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Over 48,000 baseline prostate-specific antigen measurements in young men: a 16-year time-analysis

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Introduction To broaden our understanding of baseline PSA variations over the last decades in men under 40 years old.

Material and methods We analysed the baseline total PSA of 48,896 men below the age of 40 years, grouped into 3 age groups: <30 (n = 6,123), 30–35 (n = 16,118), and >35 (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 the 16-year period of the data (2003–2018).

Results The average age and standard deviation were 34.5 ±4.6 years, and the 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 3 age groups: multiple R^2 = 0.40, estimate = 1.211e-05, p <0.0001. Mean/median PSA and age were 0.69/0.57 ng/dl and 35.6/37.2 years in 2003 and 1.04/0.66 ng/dl and 33.6/35.8 years in 2018.

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

Key Words: baseline PSA ‹› young male ‹› prostate cancer ‹› PSA kinetics ‹› PSA trend ‹› PSA reference values

INTRODUCTION

Prostate cancer is the second most diagnosed cancer and the fifth cause of death in men worldwide [1]. In 1986, the U.S. Food and Drug Administration approved measurement of 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: it was initially considered a reliable screening method until 2003 when the United States Preventive Services Task Force (USPTSF) cast doubts on its reliability and then 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 the inaccuracy of PSA screening could be incorrect reference values leading to inappropriate placement of the threshold line for marking an individual as "cancer-suspicious" [8, 9]. Some studies suggest that a 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 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.

MATERIAL AND 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 Fleury® institute is a private diagnostic centre represented by a conglomerate of 33 laboratory units in the state of São 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 period, routine validation processes have shown that their PSA measurement results were exactly the same.

Statistical analysis

The data represented men's baseline PSA levels with unique identifying numbers, showing 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.
Trend regression analysis was performed on average monthly logarithm 10 transformed PSA to discover

