APPENDIX

C

Studies of Digital Rectal Examination for Prostate Cancer Screening

APPENDIX C: STUDIES OF DIGITAL RECTAL EXAMINATION FOR PROSTATE CANCER SCREENING

Author	Biases/ methodologic weaknesses[a]	Setting	Time frame (year)	Number of patients	Age (Y) range (mean)	Abnormal criterion No. patients (%) No. patients biopsied (%)	Overall detection yield[b]	Proportion detected cancers (%) clinically localized	Positive predictive value (%)	Proportion surgically staged[c] (%)	Long-term followup
Chadwick et al., 1991[d]	3,4,6,7,8	British population-based	1 time	814 eligible 472 recruited (58%) 407 DRE	55-69	Nodule or Induration 13/407(3.2%) not specified if all 13 biopsied (only if TRUS lesion also)	1/472 (0.2%)	1/1 (100%)	1/13 (8%)	1/1 (100%) pathologic localized	NA
Chodak et al., 1984[e]	2,3,4,6,7,8	Urology screening (invitational)	1 time	811	45-80	Nodule or induration 43/811(5.3%) but only 38 complied with biopsy (88%)	11/811(1.4%)	5/11(45%)	11/38(29%) [5/38 (13%)]	2/11(18%)	
Chodak et al., 1989[f]	2,3,4,6,7,8	Urology screening (invitational)	6-year serial average 2 exams/man	2,131	45-86	Nodule Induration or asym 144/2131 (6.8%) 143/144 (99%) biopsied.	36/2131 (1.7%) (1.5% initial)	25/36 (69%)	36/144(25%)[g] 25/144(17%)	18/25(72%) 9/18(50%) path loc.	See Gerber et al., 1993[f]
Drago et al., 1992	1,2,3,5,6,7,8	Academic Urology Clinic	U.S. year with annual followup. Exact no. men enrolled each year not provided.	1940 "asymptomatic" Recruitment process not well described	55-70 (64)	Not specified ("abnormal"). No blinding 147(7.6%) Implied all were biopsied [260 others biopsied for TRUS abn].	39/1940 (2%)	Not provided for DRE-detected cancers.	39/147 (27%) [not provided]	Not provided for DRE-detected cancers.	NA
Faul, 1982	2,3,4,6,7,8	German screening	1 time 1978	9,000,000 eligible 1,500,000 recruited 17% participated	>45	Induration or nodule	0.1%	NA	1951/21,308(9%)	NA	NA
Frohmuller, 1991	2,3,4,6,7,8	German screening. Government insurance sponsored (same program as Faul et al. report, 1982).	1987 data 1 time	1,341,833 participants (approx 15% of 60 yr eligible, 8% of 45 year old eligible)	>45	Nodule or Induration exact % prostate abn not given 1.7% suspicious prostate or genitalia	0.12% (1638 cases)	NA	1638/22,590 (7%)	NA	NA
Gilbertson, 1971	2,3,4,6,7,8	University invitational (general)	Serial exams, 16-year study, average 5 exams/man	5,856	Over 45	Nodule % abnormal not given	75/5856 (1.3%) cumulative 20/5856 (0.34%) initial	Unknown (22/75 detected received radical surgery)	Unable to derive	NA	(5-year survival 91% for surgery 72% for others)[h]

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Guinan et al., 1980[i]	1,2,3.	Inpatient Academic Urology Service All symptomatic with varying levels of prostatism. Study described as multiple "screening" test evaluation, but population highly enriched with prostate cancer. Not generalizable to office-based DRE screening situation. Selection bias.	1 time	300 (consecutive admissions to urology service; not known to have prostate cancer previously)	50-90 (no data on mean or distribution)	Gross Asymmetry, Induration or Nodule (blinded assessment). All patients received DRE, as well as *prospective* determination of acid phosphatase, urine cytology (pre- and post-massage), and several other antiquated tests. All patients biopsied.	69/300 (23%)	Not provided.	48/72 (67%) [Sensitivity - 69% Specificity - 89%]	Not provided	NA
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.	1 time convenience sample (incomplete testing)	280 (imply consecutive admissions no known cancer)	(68)	Gross Asymmetry, Induration or Nodule 96/258 (37%)	78/280 (28%)	Not specified.	51/96 (53%) [Sensitivity 51/70 (73%) Specificity 143/188 (77%)]	not specified	NA
Gustafsson et al., 1992[j]	6,8	Swedish screening population-based	1 time	2400 eligible 1788 recruited (74%)	55-70	Nodule or induration asymmetry 195/1782 (11%) Implied all biopsied.	42/1782 (2.4%)	22/42 (52%) 6 patients not biopsied.	42/195 (22%) [22/195 (11%)]	NA	NA
Imai et al., 1988[k]	2,3,4,5,6,7,8	Japanese mass screening	1 time	35,055 eligible 5302 screened (15%)	>60	Not specified (minimal change) 551 Abn by first urologist, 202 biopsied.	54/5302(1%)	28/54 (52%) stage B	54/202(27%) 28/202(14%)	NA	NA

