

Appendix A. Search strategies

A.1 Search strategy for systematic reviews

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to December 2010>, EBM Reviews - Health Technology Assessment <4th Quarter 2010>, Ovid MEDLINE(R) <1996 to December Week 4 2010>

Search Strategy:

-
- 1 meta-analysis.pt.
 - 2 systematic\$ review\$.mp. [mp=ti, ab, tx, kw, ct, hw, ot, nm, ui]
 - 3 (systematic\$ adj9 overview\$).mp.
 - 4 (meta-analys\$ or meta analys\$ or metaanalys\$).mp. [mp=ti, ab, tx, kw, ct, hw, ot, nm, ui]
 - 5 evidence review\$.mp. [mp=ti, ab, tx, kw, ct, hw, ot, nm, ui]
 - 6 or/1-5
 - 7 prostate cancer.mp. [mp=ti, ab, tx, kw, ct, hw, ot, nm, ui]
 - 8 watchful waiting.mp. [mp=ti, ab, tx, kw, ct, hw, ot, nm, ui]
 - 9 active surveillance.mp. [mp=ti, ab, tx, kw, ct, hw, ot, nm, ui]
 - 10 or/7-9
 - 11 6 and 10

A.2 Search strategy for large databases

Database: Ovid MEDLINE(R) <1948 to February week 4 2011>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <March 04, 2011>

Search Strategy:

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1. ("Surveillance, Epidemiology and End Results" or "SEER" or "National Cancer Data Base" or "NCDB" or "Cooperative Studies Program" or "CSP" or "CaPSURE").mp.
 2. prostate cancer.mp. or exp Prostatic Neoplasms/
 3. 1 and 2
 4. ("Prostate Cancer Outcomes Study" or "PCOS").mp.
 5. 2 and 4
 6. 5 not 3

A.3 Search strategy for AS or WW

Ovid MEDLINE(R) 1948 to April Week 1 2011, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations April 14, 2011, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to March 2011, EBM Reviews - Cochrane Central Register of Controlled Trials 1st Quarter 2011, EBM Reviews - Health Technology Assessment 2nd Quarter 2011, Ovid MEDLINE(R) Daily Update April 14, 2011, Ovid OLDMEDLINE(R) 1946 to 1965

Search Strategy:

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1. watchful waiting.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
 2. active surveillance.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
 3. conservative management.mp.
 4. expectant management.mp.
 5. deferred treatment.mp.
 6. ((expectant\$ adj5 manage\$) or (conservative\$ adj5 manage\$) or (active adj5 surveillance) or (watchful adj5 waiting) or (watch adj5 wait) or (watchful adj5 observation) or (active\$ adj5 monitor\$) or (defer\$ adj5 treatment)).tw.
 7. prostate cancer.mp. or exp Prostatic Neoplasms/
 8. ((prostat\$ adj5 neoplas\$) or (prostat\$ adj5 cancer\$)).tw.
 9. 1 or 2 or 3 or 4 or 5 or 6
 10. 7 or 8
 11. 9 and 10
 12. limit 11 to english language
 13. limit 12 to yr="1987 -Current"
 14. (expectant\$ adj5 treatment).tw.
 15. 10 and 14
 16. limit 15 to yr="1987 -Current"
 17. 16 not 13

Appendix B. Ongoing randomized studies comparing observational management strategies with active treatment strategies for the treatment of clinically localized disease

Appendix Table B.

Study name [Registration] Country	N centers (planned enrollment) [enrollment period]	Population	Intervention	Comparator(s)	Outcomes	Current status
PIVOT [Clinical Trials.gov, NCT00007644] USA	31 (731) [1994-2002]	Clinically localized prostate cancer, within 6 mo of diagnosis, ≤75 yr	WW (expectant management with palliative therapy)	RP	OS (primary); prostate cancer-specific mortality, DFS, PFS, morbidity, QoL, and CE	Preliminary results presented at the 2011 AUA meeting
START [Clinical Trials.gov, NCT00499174] Canada, USA, UK	13 (2130) [2007-2011]	Histologically confirmed adenocarcinoma of the prostate, within 6 mo of diagnosis, clinical stage T1b- T2b, Gleason score ≤ 6, PSA ≤10 ng/mL, physical examination, DRE and transrectal US within 6 mo of randomization, radiographic studies, (if indicated) negative for metastasis, LE >10 yr	AS (PSA testing, repeat biopsy and DRE; radical intervention at biochemical, histological, or clinical progression)	RP or RT, based on patient and physician preference	Prostate cancer-specific mortality (primary); OS, QoL, distant DFS, PSA relapse/progression after radical intervention, initiation of ADT, proportion of patients on the AS arm who receive radical intervention , prognostic significance of PSA doubling-time prior to diagnosis, prognostic significance of molecular biomarkers	Terminated early (not meeting accrual target)
ProtecT [Clinical Trials.gov, NCT00632983] UK	10 (2050) [2001- ongoing]	clinically localized disease prostate cancer (T1-T2, NX, M0), 50-69 yr, PSA 3.0-19.99 ng/mL, no skeletal metastases by isotope bone scan, LE ≥10 yr	AS (repeat PSA testing q3 mo in the first year and then q 6 mo thereafter; annual review appointment with DRE, if indicated)	RP and 3d-CRT (with or without ADT) (2 comparator arms)	OS (primary); disease progression, treatment complications, general health status, anxiety, depression, and psychological state, urinary symptoms, QoL, sexual function, qualitative evaluation of outcome by in-depth interviews	Followup phase

3d-CRT = 3-dimensional conformal radiotherapy; ADT = androgen deprivation therapy; AS = active surveillance; CE = cost-effectiveness; DFS = disease-free survival; DRE = digital rectal examination; LE = life expectancy; PIVOT = Prostate Cancer Intervention Versus Observation Trial; NR = not reported; OS = overall survival; PFS, progression-free survival; ProtecT = Prostate Testing for Cancer and Treatment; PSA = prostate specific antigen; QoL = quality of life; RP = radical prostatectomy; RT = radiation therapy; START = Active Surveillance Therapy Against Radical Treatment in Patients Diagnosed With Favourable Risk Prostate Cancer trial; US = yr = year.

Appendix C. Appendix Tables of Key Question 1 to Key Question 4

Appendix Table C1.1. Descriptive characteristics of the epidemiologic studies considered relevant to KQ1^a

Author Year uid	Database	Start year	End year	Sample size	Eligibility criteria
Mebane ¹⁶ 1990 2258952	SEER, TNCS	1969	1985	NR	Data presented only for Black and White individuals.
Hankey ¹⁷ 1999 10379964	SEER, NCHS	1969	1995	229,556 [prostate cancer cases in SEER, 1975-95]	Invasive prostate cancer cases, excluding histology codes for lymphoma and patients of unknown ethnicity. Data were available for 1968-95 for mortality and 1973-95 for incidence rates.
Chu ¹⁸ 2003 12627516	SEER, NCHS	1969	1999	NR	Men with a first primary prostate cancer. Data were available from 1969-99 for mortality and 1975-99 for incidence rates.
Brawley ¹⁹ 1997 9351560	SEER	1973	1994	NR	NR
Merrill ²⁰ 1997 9229202	SEER	1973	1992	NR	NR
Farkas ²¹ 1998 9730458	SEER	1973	1994	156,598	White and African-American prostate cancer patients
Perrotti ²² 1998 9720554	SEER	1973	1994	224,595	Excluded patients with tumors of anaplastic or transitional cell histology. Two groups of patients based on year of diagnosis (1980-84 and 1990-94) were assessed to reflect patterns of cancer presentation before and after the introduction of early detection methods (PSA and trans-rectal ultrasound guided biopsies).
Dennis ²³ 2000 10679753	SEER	1973	1996	253,833	Incident prostate cancer cases, aged ≥ 45 yr. Cases ascertained from autopsy or death certificate only were excluded.
Merrill ²⁴ 2000 10792091	SEER	1973	1995	NR	NR
Clegg ²⁵ 2002 12381706	SEER	1973	1998	NR	Results were reported only for White and Black patients. The study reported age-adjusted and reporting delay-adjusted incidence rates for prostate cancer; reporting delay-adjusted rates were calculated only for 1981-98.
Stephenson ²⁶ 2002 12109343	SEER	1973	1997	261,464	Incident prostate adenocarcinoma cases. Excluded cases not confirmed histologically and cases diagnosed by autopsy or death certificate only.