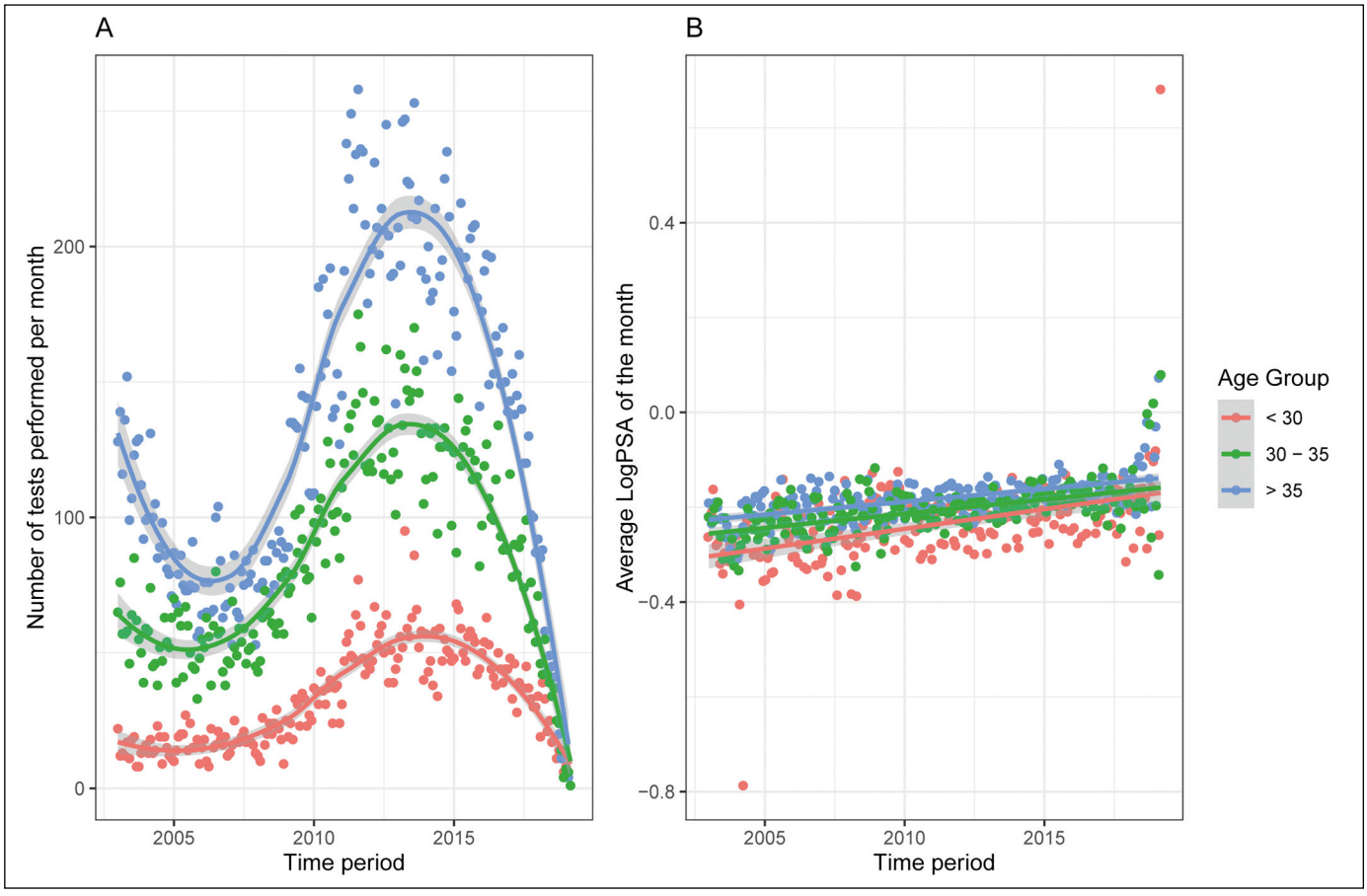

Figure 1. *Subgroup analysis of age groups shows almost identical trends.* **A***: Number of tests performed per month for each age group. Smoothed curved lines are drawn using the LOESS local regression method; the grey areas indicate 95% confidence interval.* **B***: Simple linear regression lines show that average LogPSA increased slightly for all 3 groups with almost perfect overlap.*
LogPSA – logarithm 10 transformed PSA; PSA – prostate-specific antigen

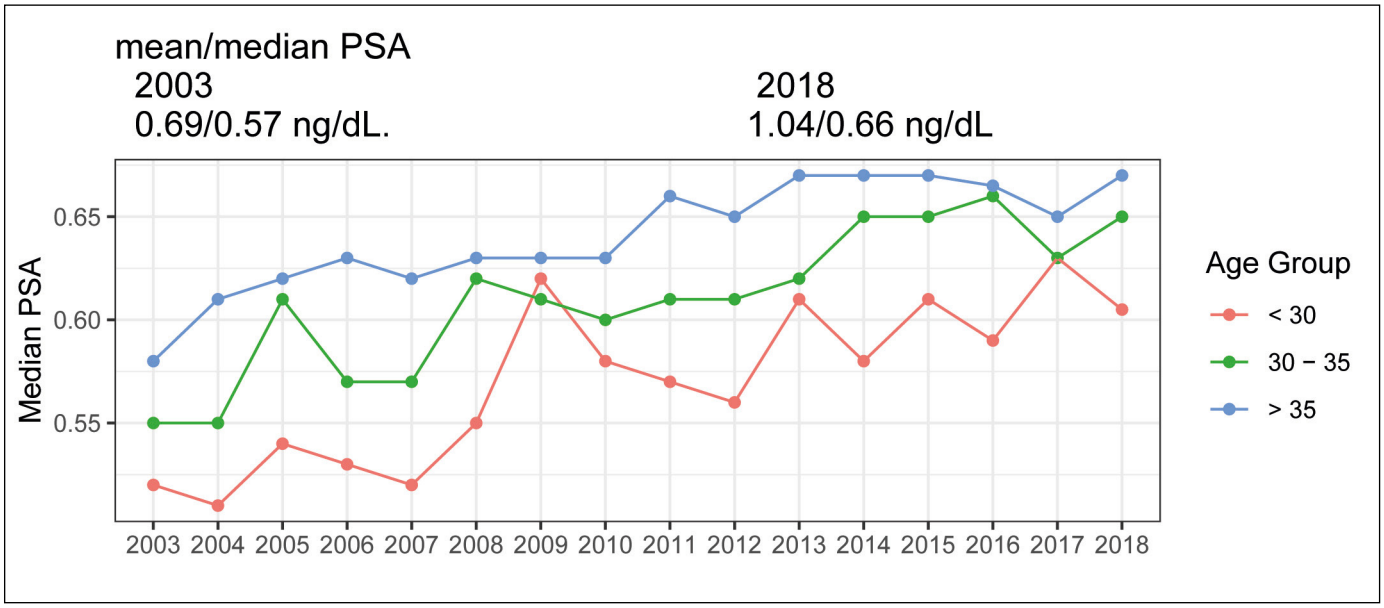

Figure 2. *Baseline PSA trend over the years 2003 to 2018 by age group.*

trends over time. Time was partitioned into monthly periods because they offer a distinct advantage over yearly intervals by providing a finer granularity, which facilitates a more nuanced analysis in multivariable regression. This granularity enables a more precise adjustment for confounding variables and enhances the accuracy of trend analysis. Due to the skewed distribution of monthly PSA levels, which deviated from normality, we employed a logarithmic transformation with a base of 10. This transformation successfully normalised the distribution of PSA values, rendering it more suitable for comparisons between months [12]. Subgroup analysis was performed to assess differences in trends among 3 age groups: <30 years, 30–35 years, and >35 years old. Data were analysed using R version 4.1.2 on RStudio platform 2022.07.1 with the package tidyverse. Temporal trends are illustrated using locally estimated scatterplot smoothing (LOESS) regression in Figure 1A, simple linear regression in Figure 1B, and a line chart in Figure 2. The grey areas in Figure 1 represent the 95% confidence interval.

