This is particularly relevant given the evidence for elevated circulating sphingolipids being persistently associated with poor outcomes across all stages of PCa[51] suggesting that this is an actionable lipid profile.

SPHK1/2 inhibitors reduce the levels of the pro-survival sphingolipid sphingosine-1-phosphate (S1P), acting in the cytoplasm and the nucleus respectively. Two agents – PF-543, a SPHK1 inhibitor, and ABC294640 (opaganib), a SPHK2 inhibitor – show the most promise.

PF-543 is a potent SPHK1 selective inhibitor and *in vitro* and *in vivo* studies demonstrated its ability to inhibit breast and colon cancer cell growth and proliferation.[172] SPHK1 inhibition in PCa cell and animal models had chemo-sensitizing effects[172,173] and reduced enzalutamide resistance.[52] Similarly, SPHK1 inhibitors sensitize PCa to irradiation *in-vitro* by enhancing apoptosis.[174]

Opaganib is a SPHK2 inhibitor that inhibits tumour proliferation and migration *in-vivo*,[175] and has an off-target effect of dihydroceramide accumulation due to dihydroceramide desaturase (DES) inhibition.[176] Opaganib overcomes *de novo* enzalutamide resistance in androgen-independent PCa cells *in-vitro*.[52] A phase 1 trial of opaganib in patients with advanced cancer demonstrated a rapid reduction in plasma levels of S1P, with 40% of evaluable patients achieving stable disease and 6% achieving partial response.[177]

These pre-clinical and early-phase studies support further investigation of SPHK1/2 inhibitors in combination with chemotherapy, radiation, or anti-androgen therapy, to overcome therapeutic resistance.

Fingolimod is a structural analogue of sphingosine and is a functional inhibitor of the S1P-receptor.[178] It reduces inflammatory relapses in multiple sclerosis by internalizing the S1P-receptor and sequestering T lymphocytes in lymph nodes.[179] Its role as an anti-cancer therapy remains under investigation. Pre-clinical studies of fingolimod show that it promotes apoptosis,[180] reduces tumour vascularization and angiogenesis,[181] and is antiproliferative[182] in PCa cells. Fingolimod also sensitizes PCa cells to radiotherapy through SPHK1 inhibition.[183] No clinical trials have assessed the efficacy of fingolimod in cancer, as its action preventing T cell trafficking and activation prevents the immune response from killing cancer cells.[184] An option could be to use fingolimod in combination with SPHK2 inhibition to prevent the phosphorylation of fingolimod to SPHK2, the by-product which causes the T cell suppression.[178]

Sonepcizumab and sphingomab are monoclonal antibodies against S1P, causing its depletion. They have anti-angiogenic and anti-tumorigenic effects, slowing tumour progression and normalizing blood vessels to minimize tumour hypoxia in murine models.[185,186] Treatment of PCa cell lines with sphingomab significantly inhibited cell proliferation.[187] A phase II trial of sonepcizumab in advanced renal cell carcinoma did not improve PFS.[188]

Fenretinide, a retinoid analogue, targets DES1, the enzyme responsible for conversion of dihydroceramide to ceramide. This increases dihydroceramide, which induces autophagy and cell cycle arrest in cancer cells.[189] Further, fenretinide induces cell death through apoptosis, ER stress and accumulation of reactive oxygen species.[184,190,191] In PCa, DES1 is a target gene of the *AR*, and knockdown of DES1 impaired migration of androgen-independent C42 PCa cells.[192] A phase II randomized, trial of fenretinide in men with localized PCa prior to prostatectomy demonstrated no change in TGF-α between those treated with fenretinide *versus* control.[193] A phase II trial of fenretinide in biochemically recurrent PCa found that 30% of patients achieved PSA-stable disease, with no patients experiencing PSA-responses.[194] A phase II trial of fenretinide in CRPC had a PSA response rate of 4%, with 52% of patients not progressing within 6 weeks of starting fenretinide.[195] It is important to note that the trials of fenretinide utilized biomarker or PSA-response endpoints rather than clinical endpoints, and there is concern that fenretinide-induced oxidative stress could cause PSA increases without cancer progression.[191] Nevertheless, trials of fenretinide in other cancers also found limited efficacy.[196,197]