^a Pre-1980 data were not extracted for this review; however, in this table we have extracted information on the first and last year covered by each eligible study.

Author Year uid	Database	Start year	End year	Sample size	Eligibility criteria
Escobedo ²⁷ 2004 15542264	SEER	1973	1998	40,548	Patients in the SEER database who reside in Connecticut, Iowa, or New Mexico; African American men only.
McDavid ²⁸ 2004 15192905	SEER	1973	1999	NR	Excluded men aged <50 yr and non-White individuals.
Hayat ²⁹ 2007 17227898	SEER	1973	2003	134,434 [number available for the last study yr]	All cancer cases in the coverage areas (subgroup results presented for prostate cancer), excluding childhood cancers. Excluded were cancer diagnosed by death certificate only, or at autopsy, and cases with in situ disease as the first cancer diagnosis.
Jani ³⁰ 2008 18845997	SEER	1974	2003	455,170	Patients with available grade and age information. Excluded stage IV disease, nonadenocarcinoma or undifferentiated histology, and those with missing data on grade or age.
Clegg ³¹ 2002 12230422	SEER	1975	1997	233,520	Incident invasive prostate cancer belonging to 6 ethnic groups: non-Hispanic Whites, Hispanic Whites, African Americans, Asian Americans (Chinese, Japanese, Filipino), American Indians and Hawaiian natives.
Merrill ³² 2002 11790678	SEER	1975	1997	NR	Black or White prostate cancer patients.
Collin ³³ 2008 18424233	SEER	1975	2004	NR	NR
Sarma ³⁴ 2002 11828352	SEER	1981	1998	NR	NR
Lu-Yao ³⁵ 1994 7905093	SEER	1983	1989	NR	Whites prostate cancer patients, 50-79 yr
Harlan ³⁶ 1995 7799048	SEER	1984	1991	67,693	Localized or regional prostate cancer; excluded cases identified by death certificate only or at autopsy.
Jani ³⁷ 2007 17505529	SEER	1984	2003	411,325	Excluded patients with stage IV disease, non-adenocarcinoma histology, missing information on stage or grade, undifferentiated disease.
Welch ³⁸ 2009 19720969	SEER	1986	2005	NR	NR
Devesa ³⁹	SEER	1987	1991	NR	Excluded in situ cancers. Rates during the period 1975-1979 were used as baseline.

Author Year uid	Database	Start year	End year	Sample size	Eligibility criteria
1995 7707404					
Merrill ⁴⁰ 2000 10647666	SEER	1988	1995	64,562 [analyses by age and stage at diagnosis were based on 64,455 and 64,463 individuals, respectively]	Men diagnosed with prostate cancer between 1973 and 1995; data reported on causes of death during the period 1988-95. Analyses stratified by age excluded patients <50 yr and analyses stratified by stage excluded patients with in situ tumors.
Miller ⁴¹ 2006 16912266	SEER	1988	2002	71,602 [an additional historical cohort of 25,826 men diagnosed during 1988-90 was used to compare treatment patterns]	Localized or regional adenocarcinoma of the prostate. Excluded men with missing information that precluded assigned to a risk group (based on age and grade criteria) and those with missing information on primary treatment, race/ethnicity, or marital status.
Shao ⁴² 2009 19713548	SEER	1988	2005	82,541 (2004-05) (NR for other yr)	Age \geq 25 yr. Excluded men of race/ethnicity other than Black or White, those with missing data on age, PSA, Gleason score, or clinical stage
Merrill ⁴³ 1996 8931614	SEER	1989	1993	80,936 [72,659 White; 8277 Black]	White and Black prostate cancer patients.
Stewart ⁴⁴ 2004 15179359	SEER, NCHS	1990	2000	NR	NR
Zhu ⁴⁵ 2009 19505907	SEER	1990	2004	42,751	NR [The study reported additional data from ACTUR, a tumor registry for military personnel; these data were not considered representative of the US population and pertained to <1000 prostate cancer cases, thus they were not extracted.]
Polednak ⁴⁶ 2002 12477140	SEER	1992	1998	46,248 [in 1992: 2969 Black, 23,347 non-Hispanic White; in 1997: 2821 Black, 17,111 non-Hispanic White]	Excluding cases ascertained from death certificate only or autopsy. Data only reported for non-Hispanic White and Black patients.
Underwood ⁴⁸ 2004 15017208	SEER	1992	1999	142,340	Localized or regional, histologically-confirmed adenocarcinoma. Patients with missing data on race, treatment received or tumor grade were excluded. Analyses were restricted to the 3 largest race/ethnicity groups in SEER (White, Hispanic, African American).
Underwood ⁴⁷	SEER	1992	1999	142,340	Localized or regional, histologically-confirmed adenocarcinoma. Patients with missing data on race,

Author Year uid	Database	Start year	End year	Sample size	Eligibility criteria
2005 15612083					treatment received or tumor grade were excluded. Analyses were restricted to the 3 largest race/ethnicity groups in SEER (White, Hispanic, African American).
Demers ⁴⁹ 1994 8203988	SEER, Detroit	1973	1991	22,632	Incident prostate cancer cases; only included White and Black individuals.
Severson ⁵⁰ 1995 7707440	SEER, Detroit	1973	1992	12,413	Prostate cancer patients aged ≥ 75 yr
Demers ⁵¹ 2001 11745285	SEER, Detroit	1973	1998	56,425	Residents of Wayne, Oakland, or Macomb Counties who died due to prostate cancer
Schwartz ⁵² 1999 10197854	SEER, Detroit	1982	1996	39,566	NR
Gilliland ⁵³ 1996 8722215	SEER, New Mexico	1983	1992	7563	Histologically-confirmed incident prostate cancer
Gilliland ⁵⁴ 2001 11176484	SEER, New Mexico	1983	1993	1535	Histologically-confirmed prostate adenocarcinoma
Newcomer ⁵⁵ 9302136 1997	SEER, Seattle- Puget Sound	1974	1994	33,086	White or African-American men, aged ≥ 35 yr with incident histologically-confirmed prostate cancer. Excluded cases identified through autopsy report only.
Stephenson ⁵⁶ 1996 8608513	SEER, Utah	1984	1993	8867 (different analytic samples were used for different analyses)	NR
Potosky ⁵⁷ 1995 7530782	SEER-Medicare	1986	1991	NR	Prostate cancer patients aged ≥ 65 yr.
Klabunde ⁵⁸ 1998 9749657	SEER-Medicare	1986	1993	52,915	Black and White men, aged 65 or older, diagnosed with prostate cancer. Excluded men whose tumor stage was recorded as in situ, distant, or unstaged, those with unknown tumor grade, those diagnosed with prostate cancer by autopsy or only on death certificates, those with incomplete Medicare claims data and those with racial/ethnic classification other than White or Black.
Sheikh ⁵⁹ 2002 11880074	SEER-Medicare	1986	1996	NR	Medicare beneficiaries aged ≥ 65 yr (for population rates); incident cases of prostate cancer (to define the population at risk of undergoing radical prostatectomy)