Bioethical standards

The current study did not require consent forms according to the ethics committee because it was a retrospective analysis using de-identified data.

RESULTS

Initial data included the test results of 48,896 men with an average age of 34.5 ±4.6 years. Table 1 includes parametric descriptions of PSA results for 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 >4.0 ng/dl and >10 ng/dl were both exceptionally rare with, on average, 8.2 and 1.6 observations per 1,000 tests.

We focused on finding trends in the data over time. There was a rise in the 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).

Trend analysis

The average monthly age of the participants slightly declined over time (simple linear regression: multiple $R^2 = 0.29$, estimate = -0.00015, $p < 0.0001$).

To evaluate temporal changes in LogPSA, we initially examined whether the testing rate might act as a potential confounding factor. Because elevated PSA levels in younger men are considered rare events, we investigated whether the frequency of testing influenced the likelihood of encountering rare PSA values. Simple linear regression showed a positive relationship between mean LogPSA and the number of tests performed in each month (multiple $R^2 = 0.14$, 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

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*

Year	No. of tests	Mean age ±SD	No. of tests per age group	Mean PSA ±SD (ng/dl)	Median PSA ±IQR (ng/dl)	APC	PSA >4 ng/dl No. (*)	PSA >10 ng/dl No. (*)
2003	2342	35.6 ±3.8	<30: 167 30–35: 714 >35: 1461	0.69 ±0.59	0.57 ±0.40	–	10 (4)	2 (1)
2004	1957	35.1 ±4.1	<30: 182 30–35: 651 >35: 1124	0.71 ±0.93	0.58 ±0.43	+1.8%	8 (4)	2 (1)
2005	1722	34.6 ±4.4	<30: 205 30–35: 622 >35: 895	0.73 ±0.59	0.61 ±0.44	+5.2%	11 (6)	0 (0)
2006	1735	34.7 ±4.2	<30: 190 30–35: 647 >35: 898	0.75 ±0.70	0.59 ±0.45	–3.3%	14 (8)	1 (1)
2007	1724	34.5 ±4.4	<30: 209 30–35: 639 >35: 876	0.72 ±0.78	0.59 ±0.43	0.0	6 (3)	2 (1)
2008	1946	34.4 ±4.4	<30: 230 30–35: 729 >35: 987	0.78 ±1.01	0.61 ±0.47	+3.4%	15 (8)	3 (2)
2009	2805	34.7 ±4.5	<30: 316 30–35: 987 >35: 1502	0.76 ±1.05	0.62 ±0.45	+1.6%	12 (4)	3 (1)
2010	3481	34.6 ±4.6	<30: 414 30–35: 1211 >35: 1856	0.80 ±1.03	0.61 ±0.46	–1.6%	31 (9)	9 (3)
2011	4822	34.6 ±4.6	<30: 623 30–35: 1587 >35: 2612	0.79 ±1.24	0.64 ±0.45	+4.9%	27 (6)	5 (1)
2012	4552	34.5 ±4.6	<30: 615 30–35: 1523 >35: 2414	0.79 ±1.29	0.62 ±0.45	–3.1%	30 (7)	5 (1)
2013	5018	34.4 ±4.7	<30: 731 30–35: 1707 >35: 2580	0.79 ±0.83	0.64 ±0.48	+3.2%	37 (7)	9 (2)
2014	4375	34.5 ±4.7	<30: 586 30–35: 1455 >35: 2334	0.82 ±0.85	0.65 ±0.50	+1.6%	41 (9)	1 (<1)
2015	4349	34.3 ±4.7	<30: 648 30–35: 1424 >35: 2277	0.84 ±1.11	0.66 ±0.48	+1.5%	43 (10)	9 (2)
2016	3817	34.4 ±4.7	<30: 564 30–35: 1255 >35: 1998	0.83 ±1.19	0.65 ±0.47	–1.5%	30 (8)	8 (2)
2017	2947	34.4 ±4.8	<30: 443 30–35: 967 >35: 1537	0.90 ±1.6	0.64 ±0.48	+3.1%	48 (16)	9 (3)
2018	1264	33.6 ±5.0	<30: 250 30–35: 433 >35: 581	1.04 ±2.16	0.66 ±0.53	–3.0%	34 (27)	8 (6)
						AAPC = +0.76%		

* Number of detected cases per 1,000 tests
AAPC – average annual percentage change of median PSA; APC – annual percentage change of median PSA; IQR – Interquartile range; No. – number; PSA – prostate-specific antigen; SD – standard deviation

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 $R^2 = 0.40$, estimate = 1.211e-05, $p < 0.0001$).