Targeting transcription factors

Targeting the transcription factors SREBP1/2 are another approach that targets multiple aspects of lipid metabolism simultaneously, as they are master regulators of many lipogenic genes. There is overexpression of SREBP1 in some PCa biopsies and xenograft models of CRPC.[198] Fatostatin, an SREBP inhibitor, has activity in *in vitro* and mouse models. Fatostatin inhibits cancer cell proliferation, invasion and migration in PCa cell lines and causes cell-cycle arrest and apoptosis and has antitumour efficacy in a xenograft mouse model. It also decreased expression of *AR* and PSA.[199,200] The combination of fatostatin and docetaxel enhanced docetaxel sensitivity compared with single agent treatment of PCa cells *in vitro* and *in vivo*.[201]

Other SREBP inhibitors such as *Ganoderma tsugae*, a Chinese herbal product,[202] micro-RNA-185 and m342,[203] and nelfinavir and nelfinavir analogues[204,205] also have activity in PCa cell lines. Silibinin decreases nuclear levels of SREBP1/2 and their target genes in PCa cells, but not in normal prostate epithelium.[206] A phase I study of silibinin in PCa found that none of the 13 patients achieved a PSA response, but several had stable PSA levels.[207] Silibinin was not taken into phase II trials.

Targeting lipid uptake into cells

CD36, a fatty acid transporter, is critical in the production of lipid biomass and the generation of oncogenic signalling lipids in PCa. Deleting CD36 in the prostate of cancer susceptible *Pten*-null mice slowed cancer progression. CD36 monoclonal antibody therapy reduced cancer severity in patient-derived xenografts.[76] CD36 binds to diverse ligands, including thrombospondin-1, and can be inhibited by thrombospondin-1 mimetics.[208] The thrombospondin-1 mimetic, ABT-510, reached phase II clinical trials of varied cancers, but failed due to ineffective performance and severe adverse events.[208–210]

Targeting lipogenesis and lipid metabolism

PCa progression is notable for its enhanced level of *de novo* fatty acid synthesis in tumour cells, which has generated considerable interest in targeting key enzymes involved in this process.[211,212] The FASN enzyme catalyses the rate limiting step of this process, and a range of FASN inhibitors have demonstrated promising efficacy in pre-clinical models of PCa.[213] However, clinical translation of this class of inhibitors has been limited, largely due to off-target effects, poor solubility and toxicity of early agents evaluated. The advent of TVB-2640, an orally available FASN inhibitor with an acceptable safety profile,[214] has renewed interest in FASN as a clinical target and studies have now been initiated across multiple cancers. Effective inhibition of FASN can also be achieved using proton pump inhibitors such as omeprazole, which is currently being evaluated in prostate (NCT04337580) and breast cancer.[215]

More recently, a novel irreversible FASN inhibitor, IPI-9119, has been developed.[216] It is orally available with acceptable pharmacology, so geared towards clinical translation. IPI-9119 was found to suppress growth of CRPC models and enhanced responsiveness to the clinical ARSI enzalutamide, which was mechanistically linked to reduced protein levels of *AR* and the *AR-V7* constitutively active variant.[217]

As agents with improved pharmacological and toxicological profiles continue to be developed, the challenge remains to define tools that will aid in selection of lipogenic tumours and patients who are most likely to respond, and which combinations of agents will be optimally used with FASN inhibitors. A broadening of focus to include inhibitors of other lipogenic enzymes beyond FASN (e.g. ACACA, ACLY),[218] some of which have been investigated preclinically,[60] may also yield new opportunities.

The reliance of PCa on mitochondrial FAO is a vulnerability that could potentially be exploited for patient benefit; moreover, the differential dependence of malignant prostate epithelial cells *versus* normal tissues represents a therapeutic window. Suppressing FAO would reduce energy production that is required for rapidly growing tumours and impinge on other features of malignancy, such as survival and metastasis.[91]

Two well-studied FAO inhibitors are etomoxir and perhexiline, both of which target carnitine palmitoyltransferase-1, an enzyme required for transport of fatty acyl chains from the cytosol into the intermembrane space of the mitochondria and subsequent FAO. We and others have demonstrated that etomoxir and perhexiline exhibit potent anti-tumour activity in various preclinical models of PCa.[63,78,219] However, clinical development of etomoxir as a treatment for heart failure and type II diabetes was terminated due to cardiac and hepatic toxicity,[220,221] casting doubt on its potential as a cancer therapy. Trimetazidine and ranolazine, anti-angina drugs that inhibit the mitochondrial trifunctional protein (TFP) involved in β-oxidation, have also shown potential in pre-clinical models of various malignancies, including PCa,[222–224] but are yet to be tested in cancer clinical trials.