Author Year uid	Database	Start year	End year	Sample size	Eligibility criteria
Godley ⁶⁰ 2003 14625261	SEER-Medicare	1986	1996	43,989	Localized prostate cancer, aged 65-84 yr, enrolled in Medicare Part A or Part B for at least one month of the study period. Patients were excluded if they had a prior cancer diagnosis, a second cancer diagnosed in the same month as prostate cancer, had non-invasive disease, were missing the month of diagnosis, were aged <65 yr, were neither Black or nor non-Hispanic White, were diagnosed at death, had no Medicare coverage during the study period, or were aged ≥85 yr at diagnosis. Patients with locally advanced, metastatic or unstaged cancer were also excluded.
Zeliadt ⁶¹ 2004 15596192	SEER-Medicare	1991	1999	90,128	White or African-American men, aged ≥65 with incident prostate cancer, clinically staged as localized or regional, eligible for Medicare Part A and Part B, not enrolled in HMO at diagnosis. Patients with metastatic disease, those who became ineligible for Medicare during the followup period and those with an orchiectomy claim more than 3 months before diagnosis were excluded.
Carpenter ⁶² 2010 20333462	SEER-Medicare	1994	2002	18,067	Black and White men, aged ≥65 yr, diagnosed with prostate cancer in the following 8 SEER registries: Atlanta, Connecticut, Detroit, Rural Georgia, Los Angeles, San Francisco-Oakland, San Jose, Seattle-Puget Sound. Included patients had to have known prostate cancer stage, no prior or concurrent cancers, no gaps in Medicare coverage for 3 yr prior to diagnosis, and no HMO coverage from enrollment to diagnosis.
Mullins ⁶³ 2010 20163844	SEER-Medicare	1998	2002	42,318 [13,447 in 1998; 28,871 in 2002]	Prostate cancer patients with Medicare, aged ≥65 yr. Excluded men with unknown mo of diagnosis, <65 yr old at time of diagnosis, races other than non-Hispanic White, AA, and White Hispanic, missing Census Tract information.
Kindrick ⁶⁴ 1998 9817332	CaPSURE	1989	1997	3557	Biopsy-confirmed prostate adenocarcinoma. Excluded patients with a missing date of diagnosis or those for whom no initial treatment was recorded. Patients included in CaPSURE between 1995-97 were included, including non-incident cases (those diagnosed since 1989).
Cooperberg ⁶⁵ 2002 12131295	CaPSURE	1989	2001	4966	Excluded those diagnosed before 1989 and those with missing information on primary treatment or clinical staging.
Cooperberg ² 2003 14610406	CaPSURE	1989	2002	6290	Unselected men with biopsy-proven prostate adenocarcinoma. Excluded those with missing data on PSA, T stage or multiple parameters.
Cooperberg ⁶⁶ 2003 12837834	CaPSURE	1989	2001	3439	Patients who received RP, EBRT, BT, PADT or WW as primary therapy. Patients with incomplete clinical staging information, those with missing data on treatment and those receiving cryotherapy as primary treatment were excluded.
Harlan ⁶⁷ 2003 14532780	CaPSURE	1989	2000	5365 (402 received WW)	Patients with biopsy-confirmed prostate adenocarcinoma, localized stage (T3a or lower, N0 M0) who chose WW or active treatment within 9 mo of diagnosis. Patients who waited more than 9 mo after diagnosis before initiating active treatment and those who received active treatment before or within 6 mo after initiating WW were excluded from the analysis. Active treatment was defined as RP, EBRT, interstitial RT, cryotherapy, or ADT.
Cooperberg ⁶⁸ 2004	CaPSURE	1989	2001	1990	Excluded patients with unknown PSA at diagnosis, diagnostic biopsy Gleason score, and/or clinical T stage. Excluded patients with unknown primary treatment, and those receiving cryotherapy as primary

Author Year uid	Database	Start year	End year	Sample size	Eligibility criteria
15169800					therapy (this group accounted for 2% of patients since 1996; 68% of cryotherapy treated patients were treated at a single practice site in the early 1990s). Only low-risk prostate cancer patients were analyzed for the temporal trends of clinical characteristics or treatments received.
Cooperberg ⁶⁹ 2007 17644125	CaPSURE	1990	2006	10,385	Excluded those diagnosed before 1990, those with metastatic or locally advanced disease (clinical stage T3b or higher) and those with missing data on PSA, T stage or biopsy Gleason score. Localized biopsy-proven prostate adenocarcinoma. Information relevant to this review is only reported for "low-risk" prostate cancer, defined as PSA≤10 ng/ml, Gleason score≤6 and clinical stage T1/2a.
Cooperberg ⁷⁰ 2010 20124165	CaPSURE	1990	2008	11,892	Biopsy-proven prostate cancer. Excluded advanced disease (stage higher than T3a N0 M0); diagnosed before 1990; those from sites contributing <30 pts; and those receiving treatments other than RP, EBRT, BT, cryoablation, WW/AS or ADT or with unknown primary treatment.
Shah ⁷¹ 2008 17997437	CaPSURE	1995	2004	6450	Unselected men with biopsy-proven prostate adenocarcinoma. Enrolled in CaPSURE within 6 mo of diagnosis with complete clinical information (PSA, Gleason score and clinical stage) and complete followup information. Excluded patients with fewer than 6 biopsy cores or unavailable biopsy details.
Greene ⁷² 2005 16194711	CaPSURE	1997	2003	3003	Patients with biopsy-proven prostate cancer; availability of pretreatment demographics and QoL data.
Mettlin ⁷³ 1994 8062197	NCDB	1985	1990	85,813	NR
Mettlin ⁷⁴ 1996 8640686	NCDB	1985	1993	349,154	Convenience sample of cancer patients in hospitals that voluntarily participated in the database.
Mettlin ⁷⁵ 1995 8625214	NCDB	1986	1992	108,717 [number of patients included in analyses of stage by time period; the analytic sample size varied between analyses]	All submitted data to NCDB in 1986-1987 and in 1992. The available data represented ~30% and 77% of all prostate cancers diagnosed in the US in 1986/1987 and 1992, respectively.
Mettlin ⁷⁶ 1998 9781963	NCDB	1992	1995	176,316	NR
Danley ⁷⁷ 1995 8580296	LAC/USC CSP	1976	1988	29,992	Invasive prostate cancer patients, aged ≥45 yr. Excluded men younger than 45 yr of age.
Hamilton ⁷⁸ 2011 20735387	POCS, NCI	1998	2002	2101 [962 in 1998 and 1139 in 2002; the weighted	The 1998 POCS included primary histologically confirmed prostate cancer patients diagnosed between Jan 1 st , 1998 and Dec 31 st , 1998. Patients with a history of previous cancer (except non-melanoma skin cancer) and those aged <21 yr were excluded. A stratified random sample of all prostate cancer

Author Year uid	Database	Start year	End year	Sample size	Eligibility criteria
				sample size was 15,547 for 1998 and 31,367 in 2002]	cases diagnosed in 10 regional population based cancer registries were selected, according to patients' race/ethnicity and age at diagnosis. For the 2002 POCS, similar procedures were followed as in 1998 with the inclusion of additional registries.

Studies are arranged by database, then chronologically by the first year of enrollment, then by year of publication.

ACTUR = Automated Central Tumor Registry; ADT = androgen deprivation therapy; BT = brachytherapy; EBRT = external beam radiation therapy; HMO = health maintenance organization; mo = months; NCHS = National Center for health Statistics; NR = not reported; POCS = Patterns of Care; PSA = prostate-specific antigen; QoL = quality of life; RT = radiation therapy; RP = radical prostatectomy; TNCS = Third National Cancer Survey; VA = Veteran's Administration; WW = watchful waiting; yr = year.

