APPENDIX

D

Studies of Prostate-Specific Antigen for Prostate Cancer Screening and Early Detection

APPENDIX D: STUDIES OF PROSTATE SPECIFIC ANTIGEN FOR PROSTATE CANCER SCREENING AND EARLY DETECTION: RESEARCH DESIGN AND FINDINGS

Author	Biases and methodologic weaknesses[a]	Setting	Age (year) (mean)	Number patients enrolled (%)	Abnormal PSA criterion (%)	Biopsy criteria	No. patients (%) with criteria No. patients (5) biopsied	No. (%) PC detected	No. (%) PC clinically localized	No. (%) PC pathologically localized	PPV %[b] PSA	Treatment
Babaian et al., 1992 ACS-NPCDP[c]	2,3,6,7,8	10 sites in U.S./Canada, hospital/ clinic-based public invited	55-70 (63)	2425 over 3.5 years (PSA in 2,227)	> 4 ng/mL (not provided)	Abnormal DRE and/or TRUS (11 additional biopsies for abn PSA, most > 10 ng/mL) blinding not specified	Not provided 520/2425 (21%) year 1 - 395 year 2 - 102 year 3 - 23	88/2,425 (3.6%) no data on grade/volume	Not provided	Not provided	59/137 (43%)	Not provided
Babaian et al., 1991	1,2,3,4,6,7,8	Urology Clinic Cancer (most symptomatic) referral and selection biases	50-75 (63 median)	362 (75 MD referral recorded)	> 4 ng/mL 90/362 (25%)	Abnormal DRE and/or TRUS, or PSA > 20 No blinding	120/362 (33%) 109/362 (30%)	37/362 (10%) 27/75 (36%) MD referred; 10/287 (3%) self referred	23/37 (62%)	Not provided	30/90 (33%)	Not provided
Brawer et al., 1992	2,3,6,7,8	U.S. Urology Clinic Public recruited	>50 (67)	1249	> 4 ng/mL 187/1,249 (15%)	If PSA > 4, then DRE/TRUS with systematic biopsy adjunct blinding not specified	187/1249 (15%) 105/1249 (8.4%)	32/1249 (2.6%) no data on grade/ volume	30/32 (94%)	9/32 (28%) 4 of the 9 capsule penetration without perforation 16 surgical staging	32/105 (30%)	RP - 15 PL - 1 RT - 10 No TX - 6
Catalona et al., 1991	2,3,6,7,8	U.S. Urology Clinic Public recruited	50-89	1653	< 4 ng/mL 137/1653 (8.3%)	If PSA > 4 on initial or 6 month re-test, then DRE and TRUS, biopsy if either abn blinding not specified	137/1653 (8.3%) 112/1653 (6.8%)	37/1653 (2.2%)[d] no data on grade/volume	36/37 (97%)	12/37 (32%) 33 surgical staging	37/112 (33%) if PSA 4-9.9 19/85 (22%) if PSA ≥ 10 18/27 (67%)	Not provided (at least 19 had RP)
Catalona et al., 1993	2,3,6,7,8	U.S. Urology Clinic Public recruited	50-90 (63)	10,251 (but 622 "protocol violations") 9,629 initial screen 9,333 serial screen (up to 37 month followup)	> 4 ng/mL 902/9629 (9.4%) initial 873/9333 (9.4%) serial	If PSA > 4 twice initially, or on any 6 month serial check then DRE an TRUS. If either abn, biopsy. No systematic biopsy	902/9629 (9.4%) 860/9629 (8.9%) initial 873/9333 (9.4%) 465/9333(5%) serial	296/9629 (3.1%) initial 195/9333 (2.0%) serial 491/9629 (5.1%) total	277/296 (94%) initial 170/175 (97%) serial, but missing data	153/262 (58%) initiate, but 27 clinically localized did not get surg stage 92/129 (71%) serial, but missing data in 46 patients	296/860 (34%) overall initial 174/652 (27%) PSA 4 - 9.9 initial 122/208 (59%) PSA > 10, initial	Of total 491: RP - 348 RT - 68 HT - 27 No TX - 16 Pending - 32
Chadwick et al., 1991	3,4,6,7,8	British population-based general practice recruitment	55-69	863 eligible 814 recruited 472 screened 437 got PSA 407 got DRE	> 4 ng/mL 63/472 (13%)	If PSA > 4 and/or DRE abnormal, TRUS recommended. If TRUS abn, biopsy recommend	75/472 (16%) 12 of 75 for abn DRE alone 29/472 (6%) biopsied	7/472 (1.5%) (mean PSA 17) No data on size/volume	7/7 (100%)	5/7 (71%) 5 surgical staging	7/63 (11%)	RP - 5 No TX - 2

