Over 48,000 Baseline Prostate Specific Antigen Measurements in Young Men: a 16-Year Time-Analysis

Diego M. Capibaribe[1], Natalia D. Avilez[1], Natássia C.C Truzzi[1], José C.C.I Truzzi[2], Mehrsa Jalalizadeh[1], Leonardo O. Reis[1]

[1] UroScience, Pontifical Catholic University of Campinas, PUC-Campinas and University of Campinas, Unicamp, São Paulo, Brazil; [2] Paulista School of Medicine, Unifesp and Fleury® Institute, São Paulo, Brazil

Correspondence to:

Prof. Dr. Leonardo Oliveira Reis, MD, MSc, PhD (orcid: **0000-0003-2092-414X)**

UroScience, Pontifical Catholic University of Campinas, PUC-Campinas and

University of Campinas, Unicamp, Campinas, SP, Brazil

+55 19 35217481

E-mail: reisleo.l@gmail.com

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Approval was obtained to access the Fleury® Institute database. The University of Campinas research ethics committee approved the protocol number 543.095 and waived consent.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

COMPETING INTERESTS

The authors declare that they have no competing interests.

FUNDING STATEMENT

National Council for Scientific and Technological Development – CNPq, Research Productivity: 304747/2018-1. The funder was not involved in study design, data collection, data analysis, manuscript preparation, and/or publication decisions.

AUTHORS' CONTRIBUTIONS

Reis LO: Funding Acquisition, Project development, Supervision. Capibaribe DM, Jalalizadeh M: Data analysis, Manuscript writing. Avilez ND, Truzzi N and Truzzi JCCI: Data collection, Data analysis, Manuscript editing.

ACKNOWLEDGEMENTS

To the involved institution(s), the patients, and those that provided and cared for study patients.

ABSTRACT

Objective: To broaden the understanding of baseline PSA variations over the last decades in young men.

Methods: We analyzed the baseline total PSA of 48,896 men below the age of 40, grouped into three age groups <30 (n = 6123), 30-35 (n = 16,118), and 35-40 (n = 25,351) years old. Multiple linear regression model predicted the average LogPSA per month as a function of time, age, and testing rate during 16-year period of the data (2003-2018).

Results: Average age and standard deviation were 34.5 ± 4.6 years and median PSA ± interquartile range was 0.63 ± 0.46 ng/dl with a leftward skew towards zero (81% of results below 1 ng/dl) in all years. The average LogPSA was steadily rising over time, independent of age and testing rate in all three age groups: multiple R-squared = 0.40, estimate = 1.211e-05, $p<0.0001$. Mean/median PSA and age were 0.67/0.57 ng/dL and 36.32/37.23 years and 0.91/0.66 ng/dL and 34.87/35.88 years in 2003 and 2018, respectively,

Conclusions: Average baseline PSA is rising in young men. Change in medical routine practice (e.g., reserving the test for those with higher suspicion) and true rise in benign or pathological prostate conditions are possible reasons.

Keywords: Baseline PSA; Young Male; Prostate Cancer; PSA Kinetics; PSA Trend; PSA Reference Values

INTRODUCTION

Prostate cancer is the second most commonly diagnosed cancer and the fifth cause of death in men worldwide [1]. In 1986, the U.S. Food and Drugs Administration (FDA) approved measuring the serum levels of prostate-specific antigen (PSA), a glycoprotein originating from the prostate tissue, to screen for prostate cancer [2].

Ever since its introduction as a screening tool, PSA has been the subject of much debate: initially considered as a reliable screening method until 2003 when United States Preventive Services Task Force (USPTSF) casted doubts on its reliability and finally in 2012 published a grade D recommendation actively recommending against routine use of PSA for screening especially in young asymptomatic men [3–5].

The controversy was mainly due to the problem of over-diagnosing prostate cancer using PSA, leading to unnecessary interventions and to adverse effects such as pain, bleeding, infection, erectile dysfunction, and incontinence. Since then, many studies have questioned PSA screening, by showing that it might not reduce prostate cancer specific mortality in some populations [6,7].

One reason for inaccuracy of PSA screening could be due to incorrect reference values leading to inappropriate placement of the threshold line for marking an individual as “cancer-suspicious” [8,9]. Some studies suggest higher baseline PSA measurement in younger age increases the individual’s chance of developing cancer later in life, indicating that we may be able to improve this screening tool by adjusting the reference values in the younger populations [10,11].

In this study we aim to provide our analysis of more than 48,000 PSA measurements in men younger than 40 years of age gathered from the database of a major laboratory conglomerate, providing a reliable reference value resource. We also studied temporal trends in this test over 16-years.