Appendix Table C1.2. Patient characteristics – age

Author, year	Database	Age groups (yr)	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
Brawley ¹⁹ 1997 9351560	SEER	Whites Blacks <i>Median age at diagnosis</i>	72 70 (1980)		72 70 (1993)				NR	
Farkas ²¹ 1998 9730458	SEER	Whites African-Americans <i>Mean age (95% CI)</i>		72.0 (71.8 to 72.3) 70.1 (69.4 to 70.8) (1985)	69.2 (69.0 to 69.3) 67.3 (66.9 to 67.8) (1994)				NR	Figure 2 of the article presents additional information (1973-94).
Hayat ²⁹ 2007 17227898	SEER	<i>Median age at diagnosis</i>	72 (1979-83)		71 (1989-93)		68 (1999-2003)		NR	
Jani ³⁰ 2008 18845997	SEER	40-49 50-59 60-69 70-79 ≥80	6% 8% 31% 40% 21% (1979-83)	5% 7% 31% 42% 20% (1984-88)	7% 8% 33% 43% 15% (1989-93)	2% 14% 36% 38% 11% (1994-98)	2% 18% 34% 34% 11% (1999-2003)		P=0.68 (chi-square comparing across all periods)	
Jani ³⁷ 2007 17505529	SEER	40-49 50-59 60-69 70-79 ≥80		5% 7% 31% 42% 20% (1984-88)	7% 8% 33% 43% 15% (1989-1993)	2% 14% 36% 38% 11% (1994-1998)	2% 18% 34% 34% 11% (1999-2003)		P=0.180 (chi-square test) RR=1.15 (CI 0.89, 1.31)	
Shao ⁴² 2009 19713548	SEER	White Black Total <i>Mean age (SD)</i>		72.3 (8.6) 70.8 (8.9) 72.2 (8.7) (1988-89)		69.5 (12.3) 67.2 (9.7) 69.2 (12.0) (1996-97)		67.6 (10.0) 64.4 (10.0) 67.2 (10.1) (2004-05)	-4.7 (P<0.001) -6.4 (P<0.001) -5.0 (P<0.001) [absolute change between 1988-1989 and 2004-05 (p-values from ANOVA with linear contrast)]	Excluding age <25 yr
Polednak ⁴⁶ 2002	SEER	<65			4717 (non-Hispanic White),	5229 (non-Hispanic			NR	Data were

Author, year	Database	Age groups (yr)	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
12477140		≥65 <i>Age at diagnosis</i>			828 (Black)	White), 1101 (Black)				not reported for patients of other racial/ethnic groups.
Severson ⁵⁰ 1995 7707440	SEER-Detroit	75-79 80-84 85-89 ≥90 <i>Count (percentage) of patients in each age group</i>	1079 (47%) 739 (32%) 378 (16%) 120 (5%) (1980-84)	1265 (50%) 772 (30%) 382 (15%) 124 (5%) (1985-88)	2290 (54%) 1260 (30%) 533 (13%) 158 (4%) (1989-1992)					Limited to men ≥75 yr
Schwartz ⁵² 1999 10197854	SEER-Detroit	0-39 40-59 60-79 80+	1% 9% 70% 21% (1982-86)	1% 8% 74% 18% (1987-91)	1% 12% 75% 13% (1992-96)					
Newcomer ⁵⁵ 9302136 1997	SEER, Seattle-Puget Sound	Mean age at diagnosis		71.7 (1989)	70.5 (1993)				P<0.001 (statistical test NR)	
		<65 65-75 >75	21.4% 41.7% 36.9% (1983-84)	19.5% 45.5% 34.9% (1987-88)	23.6% 46.8% 29.6% (1991-92)				NR	
Stephenson ⁵⁶ 1996 8608513	SEER-Utah	<70		38% (1984-90)	42% (1991-93)				P=0.002 [Fishers' exact test]	
									OR=1.178 (CI, NR)	
Mullins ⁶³ 2010 20163844	SEER-Medicare	65-69 70-74 75-79 80+				29.4% 29.0% 23.1% 18.5%	30.1% 28.6% 22.4% 18.9%		P<0.05 (for the association of year with age, 1998-2002)	

Author, year	Database	Age groups (yr)	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
Cooperberg ⁶⁵ 2002 12131295	CaPSURE	<60 60-69 70-79 ≥80			16.5% 41.8% 36.1% 5.6%	21.7% 38.2% 32.3% 7.8%	(1998)	(2002)		NR
Greene ⁷² 2005 16194711	CaPSURE	<60 60-70 >70				23% 46% 31%		28% 42% 31%		P=0.23 (chi-square p-value comparing 2 periods)
Mettlin ⁷³ 1994 8062197	NCDB	<50 50-54 55-59 60-64 65-69 70-74 75-79 80-84 ≥85		0.5% 1.5% 5.3% 12.4% 20.2% 22.7% 18.7% 12.0% 6.7%	0.5% 1.6% 4.7% 11.6% 20.8% 24.3% 19.8% 10.9% 5.8%					NR
	NCDB	Mean age		71.6 (1985)	71.6 (1990)					NR
Mettlin ⁷⁴ 1996 8640686	NCDB	<50 50-59 60-69 70-79 80+		0.6% 6.7% 31.1% 42.8% 18.7%	0.8% 7.9% 34.9% 42.8% 13.6%					
Mettlin ⁷⁵ 1995 8625214	NCDB	0-29 30-39 40-49 50-59 60-69 70-79 80+		0.1% 0% 0.5% 6.8% 31.2% 42.5% 18.9%	0.1% 0% 0.7% 8.0% 34.9% 42.9% 13.5%					
Mettlin ⁷⁶ 1998	NCDB	Median age Mean age			71 70.7	69 68.8				NR

Author, year	Database	Age groups (yr)	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
9781963		% <65			21.3% (1992)	29.8% (1995)				
Hamilton ⁷⁸ 2011	POCS, NCI	<60				20.6%	32.5%		P<0.01 (difference in distribution by yr)	
20735387		60-64			18.0%	21.5%				
		65-74			41.6%	28.5%				
		≥75			19.9% (1998)	17.5% (2002)				

Ordering of the studies follows Appendix Table C1.1.

ANOVA = analysis of variance; CI = confidence interval; NA = not applicable; NR = not reported; RR = relative risk; SD = standard deviation; yr = year.

Appendix Table C1.3. Patient characteristics – comorbidity

Author, year	Database	Assessment method	Comorbidity groups	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
Greene ⁷² 2005 16194711	CaPSURE	Number of comorbidities	0 1-2 ≥3				17% 52% 31%	15% 56% 30%		P=0.46 (chi-square comparing 2 periods)	
							(1997- 99)	(2000-03)			
Hamilton ⁷⁸ 2011 20735387	POCS, NCI	Number of comorbidities	0 ≥1				78.3% 21.7%	87.4% 12.7%		P<0.01 (difference in distribution by yr)	
							(1998)	(2002)			

Ordering of the studies follows Appendix Table C1.1.
yr = year.

Appendix Table C1.4. Patient characteristics – race/ethnicity

Author, year	Database	Race/ethnicity	1980-1984	1985-1989	1990-1994	1995-1999	2000-2004	2005-2010	Statistical analysis	Notes
Clegg ³¹ 2002 12230422	SEER	The study provided a cross-table of the proportion of patients with localized/regional, distant or unknown cancer stage, by race and period of study (1975-87 and 1988-97). The racial groups considered were non-Hispanic White, Hispanic White, African American, American Indian and Alaskan native, Asian American, and Hawaiian native.	(1975-87)		(1987-97)				P<0.001 (chi-square test for stage x race x time period)	Hispanic Whites, non-Hispanic Whites and Asian Americans had the highest proportion of cases diagnosed at localized/regional stage and the lowest proportion of cases diagnosed at distant stage. Conversely, African Americans had the lowest proportion of cases diagnosed at localized/regional stage and the highest proportion diagnosed at distant stage. These differences were generally consistent across time periods.
Jani ³⁷ 2007 17505529	SEER	Caucasian African-American Other		86.5% 10.0% 3.5% (1984-88)	85.0% 9.6% 5.3% (1989-1993)	80.0% 12.2% 7.5% (1994-1998)	80.3% 11.7% 7.9% (1999-2003)		P=0.785 (chi-square test) RR=1.45 (CI 0.73, 1.81)	Data were only reported for White and Black individuals.
Polednak ⁴⁶	SEER	Non-Hispanic White			23,347 (88.7%)	17,111 (85.8%)				Data were not