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Author	Biases and methodologic weaknesses[a]	Setting	Age (year) (mean)	Number patients enrolled (%)	Abnormal PSA criterion (%)	Biopsy criteria	No. patients (%) with criteria No. patients (5) biopsied	No. (%) PC detected	No. (%) PC clinically localized	No. (%) PC pathologically localized	PPV %[b] PSA	Treatment
Cooner et al., 1990	1,2,3,4,6,7,8	U.S. Group Urology Practice referral bias [selected population many symptomatic with prostatism of varyinge gree]	50-89	1,807	> 4 ng/mL 602/1,807 (33%) 4-10 ng/mL 366/1,807 (20%) > 10 ng/mL 236/1,807 (13%)	Abnormal TRUS (hypoechoic) No systematic biopsy. DRE, PSA performed but not basis for biopsy No blinding.	835/1,807 (46%) all biopsied	263/1,807 (14.5%) < 3.0 cc vol 172/263 (65%) > 3.0 cc vol 91/263 (35%)	136/242 (56%) of data available	43/263 (16%) 60 patients surgically staged	263/835 (32%)	RP - 57
Drago et al., 1992[e]	1,2,3,5,6,7,8	U.S. Academic Urology Clinic	55-70 (64)	1940 "asymptomatic" No clear description of recruitment process. Annual followup over 4.5 years.	> 4 ng/mL 989/1,940 (51%)	Abnormal DRE and/or TRUS systematic biopsy not used 27 of patients biopsied on basis Abn PSA but level not specified.	Not provided. 416/1940 (21%) biopsied Initial, 320 biopsied 2nd, 80 biopsied 3rd, 16 biopsied	79/1940 (4.1%) cumulative yield No data on grade/tumor [57/79 (72%) of PC had PSA >4]	64/79 (81%)	Not provided.	57/137 (42%) of the 989 patients with PSA > 4 not biopsied.	Not provided.
Guinan et al., 1987	1,2,3	Inpatient Urology Service Comparative study of 5 studies, including TRUS, PSA. All symptomatic selection bias. Not generalizable to office-based population.	Mean 68	280	Not specified "Mean plus 1 S.D." Hybritech 102/280 got PSA (36%)	Unknown for entire group: only 46/102 (45%) PSA 'pos' All 280 biopsied	Actual prevalence 78/280 (28%) of PSA tested 42/102 (41%)	Not specified.	Not specified.	31/46 (67%) sensitivity = 31/42 (74%) specificity = 45/60 (75%)	Not provided.	
Gustafsson et al., 1992	6,8	Swedish Urology Clinic Random selection population-based	55-70	2400 eligible (census database) 1,782 recruited No data on number of patients with urologic symptoms or evidence of BPH.	> 4 ng/mL 306/1782 (17%)	Abnormal DRE, TRUS or PSA > 10 ng/mL (systematic biopsy if PSA >10). Patients received all 3 tests Abn DRE (nodule, induration, asymmetry) TRUS (hypo or asymmetry).	Not provided 371/1782 (21%) biopsied Average 3 fine needle aspirates/ patient and 2-4 core biopsy/ patient.	65/1782 (3.6%) If age 55-59 7/481 (1.5%) age 60-64 26/585 (4.4%) age 65-70 32/716 (4.5%) Overall PSA alone 52/1782 (2.9%)	40/65 (62%) (2.2% of 1782) T2A or less - 22 T2B - 18 63/65 in peripheral zone	Not provided.	52/306 (17%)	Not provided.