METHODS

After local ethics committee approval, we collected de-identified data from the Fleury® institute database on total PSA levels measured by the same PSA ultra-sensitive kit in patients less than 40 years old tested between 2003 and 2018. The current study did not require consent forms by the ethics committee as it was a retrospective analysis on de-identified data. The Fleury® institute is a private diagnostic center represented by a conglomerate of 33 laboratory units in Sao Paulo, Brazil. The institute uses ultrasensitive kits of electrochemiluminescence immunoassay (electrochemiluminescence immunoassay or ECLIA) for PSA measurement. They switched to the Roche platform from 2003 onwards. In October 2019 the platform was changed to "Cobas e 801". We therefore limited our data analysis to data acquired between 2003 and 2018. The Fleury® institute assured us that during this time period, routine validation processes have shown that their PSA measurement results were exactly the same.

The data represented men baseline PSAs with exclusive identifying number that showed repeated PSA testing for some individuals. We only included the first PSA test for all subjects to assess the baseline value of this test. Exploratory data analysis was performed using parametric descriptions.

Regression analysis was performed on parametric values to discover trends in the parameters over time: time was partitioned into monthly periods and logarithm base 10 of PSA was calculated per month followed by regression analysis. Subgroup analysis was performed to assess difference in trends among three age groups of <30 years, 31-35 years, and >35 years old.

Data were analyzed using R version 4.1.2 on RStudio platform 2022.07.1 with the package tidyverse.

RESULTS

Initial data included test results of 48,896 men with average age of 34.5 ± 4.6 years. **Table 1** includes parametric descriptions of PSA results per each year. The PSA distribution was not normal in any of the years: a leftward skew was observed every year with 81% of results below 1 ng/dl. PSA results >4.0ng/dl and >10ng/dl were both exceptionally rare with on average 8.2 and 1.6 observations per 1000 tests.

We focused on finding trends in the data over the time. There is a rise in number of tests before the year 2013 followed by a decline in the years after 2013 which is almost at the same time as the 2012 USPTSF grade D recommendation against PSA testing, **Figure 1A**.

PSA was logarithm 10 transformed (LogPSA) to achieve normal distribution. Time was analyzed into monthly periods and average LogPSA was calculated per each month. The average monthly age of the participants slightly declined over the time (simple linear regression: multiple R-squared = 0.29, estimate = -0.00015, P<0.0001).

To assess temporal change in LogPSA we first assessed whether the testing rate was a potential confounder, i.e., the more tests performed the more likely it was to observe rare PSA values (high PSA values in young men). Simple linear regression showed a positive relationship between mean LogPSA and the number of tests performed on each month (multiple R-squared = 0.14, estimate = 1.146e-04, p <0.0001).

We therefore considered the number of tests per month (testing rate) as a potential confounding factor and created a multiple linear regression model to predict the mean LogPSA per month as a function of time, age, and testing rate of that month. This model showed the change in LogPSA to be independent of both testing rate and age but strongly predicted by time: multiple R-squared = 0.40, estimate = 1.211e-05, p<0.0001). Subgroup

analysis showed similar findings; data was grouped into three age groups <30 (n = 6123), 30 – 35 (n = 16,118), and 35 – 40 (n = 25,351) years old.

The mean LogPSA increased in all three age groups over time, with almost identical slopes (estimate = 1.5e-05, 1.5e-05, and 1.2e-5 respectively, P<0.0001 for all three groups), **Figure 1B**.

DISCUSSION

The prognostic value of obtaining a baseline PSA in early adulthood was seen in observational studies (12, 13). A review of eight PSA studies in younger patients have shown baseline PSA measurements to be good predictors of aggressive prostate cancer, metastasis, and disease-specific mortality many years later (12). However, only a handful of studies have been dedicated to the population below the 40-year-old threshold, especially with such large numbers in the current study. The fact that this is a population still immune to the age effects on prostate health, may be opportune to an interesting insight into the baseline PSA trends over time, and its repercussions.

Age is a well-established predictor of PSA level (14, 15) and therefore we added age to the multiple regression model as well. However, age in our data slightly declined while LogPSA slightly increased. We therefore can be assured that important confounders were considered as much as possible in our analysis before concluding that there is an increase in measured PSA levels over the time of the data.

In 2012 the US Preventive Services Task Force (USPTSF) published their grade D recommendation against routine screening for prostate cancer using PSA (4). **Figure 1A,** shows a rise in the number of PSA tests performed before the year 2013 followed by a sudden decline in this number after 2013, indicating that Brazilian doctors possibly adopted the USPTSF recommendation.