Subgroup analysis showed similar findings; data were grouped into 3 age groups: <30 (n = 6,123), 30–35 (n = 16,118), and >35 (n = 25,351) years old. The mean LogPSA increased in all 3 age groups over time, with almost identical gradients (estimate = 1.5e-05, 1.5e-05, and 1.2e-5, respectively, $p < 0.0001$ for all 3 groups; Figure 1B).

Figure 2 shows the baseline PSA time-analysis trend over the years 2003 to 2018.

DISCUSSION

The prognostic value of obtaining a baseline PSA in early adulthood was seen in observational studies [13, 14]. A review of 8 PSA studies in younger patients showed baseline PSA measurements to be good predictors of aggressive prostate cancer, metastasis, and disease-specific mortality many years later [13]. However, only a handful of studies have been dedicated to the population below the 40-year-old threshold as in the current study. The fact that this is a population still immune to the age effects on prostate health may provide interesting insight into the baseline PSA trends over time and their repercussions.

Age is a well-established predictor of PSA level [15, 16], so we added age to the multiple regression model as well. However, age in our data slightly declined while LogPSA slightly increased. We can therefore 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 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 benign and malignant conditions that could raise the PSA level in young men: increased steroid abuse, subclinical prostate disorders, chronic prostatitis due to sexually transmitted diseases, prostate enlargement due to change in habits, or even prostate cancer in young men [17, 18]. It is logical to assume that an increase in these events could increase the population PSA level. Unfortunately, our study does not have the appropriate clinical data to accept or reject this hypothesis.

Our study is the first to show a change in PSA values over time in men below the age of 40 years. Two studies in Japan assessed this trend in an older population between 50 and 79 years old. The first study was conducted between the years 1970 and 2003 [19], and the second study was conducted between the years 1992 and 2016 [20]; neither study found any trend in PSA level over time. Their conclusion contradicts the findings of our study, which may be due to differences in the age demographics between our studies.

Other published studies regarding PSA levels in young men did not assess temporal trends but mainly compared PSA levels based on race [21, 22] or tried to find a cut-off value for prostate cancer screening [8, 10, 23]. The study by Angulo et al. [11] measured this antigen in 40–49-year-old Spanish men to establish a cut-off value for detecting prostate cancer in this age group; PSA above 1.9 ng/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, especially 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, 24].

Changes in routine medical practice and clinicians' thresholds for ordering PSA might not be ruled out. Table 1 shows an increased rate of PSA >4 ng/dl per 1000 tests during the years 2017 and 2018. This may be due to physicians reserving PSA testing for patients with higher clinical suspicion after the 2012 change in USPSTF screening recommendations made PSA testing in young patients less endorsed [4]. Accordingly, in our data, a sharp fall in the number of ordered PSA tests per month is evident immediately after 2012 (Figure 2A). The Brazilian health ministry recommended against routine screening in 2010 and 2014, their recommendation is yet to be updated [25]. In another study by our group, we showed a significant change in Brazil's prostate cancer incidence rate following a change in international guidelines. We detected no change following publication of Brazilian health ministry guidelines, suggesting a strong influence of international guidelines on Brazilian clinicians' decision-making [25]. Unfortunately, in the current study, we were unable to test the hypothesis that changes in clinicians' threshold is the cause of rising PSA results.

LIMITATIONS

The main limitation of our study is the absence of clinical data for patients. Since routine PSA screening is not recommended in men younger than 40 years of age, it is reasonable to believe that our data are acquired from symptomatic patients with pain or tenderness of the pelvic floor, urinary symptoms, enlarged prostate, etc. This means that our data may not be a true representation of the population. Another limitation of our study is the unavailability of important confounding factors such as ethnicity. Furthermore, despite assurance from the laboratory conglomerate regarding the unchanged procedure, we cannot dismiss the possibility of minor changes in routine practices over the 16-year period. Nuanced changes could potentially enhance the sensitivity of PSA testing, for instance by reducing the time between blood drawing and processing or reducing the time between rectal exam and PSA testing [9].

CONCLUSIONS

The average measured PSA in young men below the age of 40 years may be rising slowly over time. This could be due to changes in the routine clinical practice of doctors (reserving the test for those with higher suspicion) or due to the increasing incidence of benign or malignant prostate conditions in this population. The main study limitation is the lack of crucial data such as patient clinical information and ethnicity. Future studies are warranted to confirm our findings and deepen our knowledge regarding the cause-effect relationship.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ETHICS APPROVAL STATEMENT

The ethical approval was not required.

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