Beyond inhibitors of enzymes directly involved in FAO, indirect strategies to block this process are being elucidated and tested as anti-cancer therapies. Loo *et al.* and colleagues recently demonstrated that retinoids reverse epithelial-mesenchymal transition and reduce tumorigenicity of triple-negative breast cancer by channelling fatty acids from FAO towards lipid storage.[92]

Targeting metabolic syndrome

Epidemiological studies of metformin in patients with PCa have shown inconsistent results (Table 2).[225] Several studies[116–122] have reported an inverse relationship between metformin and PCa risk, but others have failed to show an association.[123–129] A population-study of almost 150,000 diabetic men found that metformin use within the previous year was associated with increased PCa risk (HR 1.53, 95% CI 1.19–1.96), whereas use during the previous 2–7 years was associated with lower PCa risk (HR 0.56, 95% CI 0.37–0.93). The researchers speculated that PCa is disrupting glycaemic control shortly before diagnosis, or that surveillance bias was responsible for the increased PCa risk.[130]

Several studies have examined the relationship between metformin and recurrence following treatment for localized disease. The effect of metformin in patients treated with radiotherapy is promising, with some studies showing an association with improved outcomes, with up to a 50% reduction in biochemical relapse.[131–133] However others found no significant difference with metformin use.[134,135] In contrast, seven studies of metformin use amongst men treated with radical prostatectomy all found no association with risk of biochemical relapse.[136–142] A meta-analysis of eight studies with all treatment types found that metformin use was associated with improved recurrence free survival in men with localized PCa (HR 0.60, 95% CI 0.42–0.87).[143]

MANSMED is an RCT of metformin in addition to standard hormonal treatments in HSPC. Patients receiving metformin had a longer time to CRPC compared with those receiving standard care (HR 0.5, 95% CI 0.3–0.8).[144] This will be further investigated in the metformin arm of the STAMPEDE study for men with HSPC (Table 3).[226]

Metformin use in CRPC has been evaluated in retrospective cohorts, with improved outcomes in men treated with abiraterone,[107] but not docetaxel[145] or enzalutamide.[109] There have been two prospective clinical trials of metformin in men with CRPC, showing conflicting results. The SAKK 08/09 trial, a phase II study of metformin in CRPC, found that of the 44 enrolled patients, 36% were progression free at 12 weeks, and 9% progression-free at 24 weeks. Two men had a $\geqslant$50% reduction in PSA.[146] The MetAb-Pro trial, a phase II study of metformin in addition to abiraterone in patients with CRPC progressing on abiraterone, found no meaningful benefit of metformin therapy.[147]

Finally, metformin use in diabetic men with PCa improves OS[148] and PCSM.[149]

Targeting dietary factors

There is an association between dietary fat intake and PCa risk (Table 4). Two studies have identified an association between high saturated-fat intake and risk of advanced and fatal PCa,[227] or aggressive PCa.[150]

Numerous studies have examined the association between PCa progression and post-diagnosis fat

Table 4. Evidence for the effect of a high fat diet in prostate cancer.

