A role for cholesterol in prostate cancer: a Boston-Ireland collaboration under the Professor John Fitzpatrick Fellowship

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Prostate cancer is a common and often chronic disease in Western society, and almost half of all male cancer survivors in both the United States (US) [1] and Ireland (http://www.ncri.ie/sites/ncri/files/factsheets/FACTSHEET_prostate_1.pdf) suffer from prostate cancer. Approximately one third of prostate cancer patients will experience recurrence within a decade of primary treatment. Androgen deprivation therapy (ADT) is one of the treatments for recurrent prostate cancer. When ADT is started after cancer can be seen on scans, resistance nearly always develops within 18 months, and 10-20% of patients will develop castrate resistant prostate cancer (CRPC) within five years of initial diagnosis – currently an incurable disease [2]. Response to therapy and time to disease progression varies between individuals and a number of lifestyle factors may contribute, including obesity and its associated co-morbidities.

According to the World Health Organization, approximately one third of US adults have a body mass index of ≥30 kg/m^2 and are therefore classified as obese, whereas one quarter of adults meet this definition in Ireland. Obesity is associated with more advanced prostate cancer at diagnosis, higher risk of recurrence and increased prostate cancer-specific mortality [3]. While the mechanisms contributing to the obesity-prostate cancer link are not completely understood, a number of obesity-associated co-morbidities can influence prostate tumorigenesis. These include dyslipidemia, a metabolic disorder characterised by elevated circulating levels of cholesterol and/or triglycerides (Table 1) that affects almost 40% of adults worldwide [4].

Dyslipidemia and prostate cancer: evidence from laboratory studies

Cholesterol is an essential plasma membrane component of animal cells, being crucial in maintaining cell membrane fluidity, and in regulating intracellular signalling processes. Relative to cells of other organs, normal prostate epithelial cells have high cholesterol content, which increases during progression to prostate cancer [5], suggesting that cholesterol accumulation may accelerate tumour progression. Metabolomic profiling of human prostate tumours indicated higher levels of cholesterol in prostate cancer bone metastases compared to benign or localized disease [6]. Epigenetic silencing of the cholesterol efflux transporter, ABCA1, resulted in

Table 1: Guidelines for serum lipids levels in men, according to the National Cholesterol Education Program [22], in milligrams per deciliter (units commonly used in US) and in millimoles per liter (units commonly used in Europe)

	Desirable	Borderline	Abnormal
Total cholesterol	<200 mg/dl <5.0 mmol/l	200-249 mg/dl 5.0-6.2 mmol/l	≥240 mg/dl ≥6.2 mmol/l
Low density lipoprotein	<130 mg/dl <3.3 mmol/l	130-159 mg/dl 3.3-4.1 mmol/l	≥160 mg/dl ≥4.1 mmol/l
High density lipoprotein	≥60 mg/dl ≥1.6 mmol/l	40-59 mg/dl 1.0-1.6 mmol/L	<40 mg/dl <1.0 mmol/L
Triglyceride	<150 mg/dl <1.7 mmol/l	150-199 mg/dl 1.7-2.3 mmol/l	≥200 mg/dl ≥2.3 mmol/l