2002 12477140		Black			2969 (11.3%) (1992)	2821 (14.2%) (1997)	reported for patients of other racial/ethnic groups.
<i>Count (percentage) of men in each racial/ethnic group</i>							
Demers ⁴⁹ 1994 8203988	SEER- Detroit	White Black	74% 26% (1987)	77% 23% (1991)			P<0.001 (Mantel- Haenszel test for the linear association between year of diagnosis and race)
Schwartz ⁵² 1999 10197854	SEER- Detroit	White Black Other Unknown	73% 27% 1% 1% (1982-86)	74% 24% 1% 2% (1987-91)	69% 25% 1% 6% (1992-96)		
Gilliland ⁵³ 1996 8722215	SEER- New Mexico	White, non-Hispanic Hispanic Black American Indian Other/unknown	71.7% 22.1% <1% 3.8% 1.5% (1983-84)	69.4% 24.4% 1.9% 4.1% <1% (1987-88)	76.8% 18.9% 1.5% 2.7% <1% (1991-92)		NR
Klabunde ⁵⁸ 1998 9749657	SEER, Medicare	White Black	91.7% 8.3% (1987)	91.4% 8.6% (1992)			NR
Zeliadt ⁶¹ 2004 15596192	SEER, Medicare	White African-American		91.0% 9.0% (1991-1993)	89.3% 10.7% (1997-1999)		NR
Carpenter ⁶² 2010 20333462	SEER, Medicare	White Black		85.8% 14.2% (1994)	82.9% 17.1% (1997)	83.5% 16.5% (2002)	P=0.043 (chi-square test comparing yr of diagnosis between White and Black men, for all yr from 1994 to 2002)
Mullins ⁶³ 2010	SEER- Medicare	Non-Hispanic White African American				80.6% 12.2%	82.2% 10.7%

20163844		Hispanic White		7.2% (1998)	7.1% (2002)	
Cooperberg ⁶⁵ 2002 12131295	CaPSURE	White – non Hispanic Black/African American Hispanic Other	84.9% 11.1% 2.1% 1.9% (1989-97)	86.8% 8.8% 1.6% 2.9% (1997-2001)		NR
Greene ⁷² 2005 16194711	CaPSURE	White – non Hispanic Black/African American Asian Hispanic Alaska native/American native Other		83% 11% 2% 3% 0% 1% (1997- 99)	91% 5% 1% 1% <1% 1% (2000-03)	P<0.001 (chi-square comparing 2 periods)
Mettlin ⁷⁵ 1995 8625214	NCDB	Non-Hispanic White Hispanic African American Native American Asian Unknown	85.7% 1.6% 7.6% 0.1% 0.8% 4.2% (1986-87)	85.1% 2.1% 8.1% 0.1% 1.1% 3.5% (1992)		
Mettlin ⁷⁶ 1998 9781963	NCDB	White – non Hispanic Black/African American Hispanic Other	87.7% 8.8% 0.8% 2.7% (1992)	83.3% 11.8% 1.6% 3.3% (1995)		NR
Hamilton ⁷⁸ 2011 20735387	POCS, NCI	White African American Hispanic		78.4% 14.0% 7.6% (1998)	83.2% 12.5% 4.3% (2002)	P<0.01 (difference in distribution by yr)

Ordering of the studies follows Appendix Table C1.1.

NA = not applicable; NR = not reported; RR = relative risk; yr = year.

Appendix Table C1.5. Tumor characteristics – stage

Author, year	Database	Stage groups	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
Mebane ¹⁶ 1990 2258952	SEER	Localized disease	64.4%	59.2%						Data presented only for Black and White individuals.
		Regional disease	11.3%	11.9%						
		Distant disease	18.7%	18.9%						
		[White patients]	(1980)	(1985)						
	SEER	Localized disease	59.2%	52.2%						Data presented only for Black and White individuals.
		Regional disease	9.4%	12.0%						
		Distant disease	29.2%	26%						
		[Black patients]	(1980)	(1985)						
Dennis ²³ 2000 10679753	SEER	Positive nodes		4%	2.6% (1992)	1.3%			NR	
		Not examined		80%	75% (1994)	NR				
		Lymph node status at diagnosis		(1988)		(1996)				
Clegg ³¹ 2002 12230422	SEER	The study provided a cross-table of the proportion of patients with localized/regional, distant or unknown cancer stage, by race and period of study (1975-87 and 1988-97)							P<0.001 (chi-square test for stage x race x time period)	The cross-table suggests that the proportion of patients with distant disease decreased and the proportion of patients with localized/regional disease increased over time, across all racial/ethnic groups studied.
Jani ³⁷ 2007 17505529	SEER	AJCC stage		53%	41%	53%	65%		P=0.025 (chi-square test)	Excluded AJCC stage IV.
		0/I		20%	25%	21%	22%			
		II		26%	33%	25%	13%			
		III		(1984-88)	(1989-1993)	(1994-1998)	(1999-2003)		RR=0.86 (CI 0.70, 0.92)	
Polednak ⁴⁶ 2002 12477140	SEER	Local/regional			18,470 (Non-Hispanic White), 2094 (Black)	15,034 (Non-Hispanic White), 2406 (Black)			NR	Data were not reported for patients of other racial/ethnic groups.

		Distant			1490 (Non-Hispanic White), 380 (Black) (1992)	749 (Non-Hispanic White), 221 (Black) (1997)		
Schwartz ⁵² 1999 10197854	SEER-Detroit	local regional distant unknown	60% 7% 20% 13% (1982-86)	65% 9% 13% 13% (1987-91)	72% 9% 5% 13% (1992-96)			
Stephenson ⁵⁶ 1996 8608513	SEER-Utah	Distant <i>Percent of new cases</i>	13.9% (1984)	13.3% (1989)	4.8% (1993)		NR	Data were only presented for the subgroup of men with distant disease.
Carpenter ⁶² 2010 20333462	SEER-Medicare	OR (95% CI) for advanced versus early stage prostate cancer, 1994 is the baseline			1 (1994)	0.65 (0.55 to 0.76) (1997)	0.46 (0.38 to 0.56) (2002)	Multivariable logistic regression comparing stage at diagnosis by yr; the model included the following covariates: age at diagnosis, marital status, diagnosis yr, comorbidity score, median household income, receipt of surgery/related procedures, and comorbidity. Overall P<0.001, for all yr between 1994 and 2002.
Mullins ⁶³ 2010 20163844	SEER-Medicare	<i>OR for diagnosis with distant vs. in situ, local or</i>				Reference year (1998)	OR=0.76 (0.69, 0.83) (2002)	P<0.01 OR adjusted for patients with

		<i>regional disease, using 1998 as the reference year.</i>					marital status, urban/rural living area, state-buy- in, PSA test prior to diagnosis, census tract median household income, SEER registry.	available stage information. Additional information on interactions of patient age with time trends are presented in Table 6 of the paper.
Cooperberg ⁶⁵ 2002 12131295	CaPSURE	<i>T stage</i> T1 T2 T3 T4	21.6% 68.6% 9.1% 0.7% (1989-97)	45.4% 50.2% 3.7% 0.5% (1997-2001)			NR	
Cooperberg ² 2003 14610406	CaPSURE	<i>T stage</i> T1 T2a T2b T3-4	16.9% 48.2% 23.0% 11.8% (1989-92)	30.6% 36.0% 25.8% 7.5% (1996-99)	49.4% 27.2% 20.0% 3.5% (1999-2002)		P<0.001 (Mantel- Haenszel test for trend)	
Cooperberg ⁶⁸ 2004 15169800	CaPSURE	T2a T1c T1b T1a	74.6% 15.2% 5.4% 4.9% (1989-92)	60.2% 35.9% 2.3% 1.6% (1996-98)	36.2% 61.7% 0.5% 1.6% (1999-2001)		Low-risk prostate cancer patients only (n=1990)	
Cooperberg ⁶⁹ 2007 17644125	CaPSURE	<i>T stage</i> 1a 1b 1c 2a	3.5% 4.1% 29.9% 62.5% (1990-94)	1.6% 1.1% 49.8% 47.4% (1995-99)	<1% <1% 73.3% 25.3% (2002-03)	<1% <1% 78.3% 20.7% (2004-06)	P<0.001 ("trend in distribution of each risk characteristic")	Trend data reported only for "low-risk" prostate cancer (PSA≤10 ng/ml, Gleason score ≤6 and clinical stage T1 or T2a).
Greene ⁷² 2005 16194711	CaPSURE	<i>T stage</i> 1 2 3		43% 54% 2%	58% 41% 1%		P<0.001 (chi-square comparing 2	