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Author	Biases and methodologic weaknesses[a]	Setting	Age (year) (mean)	Number patients enrolled (%)	Abnormal PSA criterion (%)	Biopsy criteria	No. patients (%) with criteria No. patients (5) biopsied	No. (%) PC detected	No. (%) PC clinically localized	No. (%) PC pathologically localized	PPV %[b] PSA	Treatment
Labrie et al., 1992	6,8	Canadian University Center Random selection, population-based from electoral roles	45-80	1002 (number initially invited not provided)	> 4 ng/mL 124/1,002 (12.4%) >3 ng/mL 191/1,002 (19%)	Abnormal DRE and/or TRUS (PSA test for all but not biopsy for PSA alone) If abnormal DRE but TRUS neg. six random biopsies	Not Provided. Not provided.	Overall 57/1,002 (5.7%) For PSA > 4, 41/1,002 (4.1%) For PSA > 3, 46/1,002 (4.6%) No data on volume or grade	Not provided.	Not provided.	For PSA > 4, 41/124 (33%) For PSA > 3, 46/191 (24%)	Not provided.
Mettlin et al., ACS-NPCDP, 1991[f]	2,3,6,7,8	10 sites in U.S./ Canada Hospital/Clinic Public invited	55-70 (63)	2,425 over 3.5 years (PSA in 2,227) Report on initial screen	> 4 ng/mL 312/2,227 (14%)	Abnormal DRE and/or TRUS (unknown number biopsy recommended for PSA > 10 ng/mL) Blinding of tests not specified	396/2425 (16.3%) 330/2425 (13.6%) 70/312 (22%) with PSA > 4 were biopsied	57/2,425 (2.4%) 5 of 57 on basis of PSA > 10 ng/mL alone	46/51 (90%) 6 others missing stage data	21/31 (68%) 3 missing surgical stage data, 23 not staged pathologically < 1.0 cm - 10 > 1.0 cm - 40 No size data - 7 No volume data Grade: Gleason 4-6: 43 Gleason 7-8: 9 No data: 5	34/312 (11%) (5 of the 34 cancers had PSA >10) 242/312 (78%) patient with PSA > 4 were not biopsied.	RP - 34 RT - 10 HT - 3 Orchiectomy - 1 No TX - 4
Mettlin et al., ACS-NPCDP, 1993[g]	2,3,6,7,8	10 sites in U.S./Canada Hospital/ Clinic Public invited	55-70 on entry (63)	2,999 enrolled Annual evaluation up to 5 years Reporting on 1972 men with 2 sequential exams with complete data for primary variables.	> 4 nl/mL 271/1972 (21%) initial exam 248/1899 (22%) follow-up exam	71/271 (26%) with PSA >4 biopsied initial 49/248 (20%) with PSA >4 biopsied on follow-up	326/1972 (16.5%) Initial exam 216/1899 (11.4%) follow-up exam 285/1972 (14.5%) Initial 196/1899 (10%) Follow-up	73/1972 (3.7%) Initial exam 33/1899 (1.7%) Follow-up exam	79/85 (93%) No data for 21 56/61 (92%) Initial 23/24 (96%) Follow-up	Not provided 67/88 (76%) Gleason grade provided were grade 4-5.	49/271 (18%) Initial Exam 22/248 (9%) Follow-up Exam Explicit number cancer with PSA > 4 in initial and follow-up groups not provided overall 71/106 (67%) cancers had PSA >4.	RP - 59 RT - 17 No TX - 6 HT - 2 Orchiectomy - 3\ No data provided - 19