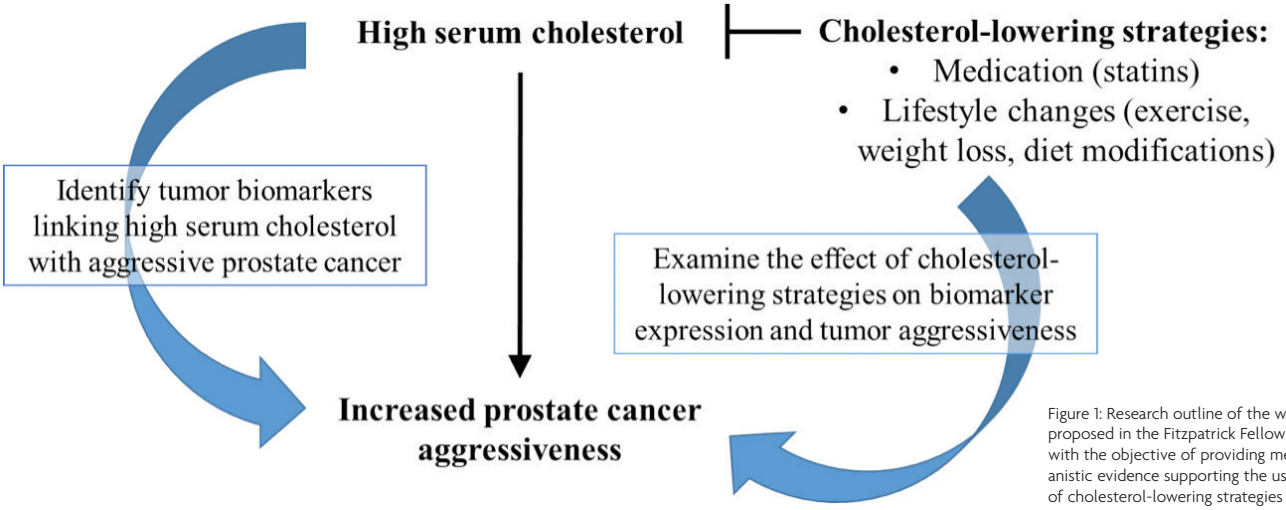

Figure 1: Research outline of the work proposed in the Fitzpatrick Fellowship, with the objective of providing mechanistic evidence supporting the use of cholesterol-lowering strategies to improve prostate cancer outcomes.

accumulation of intracellular cholesterol in prostate cancer cell lines, and was positively correlated with high Gleason grade in human prostate tumours [7]. Cholesterol is the precursor for androgen biosynthesis and may contribute to persistence of intratumoural androgens, despite achieving castrate serum levels with ADT. Indeed, high serum cholesterol increased intratumour androgen levels in mouse models of prostate cancer [8], and cholesterol-driven intratumoural de novo steroidogenesis was upregulated during progression from androgen-sensitive disease to CRPC in mice [9]. Lowering the level of serum cholesterol through dietary intervention and/or administration of the cholesterol uptake inhibitor, ezetimibe, reduced tumour androgen levels and slowed tumour growth rate in mouse prostate cancer [8]. In addition to its role as the precursor for androgen biosynthesis, cholesterol drives prostate cancer growth in mice by heightening inflammation and increasing Akt signalling [10], indicating several potential mechanisms contributing to a cholesterol-prostate cancer link.

Dyslipidemia and prostate cancer: evidence from epidemiologic studies

In support of laboratory evidence, epidemiology has shown that high serum cholesterol is associated with advanced prostate cancer, but not with all prostate cancer [11]. Although studies are few, epidemiologic data also suggest a positive association between elevated serum cholesterol and triglycerides and prostate cancer recurrence [12]. Several large prospective studies suggest a positive, albeit modest, association between dyslipidemia and prostate cancer-specific mortality. The UK-based Whitehall study, comprised of ~18,000 men and 600 prostate cancer deaths occurring during 40 years of follow-up, reported that high cholesterol was associated with a modestly elevated risk of prostate cancer-specific mortality [13]. In contrast, the Metabolic Syndrome and Cancer Project, comprising almost 300,000 Northern European men and over 1,000 prostate cancer deaths, reported similar rates of prostate cancer-specific mortality in men with normal or elevated triglyceride and cholesterol levels [14]. Finally, the findings of a large prospective study in the Asian-Pacific region indicated a positive association between high cholesterol and increased prostate cancer-specific mortality, but it was not statistically significant [15]. However, the strongest evidence for a cholesterol-prostate cancer link comes from studies of statins and prostate cancer. Statins are a class of medication that lower serum cholesterol levels by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme for cholesterol synthesis in the liver. They are among the most commonly-prescribed drugs in the US and Ireland, and are well-tolerated drugs, with few major side effects [16]. Of >30 observational studies on the use of statins and prostate cancer risk published to date, the majority support the hypothesis that statins reduce the risk of advanced prostate cancer. Other epidemiologic studies strongly support a role for statins in lowering prostate cancer-specific mortality [17]. These include an analysis of a population-based electronic database in the UK containing data from almost 12,000 men with prostate cancer, which found that taking statins reduced the risk of death from prostate cancer, with a larger effect in men who had commenced before prostate cancer diagnosis, compared with those who started taking statins after prostate cancer diagnosis [18]. Naturally there are the known benefits of controlling cholesterol levels for the purposes of cardiovascular disease prevention to consider.