			(1997-99)	(2000-03)	periods)	
Mettlin ⁷³ 1994 8062197	NCDB	0-II III IV	67.3% 13.0% 19.7% (1985)	64.7% 16.2% 19.1% (1990)	NR	
Mettlin ⁷⁴ 1996 8640686	NCDB	Stage 0-I Stage II Stage II Stage IV	44.2% 20.2% 14.6% 20.9% (1987)	29.4% 39.9% 18.4% 12.4% (1992)		
Mettlin ⁷⁵ 1995 8625214	NCDB	pAJCC/cAJCC stage 0 I II III IV Unknown	1.9% 18.8% 9.5% 6.7% 10.6% 52.6% (1986-87)	4.7% 18.9% 33.1% 15.1% 10.4% 17.8% (1992)		
Mettlin ⁷⁶ 1998 9781963	NCDB	Stage 0 I II III IV Localized disease (0-II)		5.4% 22.8% 41.1% 18.0% 12.6% 69.3% (1992)	2.0% 24.9% 49.7% 13.0% 10.3% 76.7% (1995)	NR
Danley ⁷⁷ 1995 8580296	LAC/USC CSP	Localized Regional/Metastatic <i>Percentage of cases by yr of diagnosis</i>	71% 29% (1981-84)	66% 34% (1985-88)	1.03 (0.96, 1.10) 1.29 (1.21, 1.37) (OR and 95% CIs using 1976- 80 as the baseline period)	P<0.001 for trend over time

Ordering of the studies follows Appendix Table C1.1.

AJCC = American Joint Committee on Cancer; cAJC = clinical stage according to American Joint Committee on Cancer guidelines; CI = confidence interval; NA = not applicable; NR = not reported; OR = odds ratio; pAJCC = pathological stage according to American Joint Committee in Cancer guidelines; PSA = prostate-specific antigen; SD = standard deviation.

Appendix Table C1.6. Tumor characteristics – Gleason score

Author, year	Database	Gleason score groups	1980-1984	1985-1989	1990-1994	1995-1999	2000-2004	2005-2010	Statistical analysis	Notes
Perrotti ²² 1998 9720554	SEER	Well diff. Moderately diff. Poorly diff.	37.9 34.9 24.4 (1980-84)		20.4 57.6 21.4 (1990-94)				P<0.001 P<0.001 P<0.001 (comparison of proportions between time periods, separately for each grade)	Additional information is presented in Figure 1 of the paper (1974-1994).
Jani ³⁰ 2008 18845997	SEER	Well diff. Moderately diff. Poorly diff.	41% 35% 24% (1979-83)	34% 42% 24% (1984-88)	24% 58% 18% (1989-93)	12% 69% 19% (1994-98)	4% 75% 21% (1999-2003)		P<0.001 (chi-square comparing across all periods)	
Jani ³⁷ 2007 17505529	SEER	Well diff. Moderately diff. Poorly diff.		34% 41% 23% (1984-88)	24% 58% 18% (1989-1993)	12% 69% 19% (1994-1998)	4% 75% 21% (1999-2003)		P<0.001 (chi-square test) RR=1.37 (1.21, 1.50)	Excluded undifferentiated tumors.
Polednak ⁴⁶ 2002 12477140	SEER	High grade [White]			20.6% (1992)	19.1% (1997)			P<0.001 (chi-square for linear trend in proportions for the period 1992-1998)	Data were reported only for non-Hispanic White and Black patients.
	SEER	High grade [Black]			24.7% (1992)	20.6% (1997)			P<0.005 (chi-square for linear trend in proportions for the period 1992-1998)	Data were reported only for non-Hispanic White and Black patients.
Schwartz ⁵² 1999 10197854	SEER-Detroit	Well diff. Moderately diff. Poorly diff. Undifferentiated Unknown	30.2% 28.6% 18.9% 2.3% 20.0% (1982-86)	25.5% 39.4% 19.3% 1.1% 14.7% (1987-91)	12.4% 54.4% 17.9% <1% 14.8% (1992-96)				P=0.001 (proportion of moderately differentiated tumors over time)	
Stephenson ⁵⁶ 1996 8608513	SEER-Utah	2-4 5-7 8-10	33% 30% 21% (1984)	27% 39% 18% (1989)	18% 50% 16% (1993)				NR	

Cooperberg ⁶⁵ 2002 12131295	CaPSURE	2-4 5-6 7 8-10	17.3% 50.6% 19.9% 12.2% (1989-97)	2.9% 62.8% 24.2% 10.1% (1997-2001)			NR	
Cooperberg ² 2003 14610406	CaPSURE	2-4 5-6 7 8-10	26.5% 46.4% 17.4% 9.7% (1989-92)	7.5% 57.7% 23.4% 11.5% (1996-99)	1.7% 63.8% 24.7% 9.8% (1999-2002)		P=0.003 (Mantel-Haenszel test for trend)	
Cooperberg ⁶⁸ 2004 15169800	CaPSURE	5-6 2-4	59.5% 40.5% (1989-92)	81.6% 18.4% (1996-98)	96.1% 3.9% (1999-2001)			Low-risk prostate cancer patients only (n=1990)
Cooperberg ⁶⁹ 2007 17644125	CaPSURE	2-4 5 6	40.8% 26.4% 32.9% (1990-94)	17.4% 24.9% 57.7% (1995-99)	1.3% 4.9% 93.8% (2002-03)	0.7% 2.3% 97.0% (2004-06)	P<0.001 ("trend in distribution of each risk characteristic")	Information on trends was reported only for patients with "low-risk" prostate cancer, defined as PSA≤10 ng/ml, Gleason score≤6 and clinical stage T1 or T2a.
Greene ⁷² 2005 16194711	CaPSURE	2-4 5-6 7 8-10		3% 66% 24% 6% (1997-99)	1% 66% 26% 7% (2000-03)		P=0.006 (chi-square comparing 2 periods)	
Mettlin ⁷⁴ 1996 8640686	NCDB	Well diff. Moderately diff. Poorly diff.	31.3% 38.6% 30.1% (1986)	19.8% 57.5% 22.8% (1993)				Limited to men with known tumor grade (the proportion of unknown grade declined over time, from 18.3% in 1986 to 10.2% in 1993).
Mettlin ⁷⁶ 1998 9781963	NCDB	Well diff. Moderately diff. Poorly diff. Undifferentiated	21.8% 55.6% 21.5% 1.1% (1992)	15.8% 62.2% 21.2% 0.7% (1995)			NR	
Hamilton ⁷⁸ 2011	POCS, NCI	<6 6		15.6% 31.6%	4.4% 52.4%		P<0.01 (difference in	

20735387	7	15.1%	23.5%	distribution by yr)
	8-10	5.4%	6.9%	
	Unknown	32.4%	12.8%	
		(1998)	(2002)	

Ordering of the studies follows Appendix Table C1.1.

Diff = differentiated; NA = not applicable; NR = not reported; yr = year.