There are multiple potential reasons for PSA rise over time in young man. Increased steroid use, subclinical prostate pathologies, chronic prostatitis due to sexually transmitted diseases, prostate enlargement due to change in habits, or even prostate cancer in young men (16, 17).

Our study is the first that showed a change in PSA values over time in young men below the age of 40 years. Two studies in Japan assessed this trend in older population between 50 to 79 years old. The first study was conducted between the years 1970 to 2003 (18) and the second study was conducted between the years 1992 to 2016 (19), neither

study found any trend in PSA level over time. It also could mean that the PSA rise is only observed in younger men and can help us narrow-down the potential causes (both steroid use and sexual activity are more common in younger men).

Other published studies regarding PSA levels in young men did not assess for temporal trends and mainly compared PSA levels based on race (20, 21) or tried to find a cut-off value for prostate cancer screening (8, 10, 22). The study by Angulo et al. measured this antigen in 40 – 49 years old Spanish men to establish a cut-off value for detecting prostate cancer in this age group; PSA above 1.9ng/dl in their study revealed an AUC of 92.8% in detecting prostate cancer. This impressive high accuracy is limited by the fact that not all prostate cancers require treatment specially in younger populations and multiple studies have shown that routine prostate cancer screening increases the number of detected cancers but might not reduce its specific mortality (6, 23).

Current study is not devoid limitations and included retrospective analysis of data gathered from the database of a major laboratory conglomerate. Unfortunately, the data was limited as it included a few variables (age and time), therefore it was not sufficient to prove causation, only association.

Changes in medical routine practice and their threshold for ordering PSA might not be ruled out. For example, physicians would only order PSA test for patients with larger prostate sizes in the final years of our data. In **Table 1** we see increased detection of PSA > 4ng/dl per 1000 tests during the years 2017 and 2018.

Physicians might tend to order PSA test only for those with high clinical suspicion over years, mainly after the 2012 USPTSF recommendation (4). Unfortunately, due to absence of data on history, physical exam (importantly prostate size) and further test results, we were unable to rule out this possibility and it is considered an important limitation to our study.

CONCLUSIONS

Average measured PSA in young men below the age of 40 may be rising slowly over time. This could be due to change in routine clinical practice of doctors (reserving the test for those with higher suspicion) or may be due to increasing incidence of benign or malignant prostate conditions in this population. Future studies are warranted to confirm our findings and deepen the knowledge regarding the cause-effect relations.