Study details and case numbers (n)	Study type	Outcome measures	Main observations	Reference
High-fat diet				
NIH-American Association of Retired Persons Diet and Health *n* = 288,268 (men) including *n* = 23,281 (PCa)	Prospective cohort	Risk of developing PCa	Saturated fat intake was associated with increased risk of advanced (HR 1.21, 95% CI, 1.00–1.46) and fatal PCa (HR 1.47; 95% CI, 1.01–2.15). Total, mono- and polyunsaturated fat intakes were not associated with PCa risk.	Pelser *et al.*[227]
North Carolina-Louisiana PCa Project *n* = 1854 (PCa) including *n* = 321 (aggressive PCa)	Prospective cohort	Risk of aggressive PCa	High saturated fat intake was associated with increased aggressive PCa. High cholesterol intake was associated with aggressive PCa in European, but not African Americans.	Allott *et al.*[150]
n = 405 (localized PCa post radical prostatectomy)	Prospective cohort	Biochemical failure	High-saturated fat diets were associated with increased biochemical failure, and had shorter biochemical-failure-free-survival compared to low saturated fat (26.6 *versus* 44.7 months, *p* = 0.002).	Strom *et al.*[228]
n = 525 (PCa)	Prospective Case control	Time to PCa death	High post-diagnosis total fat intake and certain saturated fatty acids were associated with worse PCa survival, particularly in localized disease.	Epstein *et al.*[229]
n = 384 (PCa)	Prospective cohort	Prostate Cancer Specific mortality	Post-diagnosis saturated fat consumption was associated with disease-specific survival (*p* = 0.008). High saturated fat (but not total fat) intake was associated with increased PCSM (RR 3.1, 95% CI 1.3–7.7).	Meyer *et al.*[230]
Physicians Health Study *n* = 926 (nonmetastatic PCa)	Prospective cohort	Prostate Cancer Specific Mortality	Men who obtained 5% more of their calories from saturated fat and 5% less from carbohydrate after diagnosis had an increased PCSM (HR 2.78, 95% CI 1.01–7.64).	Van Blarigan *et al.*[231]
Health Professionals Follow-up Study *n* = 4577 (non-metastatic PCa)	Prospective cohort	Risk of lethal PCa and All-cause mortality	Replacing 10% of energy from carbohydrates with vegetable fat associated with lower lethal PCa (HR 0.71, 95% CI 0.51–0.98). No association with saturated, monounsaturated, polyunsaturated or trans fats.	Richman *et al.*[232]

CI, confidence interval; HR, hazard ratio; OR, odds ratio; OS, overall survival; PCa, prostate cancer; PCSM, prostate cancer specific mortality; RR, relative risk.

intake, with conflicting results. Two studies found no association between total dietary fat and PCSM.[229,230] There was mixed evidence for the association between saturated fat intake and PCSM, with two studies showing an association,[230,231], two finding no association.[229,232] One study of men following radical prostatectomy found that a high-saturated fat diet was associated with increased biochemical failure.[228]

The possible mechanisms that fat intake could increase PCa carcinogenesis include the effect on hormonal regulation and androgen levels, oxidative stress, inflammation, exposure to toxic pesticides and specific effects of particular fatty acids.[233] Preclinical studies have identified numerous mechanisms for the changes seen with a high fat diet including upregulation of pro-inflammatory cytokines[234–236] including IL6[237]

