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# Relationship Among Initial Serum Prostate Specific Antigen, Prostate Specific Antigen Progression and Prostate Cancer Detection at Repeat Screening Visits

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**Purpose:** We evaluated the probability of positive serum PSA (3 ng/ml or greater) and CaP detection at annual followup visits in men with negative initial PSA (less than 3 ng/ml) to optimize the re-screening schedule.

**Materials and Methods:** Data on 5,387 men 45 to 80 years old with negative PSA and no CaP diagnosis at the first screening visit were obtained from the Laval University Prostate Cancer Screening Program database. Accelerated failure time regressions were fitted to time from baseline to positive PSA and to time from positive PSA to CaP detection. The models were combined to estimate the cumulative probability of positive PSA followed by CaP detection at re-screening.

**Results:** The 5-year cumulative probability of detecting CaP at annual visits in men with baseline PSA up to 1.5 ng/ml remained below 0.8%, while it was 1.3%, 4.8% and 8.3% in men with PSA 1.5 to less than 2, 2 to less than 2.5 and 2.5 to less than 3 ng/ml, respectively. Time to positive PSA significantly decreased with increasing baseline PSA and age, while the time between positive PSA and CaP detection depended only on age. Men with PSA below 1.0 ng/ml could wait for 4 to 5 years before being re-tested, while men with PSA between 1.0 and 1.5 ng/ml should be screened every second year and men with PSA 1.5 ng/ml or greater should be screened every year.

**Conclusions:** The proposed retesting schedule using current PSA and age decreases the number of visits by 38.1%, while delaying the detection of only 2.4% of CaPs that would have been detected using annual PSA testing.

*Key Words:* prostate, prostatic neoplasms, mass screening, prostate-specific antigen

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Several randomized studies have proved that CaP screening based on serum PSA and possibly DRE as a first line test detects almost all tumors at an early and potentially curable stage.<sup>1-5</sup> It has also been demonstrated that re-testing at regular intervals results in a shift toward lower disease stages, which is a prerequisite for any efficient screening program.<sup>1,3,6,7</sup>

Ongoing European and United States screening studies use constant 1 to 4-year re-screening intervals.<sup>8</sup> The first results of the European trial indicate that a 4-year interval does not substantially decrease the overall detection rate at re-screening compared to the first screening, while the detection rate of interval cancers is 13.3% to 18.5%,<sup>9</sup> thus,

suggesting that a 4-year interval might be too long.<sup>5</sup> Still, cancer cases detected at re-screening benefit from a shift toward lower disease stages.<sup>6,7</sup> On the other hand, while re-screening yearly can almost eliminate all metastatic disease, it is not clear whether all patients need to be tested so frequently.<sup>1</sup>

Several population<sup>10-12</sup> and randomized<sup>3,13</sup> studies have already described the progression of serum PSA and the rate of CaP detection in men with initial serum PSA below the cutoff level, that is 2 to 4 ng/ml depending on the trial.<sup>8</sup> In the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial<sup>13,14</sup> and in other reports based on Japanese population data collected at irregular intervals<sup>10,12,15</sup> the cumulative probability of PSA increasing above 4 ng/ml led to the conclusion that re-screening may be performed within the next 1 to 5 years depending on the serum PSA measured previously.

We investigated the progression of serum PSA and CaP detection rates in men with initial PSA below 3 ng/ml who attended consecutive annual re-screening visits for up to 14 years.<sup>16</sup> We used current serum PSA to adjust the interval to the next PSA testing, while maintaining the probability of CaP cancer detection at followup as evenly and optimally as possible in every individual.

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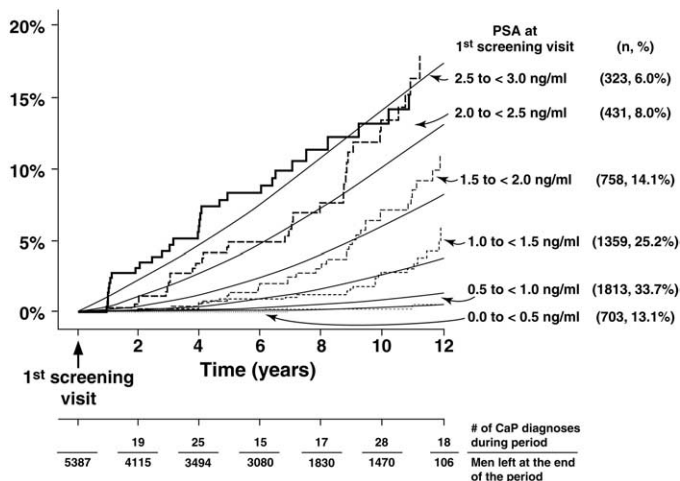


FIG. 1. Cumulative probability of CaP detection at followups in men with serum PSA less than 3 ng/ml and no CaP diagnosis at first screening visit. Solid lines indicate cumulative probabilities predicted by combination of models.

