APPENDIX

E

Studies of Repeat/Serial Prostate-Specific Antigen Testing Yield for Prostate Cancer Screening and Early Detection

APPENDIX E: STUDIES OF REPEAT/SERIAL[a] PROSTATE-SPECIFIC ANTIGEN TESTING YIELD FOR PROSTATE CANCER SCREENING AND EARLY DETECTION: RESEARCH DESIGN AND FINDINGS

Author	Biases and methodologic weaknesses[b]	Setting	Age (year) (mean)	Number patients enrolled (%)	Abnormal PSA criterion (%)	Biopsy criteria	No. patients (%) with criteria No. patients (%) biopsied	No. (%) PC detected	No. (%) PC clinically localized	No. (%) PC pathologically localized	Positive predictive value of criteria	Treatment
Brawer et al., 1993[c]	2,3,6,7,8	U.S. Urology Clinic Public recruited Second year of screening study Includes only patients whose year 1 PSA was < 4 ng/mL Many men were evaluated at non–study sites but these data not included Blinding methods not specified	> 50 (67) Similar age distribution to original cohort (Brawer 1992)	701 Reflects 66% of original cohort with PSA < 4 None of these had DRE/TRUS in year 1 of study	20% increase in PSA above year 1 level; Absolute PSA > 1.5 also used as criterion for biopsy recommendation 75/701 (11%) had PSA > 4 at year 2, but only 19/75 (25%) received biopsy Presumably all of the 75 were recommended to get biopsy, but reasons for noncompliance not specified.	If 20% increase PSA, then DRE with biopsy if positive If absolute PSA > 1.5 ng/mL, systematic biopsy with TRUS guidance regardless of DRE Abnormal DRE included asymmetry, induration, nodule Abnormal TRUS included hypoechoic peripheral zone lesion	260/701 (37%) had 20% increase PSA 82/701 (12%) biopsied overall 159/260 (61%) had PSA > 1.5; and 71/159 (45%) agreed to DRE biopsy; 50/71 (70%) had abnormal DRE; 101/260 (39%) had PSA < 1.5; 31/101 (31%) agreed to DRE; 11/31 (36%) had abnormal DRE and got biopsy	14/701 (2.0%) overall Among 260 with 20% increase in PSA over 1 year, 14/260 (5.4%) yield 5/14 cancers had only asymmetry or a benign gland on DRE 2/14 cancers (14%) had PSA > 4 17/68 benign biopsies (25%) had PSA >4	13/14 (93%)	Not known 7/8 who received surgical staging were organ–confined or had negative margins No data on prostate cancer volumes at surgery provided	14/82 (17%)	RP–8 No data for other 6
Catalona et al., 1993	2,3,6,7,8	U.S. Urology Clinic Public recruited Original cohort 10,251 men	50–90 (63)	9,333 serial screenees (up to 37 months after initial screening PSA) Actual number of patients who received multiple serial biopsies (mean, range) not specified	Overall > 4 ng/mL 873/9333 (9.4%) if age ≤ 70 years 693/8320 (8.3%) if age > 70 years 180/1013 (17.8%) PSA 4.1–9.9 ng/mL 743/9333 (8%) PSA ≥ 10 ng/mL 130/9333 (1.4%)	PSA > 4 ng/mL twice on any of 6 month serial checks, then DRE and TRUS. If either abnormal biopsy recommended No systemic biopsies on PSA alone If biopsy neg. repeat PSA at 6 month intervals and repeat DRE/TRUS, with biopsy if indicated, if PSA > 4 again	873/9,333 (9.4%) 465/9,333 (5%)	195/9,333 (2.0%) overall If age ≤ 70 years, 153/8320 (1.8%) If age > 70 years, 42/1013 (4.1%) Number Cancers detected: First biopsy 90 Second biopsy 84 Third biopsy 17 Fourth biopsy 4 Denominators not provided	170/175 (97%); missing data in 20	92/129 (71%); missing data in 46 If age ≤ 70 years, 84/111 (76%) If age > 70 years, 8/18 (44%)	195/465 (42%), overall 165/392 (42%) if PSA 4.1–9.9 ng/mL 30/73 (41%) if PSA ≥ 10 ng/mL If age < 70 years, 153/363 (42%). if age > 70 years, 42/102 (42%)	Results not stratified by initial screening or serial screening. See Appendix D for aggregated treatment outcomes for the total 491 cancers detected in both cohorts. No long–term outcome data.