Appendix Table C1.7. Tumor characteristics – PSA

Author, year	Database	PSA groups (ng/ml)	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
Kindrick ⁶⁴ 1998 9817332	CaPSURE	Median PSA at diagnosis			10.1 (1992)	9.2 (1997)			NR	Additional information is provided in the single Figure of the paper.
Cooperberg ⁶⁵ 2002 12131295	CaPSURE	<4 4-10 10.01-20 >20			9.6% 46.5% 22.8% 21.1% (1989-97)	13.8% 58.8% 16.9% 10.5% (1997-2001)			NR	Additional information is presented in the single Figure of the paper, depicting a linegraph of median PSA (measured between diagnosis and primary treatment) for patients with "low" or "intermediate" risk cancer.
Cooperberg ² 2003 14610406	CaPSURE	<4 4-10 10-20 >20			10.7% 37.2% 25.2% 27.0% (1989-92)	11.2% 54.8% 19.5% 14.5% (1996-99)	12.9% 63.2% 15.8% 8.1% (1999-2002)		P<0.001 (Mantel-Haenszel test for trend)	
Cooperberg ⁶⁸ 2004 15169800	CaPSURE	0-4 4-10			25.5% 74.6% (1989-92)	16.5% 83.6% (1996-98)	17.2% 82.8% (1999-2001)			Low-risk prostate cancer patients only (n=1990)
Cooperberg ⁶⁹ 2007 17644125	CaPSURE	<2 2-6 6-10			9.2% 42.9% 47.8% (1990-94)	4.8% 48.3% 46.9% (1995-99)	6.4% 62.0% 31.6% (2002-03)	5.8% 65.9% 28.2% (2004-06)	P<0.001 ("trend in distribution of each risk characteristic")	Information on trends was reported only for patients with "low-risk" prostate cancer, defined as PSA≤10 ng/ml, Gleason score≤6 and clinical stage T1/T2a.
Greene ⁷² 2005 16194711	CaPSURE	≤4 4.1-10 10.1-20 >20				15% 60% 18% 7% (1997-99)	16% 67% 13% 4% (2000-03)		P=0.008 (chi-square comparing 2 periods)	
Hamilton ⁷⁸ 2011 20735387	POCS, NCI	0-4.0 4.1-9.9 10.0-19.9 20.0-100.0				9.1% 53.5% 19.3% 6.2%	14.4% 51.1% 12.0% 6.2%		P<0.01 (difference in distribution by yr)	

>100.0	0.1%	1.1%
unknown	11.8%	15.2%
	(1998)	(2002)

Ordering of the studies follows Appendix Table C1.1.

NA = not applicable; NR = not reported; PSA = prostate specific antigen.

Appendix Table C1.8. Diagnostic strategies – biopsy frequency

Author, year	Database	Frequency groups	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
Schwartz ⁵² 1999 10197854	SEER-Detroit		(1982)			(1995)			P<0.001 (Cochran-Armitage test for trend in proportion of biopsies over time)	Additional information is presented in Figure 4 of the paper.
Gilliland ⁵⁴ 2001 11176484	SEER-New Mexico	Biopsy only TURP Prostatectomy Other <i>Percentage of patients diagnosed through each procedure</i>	27.1% 55.6% 12.8% 4.5% (1983-84)		43.7% 11.2% 38.8% 6.3% (1992-93)				NR	Only histologically confirmed prostate cancer samples were considered.
Potosky ⁵⁷ 1995 7530782	SEER-Medicare	<i>Age-adjusted (1970 US standard) biopsy procedure rates per 100,000 men</i>		685 (1986)	2600 (1991)				NR	Additional information is presented in Figure 2 of the paper.

Ordering of the studies follows Appendix Table C1.1.
NR = not reported; TURP = transurethral resection of the prostate.

Appendix Table C1.9.1 Diagnostic strategies – number of cores

Author, year	Database	Groups by number of cores	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
Shah ⁷¹ 2008 17997437	CaPSURE	Mean ±SD				7.5 ±2.1 (1997)	9.8 ±3.0 (2002)		Beta= 0.41, SE = 0.01; P<0.001 (regression of the number of removed cores on yr, from 1995 to 2004; adjusted for CaPSURE study site)	Excluded patients diagnosed with biopsies of fewer than 6 cores.

Ordering of the studies follows Appendix Table xxx.
SD = standard deviation; SE = standard error.

Appendix Table C1.9.2 System characteristics – including, differences in geographical access, insurance, physician types, etc.

Author, year	Database	Characteristic reported	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes	
Cooperberg ⁶⁵ 2002 12131295	CaPSURE	Insurance									
		Medicare supplemental			76.5%	66.9%				NR	
		Medicare alone			18.8%	20.4%					
		Veterans Affairs			1.8%	4.8%					
		Other			3.0%	7.9%					
					(1989-97)	(1997-2001)					
		Geographic region									
		East			48.8%	35.0%				NR	
		South			26.4%	14.2%					
		Midwest			9.0%	35.1%					
West			15.9%	15.7%							
			(1989-97)	(1997-2001)							
Setting											
Community					91.2%	86.4%			NR		
Academic					8.8%	13.6%					
					(1989-97)	(1997-2001)					
Greene ⁷² 2005 16194711	CaPSURE	Insurance									
		Medicare supplement				30%	32%			P=0.003 (chi-square comparing 2 periods)	
		Medicare				17%	12%				
		Private				52%	52%				
		Other				<1%	3%				
					(1997-99)	(2000-03)					
Mettlin ⁷⁵ 1995 8625214	NCDB	Hospital caseload									
		<150 cases		1.1%	0.9%						
		150-499		19.5%	19.3%						
		500-999		38.5%	39.9%						
		1000+		30.5%	30.2%						
Unknown size		10.4%	9.6%								
			(1986-87)	(1992)							
Hamilton ⁷⁸ 2011 20735387	POCS, NCI	Insurance status									
		Private				42.8%	39.6%			NR	
		HMO/IPA/Managed care				31.4%	34.3%				
		Medicare				12.4%	12.6%				
		Medicaid				1.2%	1.9%				
		CHAMPUS, VA, other mil.				3.2%	4.1%				
		None/unknown				9.0%	7.6%				
						(1998)	(2002)				
		Median income \$ (area)									
		<40,000					41%	19.5%			P<0.01

40,000-75,000	47.9%	46.7%	(difference in distribution by yr)
>75,000	2.8%	31.9%	
unknown	8.4%	1.9%	
	(1998)	(2002)	

Ordering of the studies follows Appendix Table C1.1.

CHAMPUS = Civilian Health and Medical Program of the Uniformed Services; HMO = health maintenance organization; IPA = independent practice association; NR = not reported; VA = Veterans Affairs; yr = year.

Appendix Table C1.10: Treatment characteristics – changes in treatment patterns over time.

Author, year	Database	Treatment	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
Escobedo ²⁷ 2004 15542264	SEER- Connecticut	RP	6.6%		21.3%					African American men only
		TURP	54.1%		19.4%					
		RT	0.0%		0.6%					
		RP and RT	0.8%		2.7%					
		Observation	1.7%		1.3%					
		All other	36.8%		54.7%					
			(1983-88)		(1989-94)					
	SEER-Iowa	RP	11.1%		25.0%					African American men only
		TURP	72.2%		15.6%					
		RT	0.0%		0.0%					
		RP and RT	0.0%		9.4%					
		Observation	1.9%		1.0%					
		All other	14.8%		49.0%					
			(1983-88)		(1989-94)					
	SEER-New Mexico	RP	5.9%		28.8%					African American men only
		TURP	55.9%		15.0%					
		RT	0.0%		0.0%					
		RP+RT	2.9%		7.5%					
		Observation	0.0%		1.3%					
		All other	35.3%		47.5%					
			(1983-88)		(1989-94)					
Harlan ³⁶ 1995 7799048	SEER	RP	11.0%		32.3%				P<0.001 (chi-square test)	Additional information is presented in Figures 1-4 of the paper (1984-91).
		RT	27.0%		29.7%					
		Other (including, ADT or careful observation with therapy reserved for clinical progression) <i>Age-adjusted proportions for initial Tx (within 4 mo of diagnosis)</i>	NR (1984)		NR (1991)					