**MATERIALS AND METHODS**

**Data.** Data were obtained from the Laval University Prostate Cancer Screening Program.<sup>5</sup> Men in the Quebec City region who were 45 to 80 years old were randomly invited to participate in the study. As authorized by the Laval University Ethics Committee, each man who provided written informed consent had serum PSA measured by the Tandem-R® PSA assay or its equivalent and underwent DRE annually. If PSA was 3 ng/ml or greater, or if DRE was positive, the subject was referred for transrectal ultrasound with biopsies performed in the hypoechoic regions or when serum PSA was at least 20% above the PSA predicted by prostate volume. DRE was withdrawn from the annual followup visits starting 4 years after study initiation.<sup>17</sup>

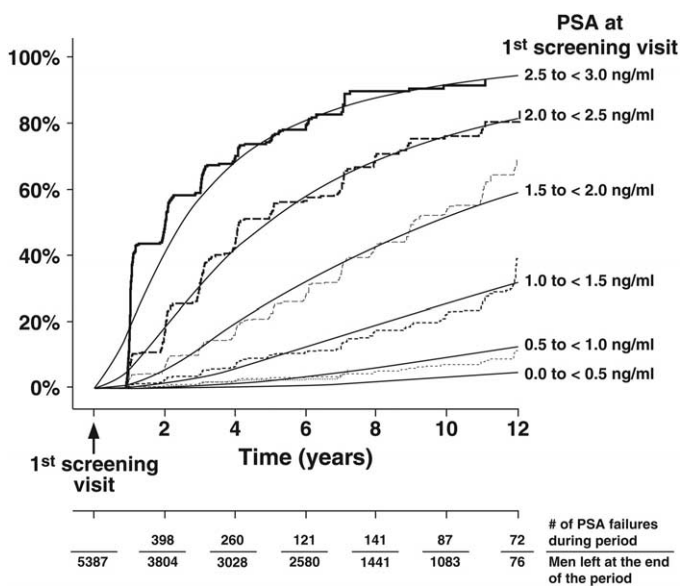


FIG. 2. Cumulative probability of first serum PSA 3 ng/ml or greater at followups in men with serum PSA less than 3 ng/ml and no CaP detected at first screening visit. Solid lines indicate predictions of accelerated failure time model.

TABLE 1. Accelerated failure time model 1—time between initial screening visit and first observation of serum PSA 3 ng/ml or greater and model 2—time between first observation of PSA 3 ng/ml or greater at annual followup visit and CaP detection, if not detected at visit when first positive PSA was observed

| Independent variables               | Model 1<br>(time to pos PSA 3 ng/ml or greater) | Model 2<br>(time between pos PSA and CaP detection in pts with no diagnosis at pos PSA at visit 1) |
|-------------------------------------|---|--|
| Visit 1 PSA/log 10 (age at visit 1) | -1.37/-1.96                                     | Age at pos PSA 1   |
| Parameter estimate                  | -1.37/-1.96                                     | -0.0277  |
| SE                                  | 0.04/0.47                                       | 0.0137   |
| p Value (Wald statistic)            | <0.0001/<0.0001                                 | 0.04   |
| OR                                  | 3.84/7.11                                       | 1.03   |

The analyzed data set includes 5,387 men with PSA less than 3 ng/ml and no CaP diagnosed at the first (baseline) screening visit who attended at least 1 annual followup visit. All PSA testing results obtained at consecutive annual visits (median 7, range 1 to 14) were retrieved from the database for a total of 40,812 PSA tests. PSA values collected after failure to present at 1 followup visit were ignored.

The first outcome variable was 1) time to CaP detection, that is time between baseline PSA and CaP detection, which was censored if no CaP was detected at the last visit. Since the clinical approach to CaP screening is a 2-step process that screens for men with positive PSA who are then referred for further investigation, time to CaP detection was separated into 2) time to positive PSA, that is time from the baseline visit to the first positive PSA, which was censored if PSA was still negative by the last visit, and 3) time between positive PSA and CaP detection, that is time to CaP detection – time to positive PSA, which was not calculated in men with censored time to positive PSA and was censored if no CaP was detected at the last visit.

**Analyses.** The 3 response variables were analyzed using Kaplan-Meier estimates and the log rank test to assess the

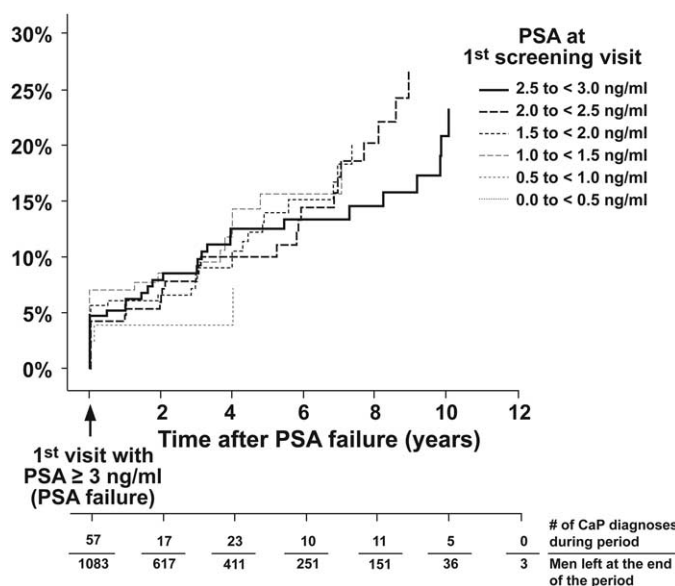


FIG. 3. Cumulative probability of CaP diagnosis at followups after first occurrence of serum PSA 3 ng/ml or greater according to serum PSA at initial screening visit.

significance of differences between various age and PSA groups. Accelerated failure time regressions were fitted to the data to identify significant independent variables correlated with the outcomes, eg age and PSA as is or after log and power transformation. Variables were kept in the model only if Wald statistic  $p < 0.05$ .