REFERENCES

1. Rawla P. Epidemiology of Prostate Cancer. World J Oncol 2019; 10:63–89.
2. Lin K, Lipsitz R, Miller T, Janakiraman S. Benefits and Harms of Prostate-Specific Antigen Screening for Prostate Cancer: An Evidence Update for the U.S. Preventive Services Task Force. Ann Intern Med 2008;149:192.
3. Grossman DC, Curry SJ, Owens DK, Bibbins-Domingo K, Caughey AB, Davidson KW, Doubeni CA, Ebell M, Epling JW, Kemper AR, Krist AH, Kubik M, Landefeld CS, Mangione CM, Silverstein M, Simon MA, Siu AL, Tseng C-W. Screening for Prostate Cancer. JAMA 2018;319:1901.
4. Moyer VA. Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2012;157:120.
5. Mottet N, van den Bergh RCN, Briers E, van den Broeck T, Cumberbatch MG, de Santis M, Fanti S, Fossati N, Gandaglia G, Gillessen S, Grivas N, Grummet J, Henry AM, van der Kwast TH, Lam TB, Lardas M, Liew M, Mason MD, Moris L, Oprea-Lager DE, van der Poel HG, Rouvière O, Schoots IG, Tilki D, Wiegel T, Willemse P-PM, Cornford P. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer—2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol 2021;79:243–262.
6. Ilic D, Djulbegovic M, Jung JH, Hwang EC, Zhou Q, Cleves A, Agoritsas T, Dahm P. Prostate cancer screening with prostate-specific antigen (PSA) test: a systematic review and meta-analysis. BMJ 2018;k3519.
7. Sherer M, Qiao EM, Kotha N, Qian AS, Rose BS. Association Between Prostate-Specific Antigen Screening and Prostate Cancer Mortality Among Non-Hispanic Black and Non-Hispanic White US Veterans. JAMA Oncol 2022;8:1471–1476.
8. Chautard D, Daver A, Mermod B, Tichet A, Bocquillon V, Soret J-Y. Values for the Free to Total Prostate-Specific Antigen Ratio as a Function of Age: Necessity of Reference Range Validation. Eur Urol 1999;36:181–186.
9. da Silva Junior MM, Capibaribe DM, Avilez ND, Jalalizadeh M, Dias LB, Laranja WW, Guimarães F, Simões FA, Alonso JCC, Rejowski RF, Cintra A, Reis LO. Digital rectal examination impact on PSA derivatives and prostate biopsy triggers: a contemporary study. Int Urol Nephrol 2022;54:2117–2123.
10. Börgermann C, vom Dorp F, Swoboda A, Ketteniß O, Becker M, Rübben H. PSA Quo Vadis? It Is Reasonable to Start with Prostate-Specific Antigen Testing at the Age of 40! Cancer Epidemiology, Biomarkers & Prevention 2011;20:1190–1195.
11. Angulo JC, Viñas MA, Gimbernat H, Fata FR de, Granados R, Luján M. Baseline PSA in a Spanish male population aged 40–49 years anticipates detection of prostate cancer. Actas Urológicas Españolas 2015;39:605–611.
12. Loeb S, Carter HB, Catalona WJ et al: Baseline prostate-specific antigen testing at a young age. Eur Urol 2012; **61:** 1
13. Vickers AJ, Ulmert D, Sjoberg DD et al: Strategy for detection of prostate cancer based on relation between prostate specific antigen at age 40-55 and long-term risk of metastasis: Case-control study. BMJ 2013; **346:** f202
14. Shahrzad Rahimifar. AM. Age-Related Prostate Specific Antigen Reference Ranges in Healthy Northern Iranian Men. Iran J Immunol 15;68–73.
15. Drazer MW, Huo D, Schonberg MA, Razmaria A, Eggener SE. Population-Based Patterns and Predictors of Prostate-Specific Antigen Screening Among Older Men in the United States. Journal of Clinical Oncology 2011;29:1736–1743.
16. Boyle P, Koechlin A, Bota M, d'Onofrio A, Zaridze DG, Perrin P, Fitzpatrick J, Burnett AL, Boniol M. Endogenous and exogenous testosterone and the risk of

prostate cancer and increased prostate-specific antigen (PSA) level: a meta-analysis. BJU Int 2016;118:731–741.
17. Linhares BL, Miranda EP, Cintra AR, Reges R, Torres LO. Use, Misuse and Abuse of Testosterone and Other Androgens. Sex Med Rev 2022;10:583–595.
18. Ohi M, Ito K, Yamamoto T, Miyakubo M, Takechi H, Kubota Y, Suzuki K. Changes in Baseline PSA Levels in Japanese Men From 1988 to 2003. Urology 2008;72:95–98.
19. Oki R, Ito K, Suzuki R, Fujizuka Y, Arai S, Miyazawa Y, Sekine Y, Koike H, Matsui H, Shibata Y, Suzuki K. Long-term longitudinal changes in baseline PSA distribution and estimated prevalence of prostate cancer in male Japanese participants of population-based PSA screening. Int J Cancer 2018;143:1611–1619.
20. Ku JH, Ahn JO, Lee CH, Lee NK, Park YH, Byun SS, Kwak C, Lee SE. Distribution of serum prostate-specific antigen in healthy korean men: influence of ethnicity. Urology 2002;60:475–479.
21. Sutcliffe S, Pakpahan R, Sokoll LJ, Elliott DJ, Nevin RL, Cersovsky SB, Walsh PC, Platz EA. Prostate-specific antigen concentration in young men: new estimates and review of the literature. BJU Int 2012;110:1627–1635.
22. Hailan M, Rifat UN. Age-specific reference ranges of serum prostate-specific antigen in Iraqi men. Arab J Urol 2011;9:273–277.
23. Kinnear NJ, Kichenadasse G, Plagakis S, O'Callaghan ME, Kopsaftis T, Walsh S, Foreman D. Prostate cancer in men aged less than 50 years at diagnosis. World J Urol 2016;34:1533–1539.

Table 1: Parametric details of baseline total Prostate Specific Antigen (PSA) levels by year measured in our data consisting of 48,896 men below the age of 40 years old.