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Moon et al., 1991	2,3,4,5,6,7,8	University/ Veterans Administration Urology Clinic General public recruited	40-59	414	> 4 ng/mL 10/414 (2.4%) Age 40-49 4/190 (2%) Age 50-59 10/224 (4.5%)	Not provided Implied that all patients received both PSA and DRE with TRUS if either positive (not specified)	Not provided 11/414 (2.7%)	Overall 5/414 (1.2%) If 40-49: 0/190 (0%) If 50-59: 5/224 (2.2%) white 2/153 (1.3%) black 3/71 (4.2%)	4/5 (80%) Little detail provided	2/5 (40%) However, no uniform whole mount histologic technique 2 organ-confined may have been understaged No data on grade/volume	5/10 (50%)	RP - 4
Muschenheim et al., 1991	2,3,4,5,6,7,8	Free screening General public recruited (Prostate Cancer Awareness Week)	not provided	565	> 4 ng/mL 59/565 (10.4%) 6 biopsies/ patient	Abn DRE (not specified) and/or PSA elevated. No independent blinding specified	118/565 (21%) 54/565 (9.6%) 34/59 (58%) Abn. PSA biopsied	20/565 (3.5%) 5/20 grade "poorly diff"	17/20 (85%) although insufficient detail provided	Not provided in sufficient detail. All 12 surgically staged had no lymph node disease. 9/12 (75%) presumed localized.	15/59 (25%) For DRE alone: 16/83 (19%)	RP - 12 RT - 4 Orchiectomy - 3 No TX - 1
Perrin et al., 1991[h]	1,2,3,4,6,7,8	French Urology Clinic Recruited within clinic men attending for "routine" of 4-year checkup	50-60	863	> 4 ng/mL 38/863 (4.4%)	If DRE Abn. for those with PSA > 4	Not provided. Not provided.	3/863 (0.3%)	Not provided.	Not provided.	3/38 (8%).	Not provided.
Powell et al., 1989	1,2,3,4,6,7,8	Single British Urology Clinic Referral population All men had prostatism symptoms prospective accrual, patients invited to "prescreen" most later got TURP	50-88 (68)	287 referred 211 enrolled	> 10 ng/mL (Hybritech) 37/211 (17.5%)	PSA > 10 DRE not uniformly performed (not available for 23%) No TRUS used	37/211 (17.5%) 36/37 (97%)	17/211 (8%)	8/17 (47%)	Not provided.	17/37 (46%)	Not provided.

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Richie et al., 1993[i]	2,3,6,7,8	6 University sites Public invited	50-96 (63)	6630 [White - 6,098 Black - 194 (3%) Other - 338 (5.1%)] Symptoms of BPH: Yes - 3,500 (53%) No - 3,130 (47%)	> 4 ng/mL 983/6630 (14.8j%) PSA ABN stratified by age: 50-59: 150/2381 (6%) 60-69: 487/2959 (17%) 70-79: 311/1161 (27%) 80+: 35/129 (27%)	Abnormal DRE (asymmetry, induration or nodule) and/or PSA elevated. If either abnormal, TRUS performed with guided biopsy if abnormal and systemic quadrant biopsies for all patients with elevated PSA even if TRUS or DRE normal	Overall 1710/6630 (26%) 1167/6630 (17.6%) Number of patients meeting criteria by age: 50-59: 364/2381 (15%) 60-69: 828/2959 (28%) 70-79: 463/1161 (40%) 80+: 55/129 (43%)	Overall 264/6630 (4%) By age: 50-59: 48/2381 (2%) 6-69: 123/2959 (4.2%) 70-79: 84/1161 (7.2%) 80+: 9/129 (7%) Not stratified by presence of symptoms	261/264 (99%)	114/160 (71%) of those received surgical staging 101 of the 261 patients with clinically localized cancers elected not to have surgery. 17/160 (11%) had poorly differentiated grade For PSA > 10 ng/mL 40% organ-confined	Among patients biopsied: Overall 216/686 (31%) By age: 50-59: 36/113 (32%) 60-69: 99/336 (29%) 70-79: 73/216 (34%) Combined Abn PSA or DRE PPV: Overall 264/1167 (23%)	RP - 160 No other data provided.