The independent chi-square test was performed to compare rates. However, contingency tables featuring cells with an expected count below 5 were analyzed using Fisher's exact test. All analyses were performed using SAS statistical software (SAS Institute, Cary, North Carolina) with significance considered at a type I error below 5%.

**Estimating the probability of CaP detection.** The probability of CaP detection at followup visits was estimated based on the combination of regression models predicting time to positive PSA, and time between positive PSA and CaP detection.

**Adjusting re-screening intervals.** To propose an optimized re-screening schedule intervals between screening visits were selected to maintain the predicted probability of CaP detection at every visit in every subject 0.5% or less. When the probability at 1 year was already estimated to be above 0.5%, annual re-screening visits were maintained. Limiting the risk at 0.5% was selected since it corresponds to the overall rate of CaP detection that was observed in our CaP screening program at annual followups.

**RESULTS**

**Time to CaP diagnosis.** The probability of detecting CaP at followup visits significantly correlated with initial serum PSA ( $p < 0.0001$ , fig. 1). There was a 13.7% probability of detecting CaP within 10 years in men with initial PSA 2 to less than 3 ng/ml. This was 3 and 74 times higher than in men with baseline PSA 1 to less than 2 and 0 to less than 1 ng/ml, respectively.

**Time to positive PSA.** Of the 5,387 men 1,083 attained at least 3 ng/ml at a followup visit. Figure 2 shows the highly significant relationship between time to positive PSA and initial PSA ( $p < 0.0001$ ). At the tenth annual visit 3%, 7%, 23%, 55%, 76% and 91% of the men with initial PSA less than 0.5, 0.5 to less than 1.0, 1.0 to less than 1.5, 1.5 to less than 2.0, 2.0 to less than 2.5 and 2.5 to less than 3.0 ng/ml, respectively, progressed to positive PSA. However, the difference between the 2 lowest PSA groups was not significant ( $p = 0.30$ ).

TABLE 2. CaP detection rate at first positive PSA (first annual followup with PSA 3 ng/ml or greater) according to serum PSA at initial visit (independent chi-square test  $p = 0.79$ )

| Screening Visit 1 Serum PSA (ng/ml) | No. Pts (%) | No. CaP Detected at First Pos PSA (%) |
|-------------------------------------|-------------|---------------------------------------|
| 0.0–Less than 0.5                   | 20 (1.8)    | 1 (5.0)                               |
| 0.5–Less than 1.0                   | 82 (7.6)    | 3 (3.7)                               |
| 1.0–Less than 1.5                   | 213 (19.7)  | 15 (7.0)                              |
| 1.5–Less than 2.0                   | 284 (26.2)  | 16 (5.6)                              |
| 2.0–Less than 2.51                  | 231 (21.3)  | 10 (4.3)                              |
| 2.5–Less than 3.0                   | 253 (23.4)  | 12 (4.7)                              |
| Totals                              | 1,083 (100) | 57 (5.3)                              |

TABLE 3. CaP detection rate at first positive PSA (first annual followup with PSA 3 ng/ml or greater) according to PSA (Fisher's exact test  $p = 0.53$ )

| Positive PSA 1 Serum PSA (ng/ml) | No. Pts (%) | No. Pos PSA at Visit 1 CaP Detected (%) |
|----------------------------------|-------------|---|
| 3.0–Less than 4.0                | 767 (70.8)  | 39 (5.1)                                |
| 4.0–Less than 5.0                | 183 (17.0)  | 13 (7.1)                                |
| 5.0–Less than 7.0                | 86 (7.9)    | 3 (3.5)                                 |
| 7.0–Less than 10                 | 26 (2.4)    | 2 (7.7)                                 |
| 10 or Greater                    | 21 (1.9)    | 0                                       |
| Totals                           | 1,083 (100) | 57 (5.3)                                |

The accelerated failure time regression model confirmed that initial PSA and to a lesser extent patient age were predictive of the odds of achieving 3 ng/ml or more at re-screening visits (table 1). The probability of positive PSA at followup visits in a 65-year-old man was 81% higher than in a 50-year old man with the same initial PSA. The risk in an 80-year-old man compared to that in a 65-year-old man was increased by 64%, thus, illustrating that the impact of the same age difference decreases as men become older. On the other hand, the probability of positive PSA increased by 284% for every initial PSA increment of 1 ng/ml.

**Time between positive PSA and CaP detection.** CaP was detected in 123 of the 1,083 men who attained at least 3 ng/ml at a followup visit at the time of the first positive PSA (57) or at a later followup visit (66). Figure 3 shows the cumulative probability of CaP detection following the first occurrence of PSA 3 ng/ml or greater. After 3 ng/ml was attained, the odds of CaP detection at the first occurrence of positive PSA or later no longer depended on initial PSA or on age (tables 2 to 4 and fig. 3).