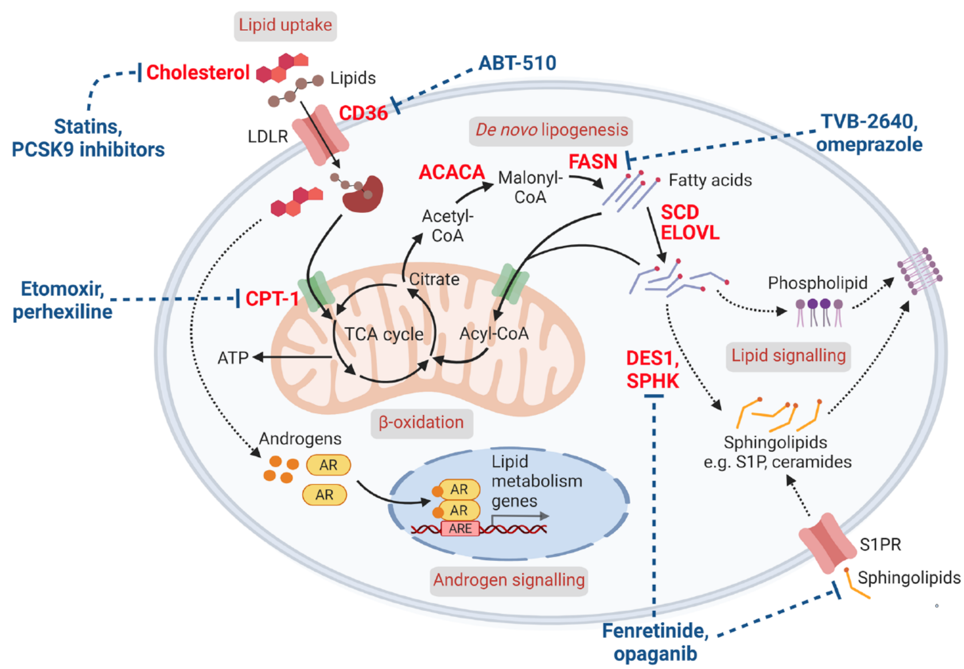

Figure 1. Intracellular lipid metabolism and targets for lipid therapy.
Key: red colour indicates therapeutic targets and blue colour indicates drug therapies.
ACACA, acetyl-coA carboxylase alpha; AR, androgen receptor; ARE, androgen response elements; ATP, adenosine triphosphate; CPT-1, carnitine palmitoyltransferase 1; FASN, fatty acid synthase; LDLR, Low density lipoprotein receptor; PCSK9, Proprotein convertase subtilisin/kexin type 9; SCD, stearoyl-CoA desaturase; SPHK, sphingosine kinase; S1P, sphingosine-1-phosphate; TCA, tricarboxylic acid.

and macrophage inhibitory cytokine-1 (MIC-1),[238] reduced antioxidants,[239] altered miRNA expression,[240] signal transducer and activator of transcription-3 (STAT3) upregulation,[241] amplification of the MYC programme,[242] and increased insulin and IGF-1 signalling.[243]

Studies examining the effects of a high fat diet in a mouse model of PCa showed increased risk of metastases,[200] and increased PCa growth, potentially mediated through histamine signalling.[244] A mouse xenograft model of PCa showed that tumour growth was higher in mice fed a high-fat diet, and exercise did not overcome these changes, suggesting that diet may be more influential in PCa progression than exercise.[245]

Future directions

Aberrant lipid metabolism appears to be associated with poor outcomes, from risk of developing PCa to the risk of dying from metastatic PCa. However, there are now opportunities to target this vulnerability by optimizing the lipid metabolic environment. For example, prevention of PCa through avoidance of obesity and potentially the use of statins is an option, although this requires prospective trials to establish this.

Lipid-targeted drugs are unlikely to replace current highly effective therapeutics in metastatic PCa, but may be used in combination to improve response rates and longevity of cancer control. The relationship between adverse genomic PCa factors and elevated sphingolipids in men with mCRPC underlines that there is interplay between many aspects of more aggressive cancers and lipid metabolism. Furthermore, new liquid-biopsy lipid biomarkers may assist in defining the best populations of men to target for lipid metabolic therapy. The potential lipid targets described in this review optimize the 'host' metabolic environment, affect the TME through interplay between lipids and immune cells and target lipid signalling pathways within prostate cancer cells. However, prospective clinical trials remain the key to identifying which strategy is most effective in humans, potentially incorporating a precision metabolic approach through companion biomarkers.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contribution(s)
Tahlia Scheinberg: Data curation; Investigation; Writing – original draft; Writing – review & editing.

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Acknowledgements
We thank Chui Yan Mah for her assistance with the preparation of figures.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: TS is supported by Australian Government Research Training Programme (RTP) Scholarship and Sydney Catalyst Top-up award. BM is supported by Australian Government RTP Scholarship and University of Sydney Merit Award. L.M.B. and L.A.S are supported by Principal Cancer Research Fellowships (PRF1117 and PRF2919, respectively) awarded by Cancer Council's Beat Cancer project on behalf of its donors, the state Government through the Department of Health and the Australian Government through the Medical Research Future Fund. L.M.B, L.A.S and L.G.H are supported by the Movember Foundation/Prostate Cancer Foundation of Australia (MRTA3). L.M.B is supported by The US Department of Defense (PC180582) and the Cancer Council NSW (2013255). Work in LAS's lab is also supported by Cancer Australia (2001432), The Hospital Research Foundation (C-PJ-126-2019), the Freemasons Centre for Male Health and Wellbeing and Flinders Foundation. LGH is supported by the National Health and Medical Research Council of Australia (GNT1196225).

Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
Not applicable

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