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APPENDIX E: STUDIES OF REPEAT/SERIAL[a] PROSTATE-SPECIFIC ANTIGEN TESTING YIELD FOR PROSTATE CANCER SCREENING AND EARLY DETECTION: RESEARCH DESIGN AND FINDINGS CONTINUED

Author	Biases and methodologic weaknesses[b]	Setting	Age (year) (mean)	Number patients enrolled (%)	Abnormal PSA criterion (%)	Biopsy criteria	No. patients (%) with criteria No. patients (%) biopsied	No. (%) PC detected	No. (%) PC clinically localized	No. (%) PC pathologically localized	Positive predictive value of criteria	Treatment
Mettlin et al ACS–NPCDP, 1993	2,3,6,7,8	10 sites in U.S./ Canada Hospital/ Clinic Public recruited Annual evaluation up to 5 years	55–70 on entry (63) 2,999 original enrollees	1899 men reported with 2 sequential exams with complete data, no cancer on first exam. Only results of followup testing reported here.	> 4 ng/mL 248/1899 (22%) follow–up PSA abnormal Patients not biopsied for PSA results alone Only 1783/1899 (94%) of patients in follow–up group received PSA test	Abnormal DRE and/or abnormal TRUS (unknown number biopsies recommended for PSA > 10 ng/mL) 49/248 (20%) biopsied with PSA > 4 in follow–up	216/1899 (11%) on follow–up testing 196/1899 (10%) biopsied on basis follow–up testing	33/1899 (1.7%) on follow–up testing If initially 55–59 years, 1% detection rate, If 60–64 years, 1.1% detection rate, If 65–70 years, 3.1% detection rate	23/24 (96%) missing data in 9 cases	Not provided for follow–up testing group	For PSA > 4, 22/248 (9%) with follow–up testing 11/33 cancers detected in follow–up testing group had PSA < 4	Not stratified by followup testing group, See Appendix D for treatment choices for overall cohort

[a] Refers to followup with PSA but in the case of Mettlin, (1993) PSA is not used as a primary criterion for biopsy. The criteria for biopsy in all 3 of these papers are different. However, we specifically do not include papers that evaluate PSA or velocity as principal issue (see Carter, 1992). Rather, serial PSA refers to the detection rate and predictive value of repeated measures of PSA testing. However, use of PSA and protocol in the 3 studies differ significantly.

[b] Legend for study biases and methodologic weaknesses: 1) not population–based or community setting; 2) selection (including self) and/or referral biases; 3) nonrandom study group accrual, 4. Explicit inclusion/exclusion criteria not provided; 5) abnormal test criteria not described; 6) incomplete application of appropriate reference (gold) standard (work–up bias); 7) lack of proper blinding in test interpretation; 8) failure to account completely for all enrolled subjects (including biopsy of all abnormal tests and reporting of clinical and pathologic stage data). For each study listed in this appendix, the presence of one or more of these deficiencies is denoted with the corresponding number (1–8). We chose not to qualify weight to the extent of each particular methodologic weaknesses.

[c] In the Brawer study, the use of the arbitrary PSA increase of 20% serially actually constitutes a form of PSA velocity. Unlike the Catalona (1993) study that followed all patients in the original cohort regardless of initial PSA and performed DRE/TRUS and biopsy on those with persistent or newly developed PSA, the Brawer followup study evaluates only those patients who had an original PSA < 4 ng/mL.