Overall the CaP detection rate at the first positive PSA was 5.3%. In men not diagnosed at the first PSA 3 ng/ml or greater age at first positive PSA was significantly related to the probability of detecting CaP at a later followup visit ( $p = 0.04$ , table 1 and fig. 4).

**Probability of CaP detection at various screening intervals.** Table 5 was used to derive the optimal re-screening intervals by selecting the age and PSA immediately superior to the current age and PSA in an individual (fig. 5). For example, the next visit of a 57-year-old man with PSA 1.3 ng/ml would be planned using the interval of a 60 year-old man with PSA 1.5 ng/ml, ie 3 years (table 6). Since time to positive PSA was not significantly different in men with baseline PSA 0.0 to 0.5 and 0.5 to 1.0 ng/ml, the 2 groups were pooled, while applying the shortest interval to everyone (table 6). At the other end of the baseline PSA range CaP

TABLE 4. CaP detection rate at first positive PSA (first annual visit with a PSA 3 ng/ml or greater) according to age (independent chi-square test  $p = 0.94$ )

| Pos PSA 1 Age | No. Pts (%) | No. CaP Detected at First Pos PSA (%) |
|---------------|-------------|---------------------------------------|
| 45–54         | 54 (5.0)    | 3 (5.6)                               |
| 55–64         | 465 (42.9)  | 23 (5.0)                              |
| 65–74         | 473 (43.7)  | 26 (5.5)                              |
| 75 or Older   | 91 (8.4)    | 5 (5.5)                               |
| Totals        | 1,083 (100) | 57 (5.3)                              |

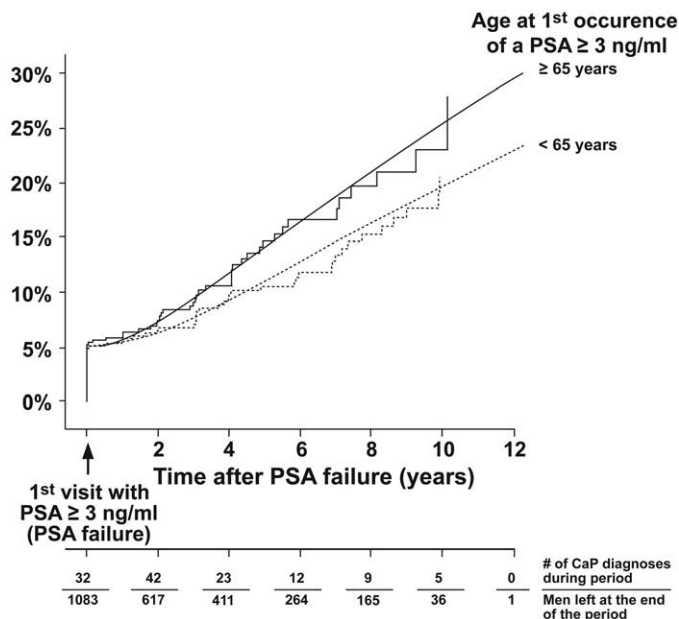


FIG. 4. Cumulative probability of CaP detection at followups after first occurrence of serum PSA 3 ng/ml or greater in men younger than 65 years and 65 years or older at first positive PSA. Solid lines indicate predictions of accelerated failure time model.

detection was 0.5% or greater in all men with initial PSA 2 ng/ml or greater, therefore, warranting annual retesting.

Re-testing intervals were tested using the data set of 5,387 men with negative PSA and no diagnosis of CaP at baseline (table 6). The actual PSA and age at each simulated re-testing interval were used to plan the next screening examinations. If according to the data collected annually positive PSA was actually measured before the next simulated visit, the case was categorized as delayed detection of first positive PSA. Similarly if CaP was actually diagnosed before the next simulated re-testing visit, the case was categorized as delayed CaP detection. Table 7 shows the results as scenario 1.

Table 7 also shows the impact of screening intervals considering wider ranges of age or completely ignoring this variable as scenarios 2 to 4. Finally, table 7 shows the impact of a 2 to 4-year constant interval between screening visits used in other prostate screening cancer trials, which was simulated in scenarios 5 to 7, respectively.

**DISCUSSION**

Our study demonstrates that the next screening visit can be efficiently scheduled according to current serum PSA and age with minimal consequences on the CaP detection rate, while decreasing the number of followup visits by 38%. Previous investigators had to rely on data collected from 2 to 4 years apart during a much shorter period<sup>3,13</sup> or at irregular intervals.<sup>10,12,15</sup> These groups limited their analyses to PSA progression to recommend a revised schedule of screening. None of these groups presented the impact that their proposed schedule would have on CaP detection.