[a] 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 weakness.

[a] BPA = benign prostate hypertrophy; PC = prostate cancer; PL = pelvic lymph node dissection (metastasis); PPV = positive predictive value; RP = radical prostatectomy; RT = radiation therapy; No TX = No treatment.

[b] ACS-NPCDP = American Cancer Society National Prostate Cancer Direction Project. The ACS-NPCDP used DRE abnormality (asymmetry, induration, or nodule) and/or TRUS abnormality (hypoechoic area greater than 5-7 mean not due to cyst, vascular structure, or artifact). Although 2,227 of 2,425 patients received PSA during first examination (with DRE and TRUS), no patient was biopsied for PSA > 4 ng/mL alone.

[c] 12 of 37 cancers detected had "non suspicious" DRE but 8 of the 12 had asymmetry or DRE that would have prompted biopsy elsewhere (Stamey). 14 of 16 cancers "missed" by TRUS had "abnormal but benign" findings (e.g., asymmetry) that would have been biopsied elsewhere. Routine systematic biopsy of PSA > 4 not recommended.

[d] This study enrolled 1940 purportedly asymptomatic men over a 4 1/2 year period and followed them with annual DRE, TRUS, and PSA. No data on exact number of men followed per year are provided, nor is it clear how many cancers were detected in each examination (apparent maximum of 3). It is also not clear whether all men received each test with each iteration. The data are presented in a confusing manner with multiple textual errors and miscalculations. PSA is not a major determinant of biopsy and less that one-half of those with PSA > 4 received biopsy.

[e] DRE detected 33 of 57 cancers found (detection rate 33/2425 = 1.4%). TRUS detected 44 of 57 cancers found (detection rate 44/2425 = 1.8%).

[f] The ACS-NPCDP continued to rely on DRE and/or TRUS abnormalities as the main determinants for recommending biopsy, although subsequent evaluations incorporated PSA testing. For 144 of the 1972 men reported here PSA data are unavailable. For clinical staging, this study uses a modification of Whitmore's classification: A1 defined here as TRUS-measured tumor volume < 0.2 cm3 (average diameter less than 0.7 cm). An unknown number of patients had biopsy within the study on the basis of PSA > 10 ng/mL, although 11 of the 106 detected cancers resulted from this effort. Patients with PSA > 10 ng/mL who had a negative set of systematic biopsies were re-evaluated with repeated TRUS and DRE in 12 months. It is not specified how many patients were rebiopsied if these studies remained negative. Six other detected cancers were found through non-protocol means (e.g., TURP in men who were not previously recommended for biopsy). Positive Predictive Value (PPV) of DRE was 22% initially and only 14% follow-up examination. The PPV for TRUS were 14% and 8%, respectively (combined DRE/TRUS PPV 37% and 32%).

[g] Overall study design and mode of data presentation is poor. Description of patient cohort and method of recruitment scant. Only patients with elevated PSA who then had abnormal DRE were eligible for biopsy. Actual number who meet criteria and then received biopsy were not reported. This study precludes fair comparison of DRE and PSA, as only patients with elevated PSA received DRE. Proper blinding was not specified. Their results have little usefulness and are not generalizable to an office-based screening population.

[h] Overall 68% compliance with biopsy performance for either/both DRE, PSA abnormal. The cancer detection rates and positive predictive values reported in the paper ignore noncompliance and assume same proportion of positive biopsies would occur if all men meeting biopsy criteria actually received systematic biopsies. Unfortunately, although 53% of study group reported symptoms of prostatism, the data for predictive values of each test and detection are not stratified by symptoms or race. PPV for abnormal DRE among those patients biopsied is 146/683 (21%).