Population-based Analysis of Normal Total PSA and Percentage of Free/Total PSA Values: Results From Screening Cohort


OBJECTIVES
To examine the distribution of total prostate-specific antigen (tPSA) and percentage of free/total PSA (%f/tPSA) values in patients undergoing prostate cancer screening in Canada.

METHODS
The data from 4 consecutive annual prostate cancer screening events held in Montreal, Canada were examined with respect to age, tPSA, and %f/tPSA in 3222 men.

RESULTS
Within the entire cohort, the median PSA level was 1.0 ng/mL and the median %f/tPSA was 26%. Using the interquartile range around the median, the upper bound for tPSA was situated at 1.9 ng/mL and the lower bound for %f/tPSA was at 19%. The 90th percentile for the median tPSA was 3.8, and the 10th percentile for the median %f/tPSA was 14. PSA and %f/tPSA showed a relation with age. The 75th percentile for the median tPSA level in the age category 40-49, 50-59, 60-69, and 70-79 years was 1.1, 1.4, 2.6, and 3.6 ng/mL, respectively. The 25th percentile for the median %f/tPSA level in the age category 40-49, 50-59, 60-69, and 70-79 years was 19, 21, 18 and 19 ng/mL, respectively.

CONCLUSIONS
Our results can guide clinicians regarding the population-based distribution of serum tPSA and %f/tPSA values. Those values can be used for the purpose of counseling, as well as in the informed consent process before prostate biopsy.

PCa Awareness Days in 2004-2007. None of the men included in the present analysis participated in annual screening event and none had suspicious digital rectal examination findings. Only men aged 40-79 years were invited. The Hybritech (Beckmann-Coulter, Mississauga, ON, Canada) assay was used for both tPSA and %f/tPSA measurements.

Statistical Analysis
The tPSA level and %f/tPSA distributions were explored and tabulated for the entire cohort and stratified by age strata of 40-49, 50-59, 60-69, and 70-79 years. We used regression plots with the intent of providing a graphic display of the relation between age and PSA and age and %f/tPSA. The Statistical Package for Social Sciences, version 15.0 (SPSS, Chicago, IL) was used for all analyses. All tests were 2-sided with the significance level set at \( P \leq 0.05 \).

RESULTS
The median age of the 3222 study participants was 58 years (mean 59.0, range 40-79). Table 1 lists the descriptive characteristics of the total cohort of 3222 men. Of all 3222 men, 526 (16.3%), 1241 (38.5%), 947 (29.4%), and 508 (15.8%) were aged 40-49, 50-59, 60-69, and 70-79 years. In the entire cohort, the median tPSA level was 1.0 ng/mL (range 0.1-47.3) and the median %f/tPSA level was 26.0 ng/mL (range 3.0-90.0).

Figure 1 shows the scatterplots of the distribution between age and tPSA level (Fig. 1A) and between age and %f/tPSA (Fig. 1B). Figure 2 shows the interquartile range around the tPSA and %f/tPSA medians derived from the entire cohort. The 25th percentile for the median tPSA level in the age category of 40-49, 50-59, 60-69, and 70-79 years was 0.5, 0.5, 0.8, and 1.0 ng/mL, respectively (Fig. 2A). The 75th percentile for the median tPSA level in the age category of 40-49, 50-59, 60-69, and 70-79 years was 1.1, 1.4, 2.6, and 3.6 ng/mL, respectively (Fig. 2A).

The 25th percentile for the median %f/tPSA level in the age category of 40-49, 50-59, 60-69, and 70-79 years was 19.0, 21.0, 30.0, and 31.0 ng/mL, respectively (Fig. 2B). The 75th percentile for the median %f/tPSA level in the age category of 40-49, 50-59, 60-69, and 70-79 years was 34.0, 36.0, 33.0, and 31 ng/mL, respectively (Fig. 2B).

COMMENT
Contemporary cases of localized PCa are predominantly not palpable. Therefore, PSA-based detection represents the best and only means of detecting these cancers. However, no definitive data are available regarding what constitutes a normal tPSA level. Similarly, no definitive data are available indicating the optimal %f/tPSA that should be applied. Several efforts have been made to improve the sensitivity and specificity of serum tPSA. Oesterling et al. pioneered the use of age-specific tPSA ranges, using data from 471 men with no evidence of PCa. Morgan et al. revised the age-specific ranges and reported substantially lower age-
specific values for white (40-49, 50-59, 60-69, and 70-79 years: 0.7, 1.0, 1.4, and 1.8 ng/mL, respectively) and black (40-49, 50-59, 60-69, and 70-79 years: 0.7, 1.1, 1.6, and 2.2 ng/mL, respectively) men without evidence of PCa. Lilja et al. assessed the PCa risk among men who participated in a cardiovascular prevention project (MPM) in Malmö, Sweden. The investigators measured the tPSA levels at the beginning of the program. Overall, 462 participants were diagnosed with PCa within a median of 18 years from start of the study. The odds ratio for a PCa diagnosis at an initial tPSA value of 0.51-1.0 ng/mL was 2.5 compared with a tPSA level of ≤0.50 ng/mL. The odds ratio increased to 7 for a tPSA of 1.0-1.5 ng/mL, and to 19 for a tPSA level of 2.01-3.0 ng/mL. In another analysis of the same cohort, the value of the PSA assessments in these younger men were compared with the blood taken from 1167 men aged 59-61 years. In that study, the prognostic accuracy of tPSA decreased with age but was not affected by the interval between the measurement and the diagnosis. In contrast, %f/tPSA added more important predictive value in older men but especially when the PCa diagnosis was close to the start of the study. European screening data have also indicated that a non-negligible proportion of patients will be diagnosed with PCa despite low tPSA levels. For example, on sextant biopsy, 7%-34% of men were found to have PCa, depending on prostate gland size.