Year	No. Tests	Mean Age ±SD	Mean PSA ±SD (ng/dl)	Median PSA ±IQR (ng/dl)	Mean LogPSA	PSA>4 ng/dl No. (*)	PSA>10 ng/dl No. (*)
2003	2342	35.6±3.8	0.69±0.59	0.57±0.40	-0.2399833	10 (4)	2 (1)
2004	1957	35.1±4.1	0.71±0.93	0.58±0.43	-0.2398307	8 (4)	2 (1)
2005	1722	34.6±4.4	0.73±0.59	0.61±0.44	-0.2179238	11 (6)	0 (0)
2006	1735	34.7±4.2	0.75±0.70	0.59±0.45	-0.2157509	14 (8)	1 (1)
2007	1724	34.5±4.4	0.72±0.78	0.59±0.43	-0.2229980	6 (3)	2 (1)
2008	1946	34.4±4.4	0.78±1.01	0.61±0.47	-0.2092579	15 (8)	3 (2)
2009	2805	34.7±4.5	0.76±1.05	0.62±0.45	-0.2047315	12 (4)	3 (1)
2010	3481	34.6±4.6	0.80±1.03	0.61±0.46	-0.2022384	31 (9)	9 (3)
2011	4822	34.6±4.6	0.79±1.24	0.64±0.45	-0.1948546	27 (6)	5 (1)
2012	4552	34.5±4.6	0.79±1.29	0.62±0.45	-0.2021698	30 (7)	5 (1)
2013	5018	34.4±4.7	0.79±0.83	0.64±0.48	-0.1917149	37 (7)	9 (2)
2014	4375	34.5±4.7	0.82±0.85	0.65±0.50	-0.1791161	41 (9)	1 (<1)
2015	4349	34.3±4.7	0.84±1.11	0.66±0.48	-0.1741685	43 (10)	9 (2)
2016	3817	34.4±4.7	0.83±1.19	0.65±0.47	-0.1797084	30 (8)	8 (2)
2017	2947	34.4±4.8	0.90±1.6	0.64±0.48	-0.1793094	48 (16)	9 (3)
2018	1264	33.6±5.0	1.04±2.16	0.66±0.53	-0.1572257	34 (27)	8 (6)

SD = Standard Deviation
IQR = Interquartile Range
LogPSA = Logarithm base 10 transformed PSA
No. = Number
* number of detected cases per 1000 tests

FIGURES

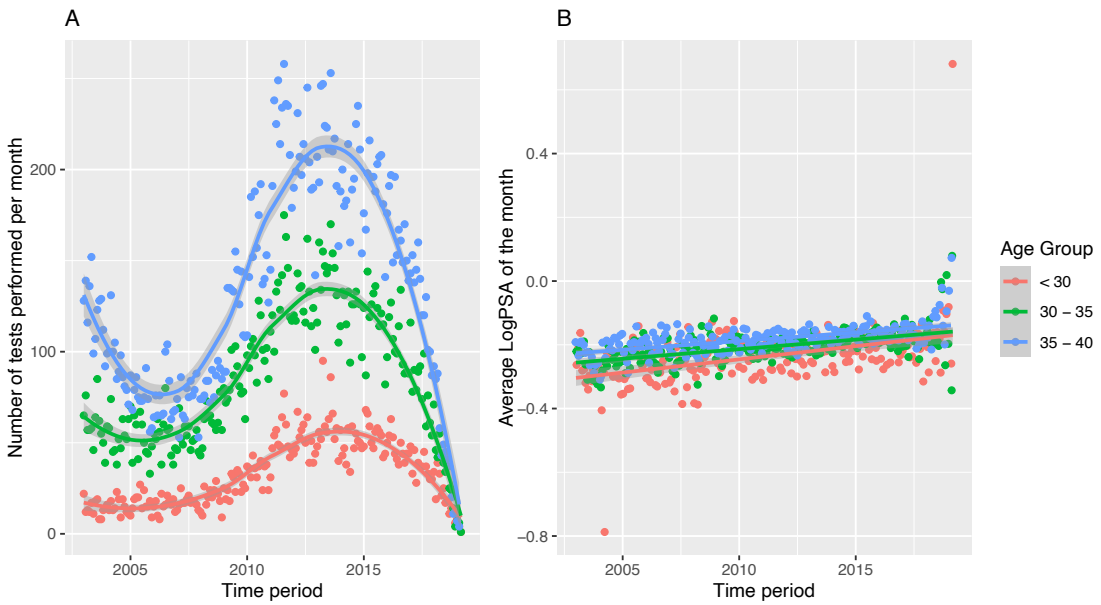

Figure 1 - Subgroup analysis of age groups shows their trends to be almost identical.

A – Number of tests performed per month for each age group.

B – Average LogPSA increases slightly for all three groups and overlap almost perfectly.

PSA: Prostate Specific Antigen; LogPSA: Logarith 10 transformed PSA.

Graphical Abstract: