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Platinum Priority – Editorial

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Statins and Prostate Cancer: Bias, Precision Medicine, or Population Health?

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Imagine there was a new therapy against prostate cancer. A therapy that delayed symptoms from distant metastases. A therapy that prolonged life. A therapy that was beneficial for comorbidities. A therapy that was taken by mouth and did not require ongoing laboratory monitoring. A therapy that had a safety profile difficult to distinguish from placebo [1]. A therapy that was available worldwide at less than $1 a day.

New medications that meet this aspirational list of requirements are rare. The mere possibility that an approved drug might tick all these boxes explains the continued interest in repurposing cholesterol-lowering statin medications for prostate cancer. Do statins meet these requirements?

In 2006, a prospective cohort study found that statin users developed metastatic or fatal prostate cancer less frequently than non-users [2]. Several observational studies since then were large, had sufficiently long follow-up for metastases and cancer death, and appropriately used the toolkit of pharmacoepidemiology. Statin users had better prostate cancer outcomes when aggressive disease was in focus (Table 1).

The study by Hamilton et al [3] in this issue of *European Urology* is among the few that evaluated statins among men treated with radiation and androgen deprivation therapy (ADT). The authors conducted an observational analysis of statin use and prostate cancer mortality in the Canadian Cancer Trials Group PR-7 trial that randomized to intermittent versus continuous ADT. The trial included patients with rising prostate-specific antigen after primary or salvage radiation therapy between 1999 and 2005. Of the 1364 patients followed for a median of 7 yr, 219 died from prostate cancer. A total of 1263 men were still on trial in 2004 when statin data were first collected among survivors using case-report forms. The main result is that statin users, compared to non-users, had lower rates of prostate cancer death and all-cause mortality.

How can this result be interpreted: as description, prediction, or causation? *Descriptions* such as the patient counts above or Kaplan-Meier curves in the current study [3] summarize the data but are not intended for claims beyond a single study. *Prediction* refers to models that quantify the association between predictors and outcomes. These can be complicated machine learning models with thousands of inputs, or a univariable Cox regression model with a single unadjusted hazard ratio for statin use and prostate cancer mortality (here: 0.64, 95% confidence interval 0.48–0.86). All the usual predictive models, and thus all the current "artificial intelligence" techniques, have a certain "conservatism" in common: they focus on the world as it is. Statin users will behave like statin users, be it because of the statin or something else. *Causation* ("counterfactual prediction"), by contrast, is about making statements about the world if one specific factor were different. What if statin non-users became statin users because we prescribed statins?

The study asks for causal interpretations, and Hamilton et al [3] caution us about potential residual confounding and confounding by indication—concerns relevant for causation, not prediction. We would not need to worry about confounding if statin users and non-users were exchangeable in their risk of prostate cancer mortality, except for their statin use. Randomization to a statin or control would guarantee exchangeability in an ideal trial. However, statin use was not randomly assigned, and statin users were presumably more likely than non-users to have clinical indications for statin use, such as cardiovascular disease

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Table 1 – Select observational studies on statin use and prostate cancer outcomes

Setting	Population	Outcome	HR (95% CI)	Refs
Population-based registry study (UK)	Cancer-free men	Total PCa	0.98 (0.85–1.13)	[4]
Prospective cohort study (USA)	Cancer-free men	Metastatic PCa or PCa death	0.76 (0.60–0.96)	[2,7]
		PTEN-intact PCa	1.18 (0.95–1.48)	[7]
		PTEN-null PCa	0.40 (0.19–0.87)	[7]
Hospital-based cohort (USA)	Men with PCa starting ADT	PCa progression on ADT	0.83 (0.69–0.99)	[6]
Population-based registry study (UK)	Men with newly diagnosed PCa	PCa death	0.76 (0.66–0.88)	[9]
Nationwide registry study (Denmark)	Men with newly diagnosed PCa	PCa death	0.83 (0.77–0.89)	[10]
	Subgroup: RT and ADT as primary therapy	PCa death	0.60 (0.45–0.80)	[10]
Clinical trial (Canada)	Men with PCa and rising PSA after RT, starting ADT	PCa death	0.65 (0.48–0.87)	[3]

ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; PCa = prostate cancer; PSA = prostate-specific antigen; Refs = references; RT = radiation therapy.

(confounding by indication) and its risk factors. Thus, we need to assume that the covariates in the multivariable regression model—age at enrolment, time since radiation therapy, prostate-specific antigen at enrolment, and prior use of ADT—are sufficient to achieve exchangeability between statin users and non-users (otherwise there is residual confounding). In this study, as in many clinical trials analyzed as observational studies, detailed and repeatedly measured data on smoking, obesity, diet, physical activity, medication and supplement use, non-oncologic diagnoses, and many other important factors were unavailable. It is comforting that the estimates are compatible with population-based and prospective cohort studies that controlled for additional confounders and had more detailed data on statin use (Table 1).

Even in an ideal world, observational analyses always have to consider confounding. Other issues in observational studies of statins, such as time-related biases, are entirely avoidable by design [4]. Hamilton et al [3] took measures to reduce immortal time bias and they assured that the late start for data collection on statin use did not introduce bias. They also show that the association between statin use and prostate cancer mortality was not entirely driven by competing risks of cardiovascular death.

Ultimately, an answer to what extent statins actually meet requirements as an effective prostate cancer treatment requires randomized controlled trials. Pioneers have been moving ahead with smaller-scale trials. One insight gained from such trials is that atorvastatin accumulates in the prostate at higher concentrations than in plasma [5]. Yet defining the inclusion criteria for trials is a challenge. Men treated with ADT are an appealing group. “Precision medicine” approaches could attempt to identify predictive biomarkers for tumors more likely to respond to statins. For example, SLCO transporters might be involved in statin effects [6]. Statins might have a greater effect against tumors with activated PI3K signaling, as preclinical work and a single observational study suggest [7].

More utility for population health might be in a less “precise” approach. A generic, inexpensive medication such as a statin may not fit well with a companion biomarker test, and a molecularly defined subset may prove elusive. Interest in statins and prostate cancer stems from large studies with modest effect sizes, not from case reports of complete tumor responses. Pragmatic, large trials of statins among men with prostate cancer with generous inclusion criteria can focus on cardiovascular events and all-cause mortality. After all, cardiovascular events are the leading cause of death among men with prostate cancer, with risks generally far beyond thresholds for primary preventative statin use [8]. Statins reliably reduce cardiovascular risk. A potential beneficial effect on cancer endpoints would be a bonus, one that studies like the one by Hamilton et al [3] continue to add hope for.

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