However, the Prostate Cancer Prevention Trial questioned the validity of some of these values and indicated that PCa can be found even in patients with tPSA values below the lowest age-specific median values reported by Morgan et al. and Lilja et al. Therefore, few reference data exist to guide clinicians regarding a cutoff for biopsy in men with otherwise no evidence of a palpable abnormality. A similar paucity of referenced data exists regarding %f/tPSA. Catalona et al. suggested a cutoff of ≤24% to detect 90% of cancers and to avoid 18% of benign biopsy findings in patients with a PSA value

Figure 1. Scatterplots illustrating (A) median total prostate-specific antigen (tPSA) values and (B) percentage of free/total prostate-specific antigen (%f/tPSA) stratified by age for 3222 asymptomatic men with no clinical evidence of prostate cancer.

Figure 2. Overall and age category-specific distribution of (A) median total prostate-specific antigen (tPSA) and (B) percentage of free/total prostate-specific antigen (%f/tPSA) level and interquartile range.
2.6-4.0 ng/mL. In an update, Catalona et al.\textsuperscript{14} examined a variety of cutoffs, some of which were as low as 10%. Other investigators have recommended cutoffs of 18%-27%.

Taken together, these previously reported tPSA and %f/tPSA data indicate a lack of consensus regarding what tPSA and %f/tPSA values should be expected in patients with no clinical evidence of PCa. Thus, we decided to examine the tPSA and %f/tPSA values of our PCa screening cohort with the objective of adding to the existing knowledge.\textsuperscript{23,24,29}

Our data showed that one half the men had a PSA value of $\leq$1.0 ng/mL. The median of the entire cohort was 1.0 ng/mL and was 0.7, 0.9, 1.3, and 1.9 ng/mL for the age strata of 40-49, 50-59, 60-69, and 70-79 years, respectively.

Regarding %f/tPSA, older reports had suggested no relationship with age.\textsuperscript{23,24,29} Moreover, a variety of cutoffs were proposed.\textsuperscript{1,2,4,8,9,14,15,23,24,29,30} The present analysis demonstrated a relationship with age, with younger patients having substantially greater %f/tPSA median values (Figs. 1B and 2B). Moreover, our results have demonstrated that most men will have a %f/tPSA value $>27\%$. This cutoff was recommended by Catalona et al.\textsuperscript{15} in patients with a PSA value of 2.6-4.0 and by Uzzo et al.\textsuperscript{30} for patients with a PSA value of 2-20 ng/mL. Our results also indicated that a relative minority of patients will have a %f/tPSA value of $<25\%$. Lower cutoffs of 10% or even 18% might lack sensitivity.\textsuperscript{14}

Taken together, our findings indicate the following points. First, patients without clinical evidence of PCa should have a PSA value $<2.5$ ng/mL. In men aged 40-59 years, the tPSA value should be predominantly $<1.5$ ng/mL. The 2.5-ng/mL cutoff appears most appropriate for men aged 60-69 years. Only men aged 70-79 years should have a tPSA value of 2.5-3.5 ng/mL. Second, the %f/tPSA is less strongly related to age. Nonetheless, an age relation is present such that younger patients will have greater values than older patients. With the lower %f/tPSA variability according to age, an overall cutoff of 27% can be proposed, which correlates perfectly with the cutoffs proposed by Catalona et al.\textsuperscript{14,15} and Uzzo et al.\textsuperscript{30}

Third, our data originate from a patient population that is distinct from those included in previous analyses that focused on men from the United States and of various ethnic backgrounds. Our data originated from a French-Canadian population that virtually exclusively consisted of whites. In that respect, it is highly interesting that the data from African Americans or even white Americans have correlated closely with our data.

The present study had limitations. The most important was that biopsies were not taken as a part of the screening initiative. Therefore, men with a “normal” tPSA level might have had PCa. Moreover, we did not adjust for the effect of race, because virtually all the participants were white. Our findings might have been affected by a “volunteer bias,” because the men who volunteer to partici-

\section*{CONCLUSIONS}

Our results can guide clinicians regarding the population-based distribution of serum tPSA and %f/tPSA values. Those values can be used for the purpose of counseling and in the informed consent process before prostate biopsy.

\section*{References}


15. Catalona WJ, Smith DS, Ornstein DK. Prostate cancer detection in men with serum PSA concentrations of 2.6-4.0 ng/mL and benign prostate examination: enhancement of specificity with free PSA measurements. JAMA. 1997;277:1452-1453.

serum prostate-specific antigen levels of 2-4 nanograms per milliliter. Urology. 2002;60:31-35.