A role for exercise and weight loss?

A number of lifestyle changes can help to lower cholesterol levels, including exercise and weight loss. Although obesity and increased co-morbidity effects relate to prostate cancer-specific mortality, the effect of weight loss on prostate cancer-specific outcomes has not been widely studied [11]. One goal of the Fitzpatrick Fellowship is to identify tumour biomarkers associated with dyslipidemia where their expression is counteracted by cholesterol-lowering lifestyle changes, including statins, exercise and/or weight loss (Figure 1). This objective should be achieved in an observational setting using the Harvard-based Health Professionals Follow-up Study (HPFS), where biennial questionnaires are used to record changes in anthropometric characteristics and physical activity levels with time, and to assess baseline obesity status and

calculate weight change in the years preceding diagnosis of prostate cancer. This will also be studied in a clinical trial setting using ExPeCT, an ongoing exercise intervention trial in Irish patients with metastatic prostate cancer.

Public health relevance

Understanding the effects of dyslipidemia in prostate cancer will be important for improving public health. The most recent estimate of the global prevalence of high cholesterol was 39%, with the highest prevalence in Europe (54% for both sexes), followed by the US (48% for both sexes; WHO - http://www.who.int/gho/ncd/risk_factors/cholesterol_text/en/). The prevalence of dyslipidemia is even higher among men with advanced prostate cancer and CRPC, given that long-term ADT exacerbates metabolic abnormalities [19]. As such, understanding mechanisms linking dyslipidemia with prostate cancer progression will be of considerable importance for a large proportion of prostate cancer patients. Furthermore, high cholesterol can be effectively treated in the vast majority of individuals by dietary changes (e.g. lowering saturated fat intake), exercise and weight loss, and/or cholesterol-lowering medication (statins). Therefore, in contrast to established risk factors for prostate cancer (age, African American race, and family history of prostate cancer; none of which can be modified), patients can try to normalize their lipid levels. Prostate cancer diagnosis can be a "teachable moment" (i.e. an event which could trigger a change in patient behaviour); if a causal link could be established between dyslipidemia and progression, this might influence treatment protocols. Finally, it is estimated that 45% of deaths worldwide can be attributed to either cardiovascular disease or cancer [20], with prostate cancer being the second most common cause of male cancer deaths [21]. Therefore, understanding the role of dyslipidemia as a shared risk factor for both of these common causes of mortality has potential not only to extend prostate cancer-specific survival, but to improve quality of life and extend overall survival in these patients.

Conclusions

Identification of risk factors contributing to therapeutic resistance and disease progression is an important challenge in prostate cancer research. Treatment strategies for CRPC are evolving, with some novel agents showing improvements in overall survival rates. However, it is currently impossible to predict individual response to therapy and there is no way of selecting which patients should receive specific therapies. The contribution of the work outlined in the Fitzpatrick Fellowship is expected to be the identification of dyslipidemia-associated tumour biomarkers that can be predictive of response to therapy and prostate cancer-specific outcomes, and that can be reversible through statins, exercise and/or weight loss. This contribution will be important in customising therapies to individuals likely to show the best responses, alongside complementary approaches that will prolong survival of prostate cancer patients. The work proposed in this Fitzpatrick Fellowship bridges epidemiology and molecular biology, linking colleagues in biostatistics, molecular pathology, cancer biology and genetics in Boston and Ireland. A notable strength of the Harvard School of Public Health is its integration into the Dana Farber/Harvard Cancer Centre, the largest comprehensive cancer centre in the world, increasing opportunities for collaboration with clinical colleagues, and acting as a venue for epidemiologic studies, including the HPFS. Finally, the Fitzpatrick Fellowship will strengthen existing ties between the Harvard School of Public Health and the Institute for Molecular Medicine at Trinity College Dublin in cancer biology, epidemiology, clinical practice and population health, with the ultimate goal of making a real and lasting difference to prostate cancer patients and their families on both sides of the Atlantic and worldwide.

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