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Jenson, 1960	2,3,4,6,7,8	University Invitational (General) asymptomatic	Serial exams, 11-year study, average 7.6 exam/man	4,367	Over 45	Nodule or In duration	37/4367 (0.8%) cumulative (0.32% initial exam)	NA	NA	NA	Overall survival 57% for cancers detected first exam, 86% subsequent exams
Lee et al., 1988[l]	1,2,3,5,6,8	Screening invitational/ referral	1 time	784	60-86 (65)	NA	10/784 (1.3%)	Unknown for DRE itself	10/29 (34%) [not provided]	NA	NA
Mettlin et al., 1991 ACS-NPCDP	2,3,6,7,8	10 Centers in U.S./Canada Hospital/Clinic Invitational	Initial Screen	2,425	55-70 (63)	Nodule, Induration or Asymmetry 153/2425 (6.3%) 118/2425 (4.9%)	33/2425 (1.4%)	27/32 (84%) [missing data]	33/118 (28%) Among patient biopsied [27/118 (23%]	20/30 (66%) Radical Surgery-20 (missing data in 9 of 57 total cancers detected but not specified which were DRE detected.)	NA
Mettlin et al., 1993 ACS-NPCDP	2,3,6,7,8	10 Centers US/ Canada Hospital/Clinic Invitational	5-year annual followup. Report on 1972 men with 2 sequential exams with complete data.	2,999 enrolled overall Data provided for 1972 initial exam 1899 second exam.	55-70 entry (63)	Nodule, Induration of Asymmetry Initial exam. 139/1972 (7%) 117/1972 (6%) Second Exam 82/1899 (4.3%) 75/1899 (4%)	38/1972 (1.9%) initial exam 16/1899 (0.8%) Second exam.	32/37 (86%) initial[l],/missing 13/13 (100%) second, 3 missing.	38/117 (32%) [32/117 (27%)] initial 16/75 (21%) [13/75 (17%)] Second	18/32 (56%) resurg. 7/32 (22%) XRT 6 missing data initial 12/13 (92%) surgery 1/13 (8%) XRT 3 missing data.	NA
Moon et al., 1991	2,3,4,5,6,7,8	University/ Veterans Administration Urology Clinic Invitational	1 time	417 3 patients not biopsied.	40-59	Not specified	30/414 (7%) overall abnormal gland (0/190 40-49 years) 29/30 (97%) implied biopsied	1/414 (0.24%) overall 1/224 (0.45%) for age 50-59 year.	1/1 (100%)	1/30 (3.3%)	1/1 (100%) Stage C pathologic.
Mueller et al., 1988	1,2,3,4,5,6,7,	Military Urology Clinic Retrospective of ongoing study; used years 1979-85.	7-year serial average 2-4 exams/year	4,843	40-79	Nodule 312/4843 (6.4%) imply 100% biopsy late	122/4843 (2.5%) (1.7% initial exam 0.63% per subsequent exam	77/122 (63%) 58% initial 74% subsequent exam	122/312 (39%)	73% (46% initial pathologic local, 58% subsequent exam)	NA

