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We read with great interest two studies on the association between androgen-deprivation therapy (ADT), a widespread therapy for advanced prostate cancer, and coronavirus disease 2019 (COVID-19) published in the *Annals*.<sup>1,2</sup> Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry into host cells is facilitated by the transmembrane protease TMPRSS2, whose expression can be modulated by the androgen receptor.<sup>3</sup> Preclinical data suggest that ADT may protect from SARS-CoV-2 infection and decrease COVID-19 severity.<sup>3</sup> A registry study reported by Montopoli et al.<sup>1</sup> demonstrated that ADT was associated with decreased COVID-19 incidence in Venetian men with prostate cancer. However, this relationship was not observed by Koskinen et al.<sup>2</sup> in a study of Finnish men. This relationship has not been examined in a diverse population.

We sought to determine the association between ADT and COVID-19 incidence in men with prostate cancer in the University of California Health System (UCHS) in California, USA. The UC Health COVID Research Data Set, which includes electronic health data of all patients who underwent testing for SARS-CoV-2 at five UCHS academic medical centers and 12 affiliated hospitals across California, was used for men tested between 1 February 2020 and 20 December 2020.<sup>4</sup> Association of SARS-CoV-2 positivity with ADT [GnRH (gonadotropin-releasing hormone) agonist/ antagonist] within 6 months of COVID-19 testing was determined using the chi-square test. Multivariable logistic regression to predict SARS-CoV-2 infection based on ADT, race/ethnicity, birth year, and comorbidities was performed. This study was approved by the University of California, San Francisco Institutional Review Board.

Overall, 5211 men with prostate cancer who underwent SARS-CoV-2 testing were identified, of whom 97 (1.9%) tested positive. Of these men, 3812 (73%) were white; 369 (7%) black or African-American; 350 (7%) Asian, American Indian/Alaska Native, or Native Hawaiian/Pacific-Islander; 238 (5%) Other/Multiple race; and 442 (8%) Unknown race. There were 385 (7%) Hispanic/Latinx men.

Of 799 men who received ADT, 18 (2.3%) tested positive. Of 4412 men who did not receive ADT, 79 (1.8%) tested positive (odds ratio 1.30, 95% confidence interval 0.78-2.19, P = 0.31). No statistically significant association between ADT and SARS-CoV-2 infection was found within the race/ ethnicity subgroups. Multivariable logistic regression revealed that ADT was not independently associated with SARS-CoV-2 infection (Table 1). By contrast, known risk factors (diabetes, black race, Other/Multiple race, and Hispanic/Latinx ethnicity) were associated with infection.

Among 97 COVID-19-positive men with prostate cancer, 1/19 men (5.3%) who received ADT died, versus 7/78 men who did not (9.0%; odds ratio 0.56, 95% confidence interval 0.07-4.88, P = 0.60).

 Table 1. Multivariable logistic regression of SARS-CoV-2 infection in men

 with prostate cancer

Characteristic	N	Odds ratio	95% confidence interval	P value
ADT				
Received	799	1.18	(0.70-1.99)	0.541
Birth year				
<b>≤1955</b>	3999	0.91	(0.57-1.45)	0.680
Race				
White	3812	Reference		
Black or African-American	369	1.96	(1.04-3.68)	0.037
Asian, Native Hawaiian/	350	0.34	(0.08-1.41)	0.136
Pacific Islander, or American				
Indian/Alaska Native				
Other or Multiple	238	2.16	(1.03-4.50)	0.041
Unknown	442	1.59	(0.83-3.05)	0.165
Ethnicity				
Hispanic/Latinx	385	1.94	(1.04-3.63)	0.038
Comorbidities				
Diabetes mellitus	763	1.86	(1.13-3.06)	0.015
Chronic kidney disease	658	1.08	(0.61-1.92)	0.800
Chronic obstructive	321	1.60	(0.82-3.15)	0.171
pulmonary disease				
Coronary artery disease	243	1.36	(0.62-3.02)	0.444
Congestive heart failure	334	0.99	(0.46-2.10)	0.974
Obesity	340	1.22	(0.62-2.44)	0.569

ADT, androgen-deprivation therapy; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Our results do not suggest a benefit of ADT for SARS-CoV-2 infection or mortality, though deaths were few. Differences between our study and those in Italy and Finland are exclusion of oral anti-androgen therapies and COVID-19 community prevalence. Other factors such as socioeconomic determinants, stage, chemotherapy use, and ADT duration are unreported potential confounders. ADT duration may be important, as Patel et al.<sup>5</sup> recently reported that longer ADT duration was associated with decreased mortality.

In conclusion, no association between ADT and SARS-CoV-2 infection was identified in this large, diverse population of men with prostate cancer. Racial/ethnic disparities in SARS-CoV-2 infection rates described in the United States are also observed in men with prostate cancer.