PSA progression most commonly results from highly frequent benign hyperplasia.<sup>18</sup> Prostatitis is also a frequent cause of increased PSA. This explains that no CaP was

detected in 77% of men within 10 years of positive PSA and it makes the use of additional predictors, such as PSA density, useful tools to improve the positive predictive value.<sup>19</sup>

According to Hugosson et al the probability of PSA 3 ng/ml or greater 2 years after the baseline visit is 6.4%,<sup>3</sup> a value that is in agreement with the 8.4% observed in the current study. The higher percent could well have resulted from the older cohort in our study (ages 45 to 80 vs 55 to 65 years). Furthermore, no CaP was diagnosed at re-screening in men with baseline PSA below 1 ng/ml. By our analyses the predicted probability of CaP detection is only 1 in 3,000 in 60-year-old men with baseline PSA less than 1 ng/ml 2 years earlier. The cancer detection rate in the study of Hugosson et al at the first followup visit, including interval

TABLE 5. Cumulative probability of CaP detection at 1 to 4-year re-screening intervals, as predicted by models according to patient age and serum PSA at initial screening

| Initial PSA (age)  | % CaP Detection |        |        |       |
|--------------------|-----------------|--------|--------|-------|
|                    | Yr 1            | Yr 2   | Yr 3   | Yr 4  |
| <b>0.5 Ng/ml:</b>  |                 |        |        |       |
| 45                 | 0.0001          | 0.0018 | 0.0073 | 0.018 |
| 50                 | 0.0002          | 0.0025 | 0.0098 | 0.024 |
| 55                 | 0.0002          | 0.0033 | 0.013  | 0.030 |
| 60                 | 0.0003          | 0.0043 | 0.016  | 0.038 |
| 65                 | 0.0004          | 0.0054 | 0.020  | 0.047 |
| 70                 | 0.0006          | 0.0067 | 0.024  | 0.056 |
| 75                 | 0.0007          | 0.0081 | 0.029  | 0.068 |
| 80                 | 0.0009          | 0.0097 | 0.034  | 0.081 |
| <b>1.0 Ng/ml:</b>  |                 |        |        |       |
| 45                 | 0.0017          | 0.017  | 0.053  | 0.11  |
| 50                 | 0.0023          | 0.022  | 0.067  | 0.14  |
| 55                 | 0.0031          | 0.028  | 0.083  | 0.17  |
| 60                 | 0.0040          | 0.034  | 0.10   | 0.20  |
| 65                 | 0.0050          | 0.041  | 0.12   | 0.24  |
| 70                 | 0.0062          | 0.049  | 0.14   | 0.28  |
| 75                 | 0.0075          | 0.058  | 0.16   | 0.33  |
| 80                 | 0.0090          | 0.067  | 0.19   | 0.39  |
| <b>1.5 Ng/ml:</b>  |                 |        |        |       |
| 45                 | 0.016           | 0.10   | 0.26   | 0.46  |
| 50                 | 0.021           | 0.13   | 0.31   | 0.55  |
| 55                 | 0.026           | 0.15   | 0.37   | 0.64  |
| 60                 | 0.032           | 0.18   | 0.43   | 0.74  |
| 65                 | 0.039           | 0.21   | 0.49   | 0.86  |
| 70                 | 0.046           | 0.24   | 0.56   | 0.98  |
| 75                 | 0.054           | 0.28   | 0.63   | 1.13  |
| 80                 | 0.062           | 0.31   | 0.72   | 1.29  |
| <b>2.0 Ng/ml:</b>  |                 |        |        |       |
| 45                 | 0.098           | 0.43   | 0.85   | 1.32  |
| 50                 | 0.12            | 0.50   | 0.98   | 1.51  |
| 55                 | 0.15            | 0.58   | 1.12   | 1.71  |
| 60                 | 0.17            | 0.66   | 1.25   | 1.92  |
| 65                 | 0.20            | 0.74   | 1.40   | 2.16  |
| 70                 | 0.23            | 0.83   | 1.56   | 2.43  |
| 75                 | 0.26            | 0.91   | 1.73   | 2.74  |
| 80                 | 0.29            | 1.00   | 1.92   | 3.10  |
| <b>2.5 Ng/ml:</b>  |                 |        |        |       |
| 45                 | 0.41            | 1.22   | 2.00   | 2.72  |
| 50                 | 0.48            | 1.38   | 2.21   | 3.01  |
| 55                 | 0.56            | 1.52   | 2.42   | 3.31  |
| 60                 | 0.63            | 1.67   | 2.65   | 3.65  |
| 65                 | 0.70            | 1.82   | 2.88   | 4.04  |
| 70                 | 0.78            | 1.97   | 3.15   | 4.48  |
| 75                 | 0.85            | 2.12   | 3.44   | 5.00  |
| 80                 | 0.92            | 2.28   | 3.78   | 5.61  |
| <b>2.99 Ng/ml:</b> |                 |        |        |       |
| 45                 | 1.19            | 2.50   | 3.44   | 4.26  |
| 50                 | 1.33            | 2.70   | 3.69   | 4.60  |
| 55                 | 1.47            | 2.89   | 3.95   | 4.98  |
| 60                 | 1.60            | 3.07   | 4.22   | 5.42  |
| 65                 | 1.73            | 3.25   | 4.53   | 5.93  |
| 70                 | 1.84            | 3.44   | 4.88   | 6.53  |
| 75                 | 1.96            | 3.63   | 5.29   | 7.24  |
| 80                 | 2.07            | 3.85   | 5.77   | 8.09  |