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Muschenheim et al., 1991	2,3,4,5,6,7,8	Invitational Free Screen. Prostate Cancer Awareness break Madison County New York 2 Sites 2 urologists.	1 time	565 incomplete followup	not provided	Not specified 83/565 (19.6%) Abnormal DRE 37/565 (6.5%) biopsied. Patients not all biopsied at Central study sites.	16/565 (2.8%) 5/16 (31%) grade "poorly diff" (Gleason grade not performed)	13/16 (81%) although insufficient detail provided	16/37 (43%) of those biopsied.	Insufficient detail 11/16 surgical treatment (3 RT) All 11 surgically staged had no lymph node disease.	Treatment: RP 11 RT 3 Orchiectomy 2 No. Tx 1.
Naito, 1988	1,2,3,4,5,7	Japanese Urology Clinic Cooperative referrals for variety untreated prostate symptoms Highly selected all received DRE (unclear if blinded assessment) and TRUS (blinded) 3.5 $_{m}$ H_2	1 time	109	35-89 (70)	Poorly specified 2 levels of Abnormal "malig. cancer not ruled out" 19/109 (17%) "malig. cancer highly suggestive" 19/109 (17%) All patients biopsied but technique not specified	22/109 (20%)	NA No data provided on clinical/path stage or grade	22/38 (69%) if lump both levels of abnormal DRE (not provided) 'sensitivity'= 22/32 (69%) 'specificity'= 61/77 (79%)	NA	NA
Pederson et al., 1990[m]	4,6,8	Swedish population screening random selection.	1 time	1494 (1163 participate (78%)	50-69	Nodule Induration	13/1163 (1.1%)	12/13 (92%)	13/44 (30%) 12/44 (27%)GP 15/44 (35%) Urology	10/13 (77%) 10 surgeries (7 extracap. by pathology 1xRT	NA
Perrin et al., 1991[n]	1,2,3,4,6,7,8	French urology clinic asymptomatic health check	1 time	863	50-60	Nodule or induration	0.35%, 1.9% adjusted	NA	3/11 (27%)	NA	NA
Richie	2,3,6,7,8	6 Urology clinics. General public recruited.	Initial screen data	6630	50-96 (63)	DRE: Asymmetry, In duration or Nodule All patients had PSA; biopsy received if PSA > 4 Abnormal DRE in 982/6630 (15%) 683/982 (70%) biopsied	146/6630 (2.2%) Cancer on basis DRE alone	143/146 (98%)	146/683 (21%)	92/146 (63%) 64/92 (70%) pathologic, confined	NA

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Thompson, 1984	1,2,3,4,6,7	Military Urology Clinic retrospective random review of ongoing screening study, from 1979-83. Data likely part of Mueller 1988 study.	4 year serial 1.3 exam/ patient	2005 part of routine exam 43% patients with negative biopsy had urologic symptoms.	40-92 (58)	Nodule both lobes biopsied routinely # per patient not specified	17/2005 (0.8%) 0.55% initial 0.25% second	15/17 (88%)	[17/65 (26%)] [15/65 (22%)]		NA See Gerber et al 1993.[f]
Varenhorst et al., 1992[o]	4,6,8	Swedish population invitational screening random selection. 9,026 males eligible from geographic area. Only general practitioners involved with second round.	Second follow up to Pederson et al study.	1994 invitational initially; 1,163 participating first screen (78%) 1363 invited second screen 953 participating second (70%).	50-69	Nodule or Induration (similar FNA biopsy technique as in first screening).	7/953(0.7%)	5/7(71%) not specified whether 2 advanced cancers were the 2 not screened first cycle.	7/42 (17%) [5/42 (12%)]	3/7 (43%)	NA
Vihko	1,2,3,4,5,6,7,8	Veteran's Rehabilitation Urology clinic	4 year serial	771 imply full compliance biopsy if tests abn.	54-76	Not specified 27/771 (3.5%) DRE abnormal	6/771 (0.89%)	4/6 (67%)	6/27 (22%) [4/27 (15%)]	NA	NA
Waaler	1,2,3,4,5,6,7,8	German Occupational Health Program screening	1 time	480	45-67	Not specified; Abnormal did not include "adenomatous enlargement" 26/480 (5.4%) referred to urology, 9/26 specifically suspicious for PC in first screen. Urologists suspected PC in 10/26 referred. 16 patients biopsied.	1/480 (0.2%)	0/1 (0%)	1/16 (6%) [0/16 (0%)]	0	NA

[a] Legend for study bias/methodological weaknesses: 1) not population-based community setting; 2) selection/referral bias; 3) nonrandomly sampled study group; 4) explicit inclusion/exclusion criteria not provided; 5) abnormal test criterion 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 (include biopsy of all abnormal tests and reporting of clinical and pathologic staging information). Note that for each study listed, the presence of one or more of these methodologic deficiencies will be devoted with the particular number (1-8) in the proper cell. We chose not to grade or weigh to degree to which a study bias was present.

[b] Detection yield = number of patients with prostate cancer detected/number patients screened. Numbers in parenthesis refer to yield of each individual examination.

[c] Refers to proportion of patients clinically localized who receive surgical staging.

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[d] No apparent selection bias. 407 of 472 recruited patients who agreed to at least part of the "health screen" received DRE by general physician. Total of 7 cancers detected but only 1 had an abnormal DRE; remaining 6 had elevated PSA (see table 11). Work-up bias. Only 68 of 472 received TRUS, based on either abnormal PSA or DRE. 29 patients were biopsied based on hypoechoic TRUS lesion and/or abnormal DRE.

[e] The 811 patients in this invitation screening study are also included in the subsequent study of 2,131 patients by Chodak (1989).