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Available online 8 February 2021

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https://doi.org/10.1016/j.annonc.2021.01.067

### ACKNOWLEDGEMENTS

HTB, RRA, and FWH are funded by the Prostate Cancer Foundation.

## FUNDING

None declared (no grant number).

## DISCLOSURE

RRA reports receiving honoraria from Clovis Oncology; performing consulting or advisory role for AstraZeneca, Dendreon, Advanced Accelerator Applications, Clovis Oncology, Axiom Biotechnologies; research funding (for institution) from Zenith Epigenetics, Novartis, Xynomic Pharma, Cancer Targeted Technology, Janssen, Merck, AbbVie, Amgen, AstraZeneca, BioXcel Therapeutics. AJB is a cofounder and consultant to Personalis and NuMedii; consultant to Samsung, Mango Tree Corporation, and in the recent past, 10x Genomics, Helix, Pathway Genomics, and Verinata (Illumina); has served on paid advisory panels or boards for Geisinger Health, Regenstrief Institute, Gerson Lehman Group, AlphaSights, Covance, Novartis, Genentech, Merck, and Roche; is a shareholder in Personalis and NuMedii; is a minor shareholder in Apple, Facebook, Alphabet (Google), Microsoft, Amazon, Snap, Snowflake, 10x Genomics, Illumina, Nuna Health, Assay Depot (Scientist. com), Vet24seven, Regeneron, Sanofi, Royalty Pharma, Pfizer, BioNTech, AstraZeneca, Moderna, Biogen, Twist Bioscience, Pacific Biosciences, Editas Medicine, Invitae, and Sutro, and several other nonhealth-related companies and mutual funds; and has received honoraria and travel reimbursement for invited talks from Johnson and Johnson, Roche, Genentech, Pfizer, Merck, Lilly, Takeda, Varian, Mars, Siemens, Optum, Abbott, Celgene, AstraZeneca, AbbVie, Westat, several investment and venture capital firms, many academic institutions, medical or disease-specific foundations and associations, and health systems; receives royalty payments through Stanford University, for several patents and other disclosures licensed to NuMedii and Personalis. his research has been funded by NIH, Northrup Grumman (as the prime on an NIH contract), Genentech, Johnson and Johnson, FDA, Robert Wood Johnson Foundation, Leon Lowenstein Foundation, Intervalien Foundation, Priscilla Chan and Mark Zuckerberg, the Barbara and Gerson Bakar Foundation, and in the recent past, the March of Dimes, Juvenile Diabetes Research Foundation, California Governor's Office of Planning and Research, California Institute for Regenerative Medicine, L'Oréal, and Progenity. FWH has stock or other ownership in GlaxoSmithKline and AbbVie. All remaining authors have declared no conflicts of interest.

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# Combined small-cell lung carcinoma revealed to be an intratumoural metastasis by genetic analysis

Combined small-cell lung carcinoma (SCLC) consists of SCLC component and another histologic type of non-SCLC. Reports have shown that the subcomponents of combined SCLC originate from a common precursor tumour cell<sup>1,2</sup> or a collision of multiple primaries growing at a same site.<sup>3</sup> We present a case of a 73-year-old male ex-smoker presenting with haemoptysis. Investigations identified a left lower lobe mass and a left mainstem endobronchial tumour. A bronchial sleeve resection was carried out revealing a 4.3-cm pulmonary combined SCLC and adenocarcinoma (Figure 1A and B). The endobronchial tumour showed only SCLC (Figure 1C). Regional lymph nodes showed foci of metastatic adenocarcinoma in stations 9 and 11 (Figure 1D and E). The patient received post-operative chemoradiotherapy and was without apparent evidence of disease recurrence at the time of submission of the manuscript ( $\sim$  3.5 years post-operatively). Standard histological, histochemical and immunohistochemistry (IHC) assessments were carried out. The SCLC had an elevated mitotic index with large areas of necrosis. IHC showed neuroendocrine marker-positive staining limited to the SCLC, while napsin A and mucicarmine stains were positive in the adenocarcinoma only. All components were positive staining for Thyroid transcription factor-1 protein. The adenocarcinoma consisted of an acinar predominant architecture with some areas showing a solid architecture.

Multi-region whole-exome sequencing (WES) was carried out from relevant areas of interest arising from formalinfixed paraffin-embedded tissues (respective driver mutations in Figure 1). Both the SCLC components of the pulmonary and endobronchial sites harboured characteristic single-nucleotide variants or small insertions or deletions in multiple genes, including retinoblastoma 1 gene (*RB1*), tumour protein p53 (*TP53*) and mucin 16 (*MUC16*). By comparison, the adenocarcinoma components showed characteristic mutations in KRAS proto-oncogene