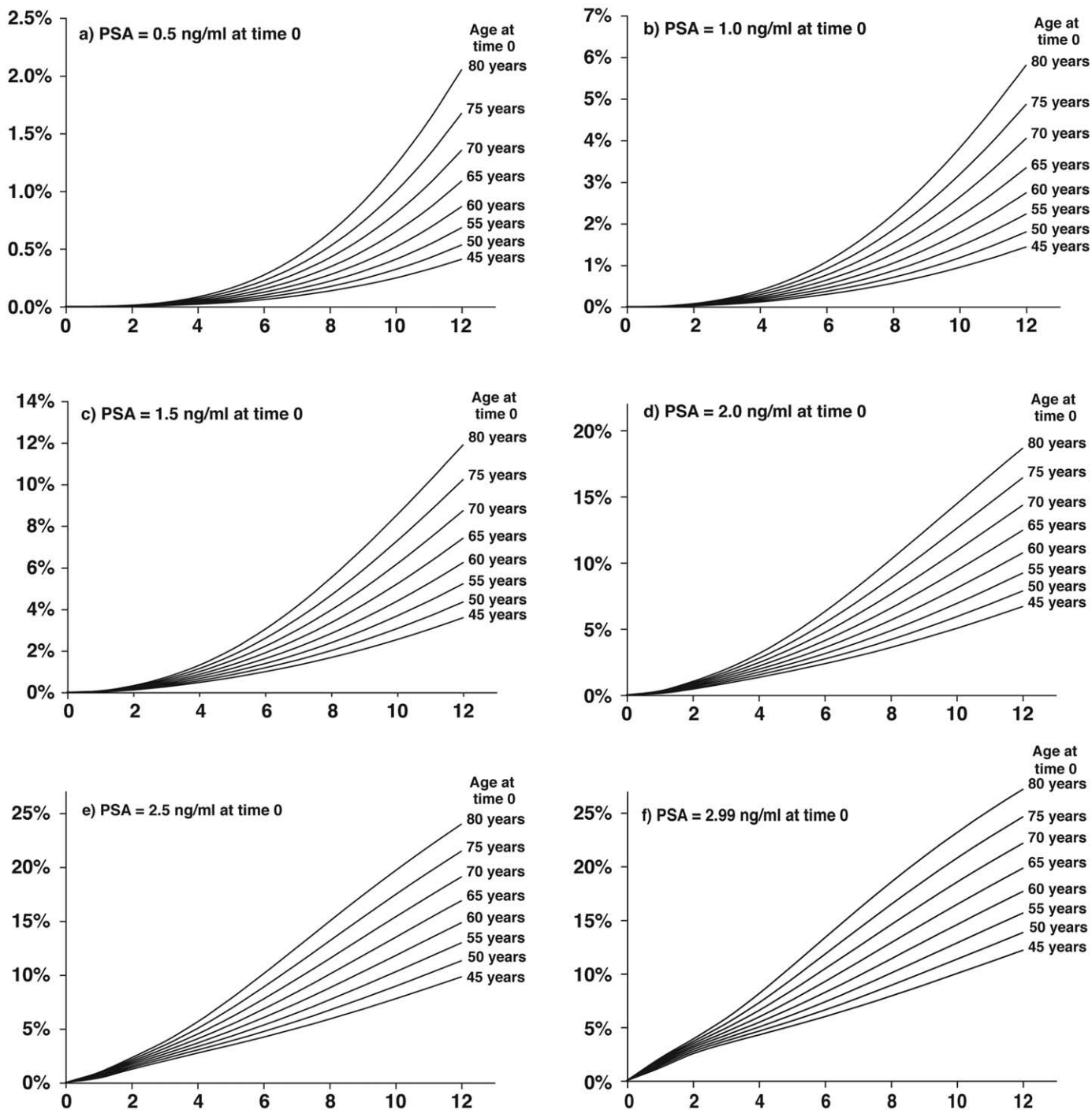


FIG. 5. Predicted cumulative probabilities of CaP detection at followup visits in 45 to 80-year-old men with initial serum PSA 0.5, 1.0, 1.5, 2.0, 2.5 and 2.99 ng/ml.

cancers, was 1.1% in men with initial PSA 3 ng/ml or less, while our estimate is 0.45%. Our lower detection rate likely resulted from the use of DRE at the baseline visit in our trial. At the baseline visit we reported a detection rate of 0.35% in men with positive DRE and negative PSA.<sup>1</sup> Had DRE not been used, these cases would have increased the estimated detection rate at 2 years, which would be much closer to the evaluation of Hugosson et al.<sup>3</sup>

In men with PSA between 1 and less than 2 ng/ml the recommendation of Hugosson et al to perform screening

procedures every second year<sup>3</sup> is consistent with our data, although it results from averaging the risks of all men in this range. We established that men with PSA below 1.5 ng/ml could be re-screened only every 2 to 3 years depending on their age, while men with PSA 1.5 ng/ml or greater must be screened yearly. At the upper end of the negative PSA range, ie 2.5 ng/ml or greater, repeating the screening procedures may even be considered before 1 year since at such a short interval the cumulative probability of CaP is already 2.7%.