[f] Detection rate for initial screen 1.5% (32/2131), 0.2% for second-year exam (3/1321). Long-term disease-specific survival for patients in this cohort and the similar design of Thompson et al. (1984) are reported in Gerber et al. (1993). 56 men (mean age 65 years) were followed for median of 75 months; 3/56 men were not reported in the 2 original reports. Clinically localized cancer diagnosed in 73% on initial screen and for 83% of cancers detected in subsequent examinations. Patients were treated by variety of strategies initially but in general aggressive treatment (surgery or radiation) used for those clinically localized. However, 10-year disease-specific survival was 86% for men diagnosed during first screen and only 57% for subsequent exams (p=.02). This data suggest presence of length bias. Only 63% and 22% of patients in Chodak (1989) cohort returned for second and third examinations, respectively.

[g] Overall PV + for entire period of study; PV + for initial exam abnormalities versus subsequent ones not provided.

[h] Unable to assess effect of lead-time and length bias.

[i] This is the single study available that is not flawed by work-up bias. All patients received transrectal biopsies, using a modification of the Vim-Silverman needle. However, the population studied is very atypical of men without suspected prostate cancers being followed in a routine office-based primary care setting. All men were symptomatic inpatients on urology service. The high prevalence of detected cancers, 10 to 20 fold higher than typical screening studies of DRE, suggests significant selection biases. Although the comprehensive biopsy protocol explains some of this discrepancy, the prevalence is still nearly twice as high as an earlier hospital-based study employing routine "wedge" biopsy in a population enriched with prostatism but no suspected cancer (Hudson, 1954).

[j] The study cohort was derived from 2,400 patients in this age group randomly selected from a defined catchment area of the study hospital. All cases in group with prior history of prostate cancer were excluded. Patients were invited to participate in multiphasic 1 time screening program. All 1,788 recruited patients received DRE, TRUS, and PSA with proper blinding performed. A preliminary report of this data was published by Norming et al. (1991). Biopsy performed selectivity for DRE positive and/or TRUS positive patients (small unspecified number for elevated PSA above 10ng/ml). Clinical staging performed by TNM system. 11/42 DRE positive cancers were T2A, 11 were T2B.

[k] "Mass screening" study organized between 1981 and 1985 by the urology department at Gunma Cancer Center Hospital. Intervention involved questionnaire, acid phosphatic (PAP), and DRE in a "field" type approach. "Any small change" in DRE led to "suspicious" categorization (N=551), however, only 202/551 (37%) were biopsied after second evaluation by urologist. Thus, actual PV+ for patients receiving biopsy was 54/202 (27%) for all cancer. The mean age of patients with detected cancer was 73 years (63-87 range). The average cost of detecting each case was calculated to be equivalent to $5,358. Authors compared clinical stage distribution in study group (52% stage B) with 93 patients diagnosed in outpatient clinic ("controls") over same time period (16% stage B). Crude survival curves of patients (by stage) in both groups indicate no differences at mean followup of 3 years. However, only 3/28 (11%) of stage B patients in the study agreed to surgery.

[l] Bias against DRE (vs. transrectal ultrasound comparison); 50% of patients reportedly had normal DRE within 1 year of study.

[m] From a population of 9,026 men ages 50 through 69 in a defined catchment area in Sweden, 1,494 were randomly selected and invited to receive DRE by both a general practitioner and a urologist, performed independently. These data were also presented, in virtual identical fashion, in E. Varenhorst, et al. Biopsy technique included fine needle aspiration (FNA) of suspected area and 3 samples from each lobe, using cytologic analysis. It is not specified whether a "geographic" approach to FNA of nonsuspected areas is used.

[n] This study has significant methodologic flaws. The 863 patients receiving a "screening" DRE represent one subgroup receiving different interventions. The men are reportedly asymptomatic. No description of how these men are selected for study. 61 (7%) had suspicious DRE but only 11 got biopsied revealing cancer in 3. Assuming same PV+ would apply if all 61 received biopsy, the estimated "adjusted" yield of DRE is 1.9%. Because of potential uncharacterizable selection bias, the study population cannot be considered a screening cohort.

[o] This publication presents the second screening yield from the original study of Pederson et al. (1990). Thirteen cancers were detected in the initial round and 7 cancers during the second round 3 years later. Six other cancers were diagnosed through routine care (4 incidentally at TURP) between screening cycles for this population. Of the combined 20 cases detected by screening, 14 (70%) had PSA > 4ng/mL, although PSA was routinely performed in this protocol. Of the 7 cancers detected in the second round, 5 had normal DRE in the first round and 2 had not participated in first round.