TABLE 6. Delay to next re-screening visit predicted by models to maintain 0.5% or less probability of CaP diagnosis at this next screening visit and modified to account for nonsignificant differences and identical re-screening intervals with minimum 1-year interval

| Age   | Yrs Delayed (ng/ml PSA) |                   |                   |                   |                   |                   |
|---|-------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
|   | 0.0-Less Than 0.5       | 0.5-Less Than 1.0 | 1.0-Less Than 1.5 | 1.5-Less Than 2.0 | 2.0-Less Than 2.5 | 2.5-Less Than 3.0 |
| Model 1 prediction:                           |                         |                   |                   |                   |                   |                   |
| 49 or Younger                                 | 11                      | 6                 | 3                 | 2                 | 1                 | <1                |
| 55-59   | 10                      | 6                 | 3                 | 1                 | <1                | <1                |
| 60-64   | 9                       | 5                 | 3                 | 1                 | <1                | <1                |
| 65-69   | 9                       | 5                 | 3                 | 1                 | <1                | <1                |
| 70-74   | 8                       | 5                 | 2                 | 1                 | <1                | <1                |
| 75-79   | 7                       | 4                 | 2                 | 1                 | <1                | <1                |
| 80 or Older                                   | 7                       | 4                 | 2                 | 1                 | <1                | <1                |
| Combining 2 lowest and 2 highest PSA ranges:* |                         |                   |                   |                   |                   |                   |
| 49 or Younger                                 | 6                       |                   | 3                 | 2                 |                   | 1                 |
| 55-59   | 6                       |                   | 3                 | 1                 |                   | 1                 |
| 60-64   | 5                       |                   | 3                 | 1                 |                   | 1                 |
| 65-69   | 5                       |                   | 3                 | 1                 |                   | 1                 |
| 70-74   | 5                       |                   | 2                 | 1                 |                   | 1                 |
| 75-79   | 4                       |                   | 2                 | 1                 |                   | 1                 |
| 80 or Older                                   | 4                       |                   | 2                 | 1                 |                   | 1                 |

\* Because time to positive PSA was not significantly different (0.0 to less than 1 ng/ml) and re-screening was set at the minimal interval (2.0 to less than 3.0 ng/ml).

Not surprisingly Crawford et al, who used a 4 ng/ml cutoff, reported cumulative probabilities of progression to positive PSA that are much lower than our estimates based on a 3 ng/ml threshold.<sup>13</sup> Ito et al also used the 4 ng/ml cutoff and reported cumulative probabilities much lower than Crawford et al<sup>13</sup> as well as a clear relationship between the rate of positive PSA and age.<sup>10,12</sup> The 2 groups recommended screening intervals using the baseline PSA level that is compatible with our findings. However, their cutoff leaves men with PSA between 3 and 4 ng/ml with no further investigation until PSA is 4 ng/ml. The current study demonstrates that, at the time that 3 ng/ml is attained or exceeded, men have already a 5.3% probability of being

diagnosed with CaP and the risk continues to grow with time. This was also confirmed by Hugosson et al, who reported that in men with negative baseline PSA 75% of cancers detected at the second round were in the range of 3 to 4 ng/ml.<sup>3</sup> The efficacy of a cutoff at 3 ng/ml while omitting DRE has already been well established.<sup>1,2,5,20</sup>

**CONCLUSIONS**

According to the strategy presented in this report scheduling re-screening based on the current PSA value and accounting for 2 age ranges, ie younger than 65, or 65 years or older, de-

TABLE 7. Percent decrease in number of followup visits vs annual re-screening resulting from various screening schedules and their impact on the number of men with delayed identification of first positive PSA and of CaP detection

| Scenario (age)                | Yr Intervals (ng/ml PSA) |                   |                   |                   | Vs Annual Visits                         |                                    |                                    |
|-------------------------------|--------------------------|-------------------|-------------------|-------------------|--|------------------------------------|------------------------------------|
|                               | 0.0-Less Than 1.0        | 1.0-Less Than 1.5 | 1.5-Less Than 2.0 | 2.0-Less Than 3.0 | No. Pos PSA 1 Delayed Detection (95% CI) | No. Delayed CaP Detection (95% CI) | % Followup Visit Decrease (95% CI) |
| Scenario 1:                   |                          |                   |                   |                   |  |                                    |                                    |
| Younger than 50               | 6                        | 3                 | 2                 | 1                 | 112 (10.38.6-12.3)                       | 3 (2.4, 0.5-7.0)*                  | 39.6 (39.1-40.1)                   |
| 50-54                         | 6                        | 3                 | 1                 | 1                 |  |                                    |                                    |
| 55-59                         | 5                        | 3                 | 1                 | 1                 |  |                                    |                                    |
| 60-64                         | 5                        | 3                 | 1                 | 1                 |  |                                    |                                    |
| 65-69                         | 5                        | 2                 | 1                 | 1                 |  |                                    |                                    |
| 70-74                         | 4                        | 2                 | 1                 | 1                 |  |                                    |                                    |
| 75 or Older                   | 4                        | 2                 | 1                 | 1                 |  |                                    |                                    |
| Scenario 2:                   |                          |                   |                   |                   |  |                                    |                                    |
| Younger than 50               | 6                        | 3                 | 2                 | 1                 | 106 (9.8, 8.1-11.7)                      | 3 (2.4, 0.5-7.0)*                  | 37.6 (37.1-38.1)                   |
| 50-59                         | 5                        | 3                 | 1                 | 1                 |  |                                    |                                    |
| 60-69                         | 5                        | 2                 | 1                 | 1                 |  |                                    |                                    |
| 70 or Older                   | 4                        | 2                 | 1                 | 1                 |  |                                    |                                    |
| Scenario 3:                   |                          |                   |                   |                   |  |                                    |                                    |
| Younger than 65               | 5                        | 3                 | 1                 | 1                 | 110 (10.2, 8.4-12.1)                     | 3 (2.4, 0.5-7.0)*                  | 38.10 (37.6-38.6)                  |
| 65 or Older                   | 4                        | 2                 | 1                 | 1                 |  |                                    |                                    |
| Scenario 4: no age group      |                          |                   |                   |                   |  |                                    |                                    |
| Scenario 5: constant interval | 4                        | 2                 | 1                 | 1                 | 74 (6.8, 5.4-8.5)                        | 4 (3.3, 0.9-8.1)                   | 31.9 (31.5-32.4)                   |
| Scenario 6: constant interval |                          | 2                 |                   |                   | 636 (58.7, 55.7-61.7)                    | 68 (55.3, 46.1-64.3)               | 50                                 |
| Scenario 7: constant interval |                          | 3                 |                   |                   | 803 (74.1, 71.4-76.7)                    | 85 (69.1, 60.1-77.1)               | 67                                 |
|                               |                          | 4                 |                   |                   | 888 (82.0, 79.6-84.2)                    | 96 (78.1, 69.7-85.0)               | 75                                 |

\* Median delay 3 years, 3 patients with stage B.

increases the number of followup visits by 38% compared to annual screening. Adopting a constant interval of 2 years decreases the number of visits by an extra 11.9% but leads to a delayed diagnosis in 55.3% of CaP cases. Finally, a constant 4-year interval decreases the number of screening visits by 75% at the cost of delaying the diagnosis of CaP in 78.1% of cases.

#### Abbreviations and Acronyms

|     |   |                            |
|-----|---|----------------------------|
| CaP | = | prostate cancer            |
| DRE | = | digital rectal examination |
| PSA | = | prostate specific antigen  |

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#### EDITORIAL COMMENT

It would be important to set the optimal screening interval in terms of not only maintaining the sensitivity of detecting clinically significant cancer, but also saving the cost of screening. These authors clearly report that the cumulative probability of CaP detection and increased PSA above 3.0 ng/ml increased significantly with increasing initial PSA. The cumulative probability of CaP detection may underestimate the true risk of CaP cancer because not all men with abnormal findings on PSA and DRE on consecutive screening agree to undergo prostate biopsy. Alternatively the cumulative probability of increased PSA above 3.0 ng/ml may overestimate the true cancer rate because some men may have a noncancer related PSA increase.

However, these authors clearly report that setting the re-screening interval as stratified by age and baseline PSA may be much better than setting constant intervals between 2 and 4 years in terms of the risk of delayed detection of a PSA increase above 3.0 ng/ml and the risk of delayed cancer detection.

There has been concern that establishing an internationally standardized screening system might be difficult because of racial and ethnic differences around the world as well as the huge difference in the risk of CaP between men from Western countries and those from Asian countries. Most recently we noted that there appeared to be no significant difference in the risk of CaP between Dutch and Japanese males in whom baseline PSA was within the same range based on a cooperative study between Europe and Japan.<sup>1</sup> The current study supports the hypothesis that

baseline PSA may be a key issue for establishing an internationally standardized and optimal screening system regardless of race.

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1. Ito, K., Raaijmakers, R., Roobol, M., Wildhagen, M., Yamanaka, H. and Schröder, F. H. Prostate carcinoma detection and increased prostate-specific antigen levels after 4 years in Dutch and Japanese males who had no evidence of disease at initial screening. *Cancer*, **103**: 242, 2005

**REPLY BY AUTHORS**

In our study annual screening was clearly not necessary for all men, thus decreasing the costs appreciably. In fact, the costs were reduced by 38.1% using our calculations with no loss of efficacy of screening for detecting early stage cancer. Since our men were seen every year, lack of biopsy acceptance should be equally distributed between those in whom prostate cancer was confirmed on biopsy and those in whom

biopsies were negative. In fact, there was no relationship between the compliance to biopsies and cancer. Moreover, because men were seen annually the opportunity to repeat the recommendation for biopsy every year if required was provided. In clinical practice the lack of biopsy acceptance is always an issue having no relation with the screening strategy chosen. However, medicine will have done the best it can for each of these men. It remains to the physician to clearly explain the risk of no biopsy when such a biopsy is medically indicated. In fact few patients refuse biopsy following proper explanations.

A PSA increase to greater than 3.0 ng/ml is not equivalent to the presence of cancer, but only serves as a red light indicating a higher risk of cancer that must be investigated further. There is no risk of overestimating the true cancer rate when one relies on positive biopsies.

The demonstration that there is no significant difference in the risk of developing prostate cancer for Dutch and Japanese men with a serum PSA within the normal range is useful. In fact, such an observation suggests that the data obtained in our study could potentially be applied internationally.