Author, year	Database	Treatment	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
Miller ⁴¹ 2006 ^a 16912266	SEER	EM/ADT RP RT [higher-risk]					20.0% 43.1% 36.9% (2001)		P=0.042 (overall chi-square test for 2000-02)	Higher-risk patients were those with poorly diff. tumors regardless of age or those with moderately diff. tumors aged <70 yr.
	SEER	EM/ADT RP RT [lower-risk]		NR 17% 31% (1988-90)			43.6% 10.6% 45.9% (2001)		P=0.008 (overall chi-square test for 2000-02)	The historical cohort (1988-90) was used for comparison of treatment patterns among lower-risk patients only. Lower-risk patients were those with well-diff. tumors regardless of age or those with moderately diff. tumors aged ≥70 yr.
Underwood ⁴⁸ 2004 15017208	SEER	Definitive therapy (defined as any Tx other than ADT/EM)			(1992)	(1999)			Logistic regression for trends in definitive Tx: 1. Racial/ethnic disparities improved with time in Hispanic men but less so in	A cross-table of odds ratios for ethnicity and Tx year (1992-99) was provided, stratified by tumor grade (well-moderately-poorly differentiated); i.e.

^a The study reported data for the period 2000-02, which fits entirely in one of our table's 5 yr bins. We extracted data for the midpoint of the study period (i.e., 2001) along with the p-value from tests comparing the frequency of treatments across all 3 study years. Readers are referred to the full text of the paper for additional information.

Author, year	Database	Treatment	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
									<p>Black men.</p> <p>2. In 1992 Hispanic men with moderately/poorly differentiated cancers were less likely to receive definitive therapy than White men (OR 0.62 and 0.50 for moderately and poorly differentiated tumors respectively, $P < 0.001$ vs. White men), whereas by 1999 the odds that Hispanic men would receive definitive therapy were not significantly different from those of White men ($p = 0.20$ and 0.96 for moderate and poorly differentiated cancers, respectively).</p> <p>3. A disparity in the use of definitive therapy by Black men with moderately or poorly</p>	a 2x3x3 table. Data were not available for assessing ADT and EM separately.

Author, year	Database	Treatment	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
									differentiated cancers compared to White men persisted in 1999 (OR 0.60 and 0.45, respectively, $p < 0.001$ for definitive therapy in each yr compared to White men). This disparity was less profound than it had been in 1992 (OR 0.56 and 0.38, respectively).	
Underwood ⁴⁷ 2005 15612083	SEER	ADT/EM			(1992)	(1999)			Logistic regression for trends in Tx $P < 0.001$	"the utilization of ADT/EM decreased significantly over time". Additional information (1992-99) was presented in a figure in the article. Data were not available for assessing ADT and EM separately.
Klabunde ⁵⁸ 1998 9749657	SEER, Medicare	RP RT Conservative Tx (not radiotherapy or surgery)		(1986)	(1993)				RP: + 58.5% RT: +39.2% Conservative Tx: - 38.4% (change in the proportion of men receiving	White men only

Author, year	Database	Treatment	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
		RP RT Conservative Tx (not radiotherapy or surgery)		(1986)	(1993)				each Tx over the study period, 1986-93). RP: + 63.5% RT: +73.5% Conservative Tx: - 37.4% (change in the proportion of men receiving each Tx over the study period, 1986-93).	Black men only
		Baseline yr = 1986 OR (95% CI) receiving aggressive Tx versus non aggressive Tx		1.12 (1.00 to 1.24)	1.39 (1.27 to 1.53)				Logistic regression predicting Tx received based on diagnosis yr; adjusted for age, socioeconomic status, SEER registry, tumor grade, comorbidity score, and the race x TURP interaction	
Cooperberg ² 2003 14610406	CaPSURE	BT EBRT RP PADT WW [Low risk]			3.7% 15.3% 62.6% 4.6% 13.7% (1989-92)	5.7% 10.0% 54.6% 16.7% 12.9% (1996-98)	18.4% 6.8% 51.9% 14.2% 8.3% (1999-2001)			PSA≤10.0 ng/ml, Gleason score≤6, and clinical stage T1 or T2a; excluded patients undergoing cryotherapy
		BT EBRT RP PADT WW [Intermediate risk]			3.3% 22.5% 55.3% 8.9% 10.0% (1989-92)	5.6% 18.0% 49.4% 21.3% 5.6% (1996-98)	11.8% 19.1% 45.0% 19.7% 4.5% (1999-2001)			PSA≤10.1-20.0 ng/ml, Gleason score=7, or clinical stage T2a; excluded patients undergoing cryotherapy

Author, year	Database	Treatment	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
		BT			3.1%	4.2%	2.4%			PSA \geq 20.0 ng/ml, Gleason score 8-10, or clinical stage T3 or T4; excluded patients undergoing cryotherapy
		EBRT			29.0%	19.6%	22.9%			
		RP			27.3%	23.3%	22.7%			
		PADT			32.8%	49.7%	48.2%			
		WW [High risk]			7.6% (1989-92)	3.2% (1996-98)	4.8% (1999-2001)			
Harlan ⁶⁷ 2003 14532780	CaPSURE (overall)	AS/WW		7.5% (1989-91)	9.5% (1992-94)	7.9% (1995-97)	5.5% (1998-2000)		P<0.001 (Mantel-Haenszel test for trend)	
	CaPSURE (low risk)	AS/WW		7% (1989-91)	16.9% (1992-94)	11.9% (1995-97)	7.2% (1998-2000)		P=0.003 (Mantel-Haenszel test for trend)	
									Controlling for risk group, age, comorbidity, insurance status and study site, OR for WW, compared to 1998-2000: 1995-97: OR=1.8 (1.3, 2.5) 1992-94: OR=1.8 (1.3-2.6) 1989-91: OR=1.09 (0.7, 1.7)	
	CaPSURE (intermediate risk)	AS/WW							P=0.46 (Mantel-Haenszel test for trend)	A trend line for the frequency of undergoing WW is presented in the single Figure of the paper.
	CaPSURE (high risk)	AS/WW							P=0.14 (Mantel-Haenszel test for trend)	A trend line for the frequency of

Author, year	Database	Treatment	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
									test for trend)	undergoing WW is presented in the single Figure of the paper.
Cooperberg ⁶⁸ 2004 15169800	CaPSURE	WW ADT EBRT BT RP			13.8% 3.1% 16.1% 5.1% 63.8% (1989-92)	12.5% 12.8% 8.9% 8.9% 56.9% (1996-98)	7.9% 12.0% 6.8% 21.7% 51.6% (1999-2001)		P for trend <0.001 for all Tx except RP; P=0.0019 for RP.	Low-risk prostate cancer patients only (n=1990)
Cooperberg ⁷⁰ 2010 20124165	CaPSURE	AS/WW RP RT ADT (CAPRA 0-2)			12.8% 61.6% 14.1% 4.7% (1990-94)	7.1% 61.6% 22.8% 6.3% (1995-99)	7.2% 59.6% 23.2% 7.1% (2002-03)	8.5% 59.5% 20.9% 6.4% (2004-07)		
	CaPSURE (CAPRA 3-5)	AS/WW RP RT ADT			4.4% 54.9% 24.1% 9.4% (1990-94)	5.7% 47.2% 28.6% 14.7% (1995-99)	3.3% 48.6% 26.9% 17.2% (2002-03)	5.9% 48.7% 23.5% 14.9% (2004-07)		
	CaPSURE (CAPRA 6-10)	AS/WW RP RT ADT			1.7% 27.5% 29.7% 36.7% (1990-94)	2.7% 22.1% 28.6% 41.9% (1995-99)	1.1% 23.3% 25.2% 43% (2002-03)	1.9% 22.9% 21% 45.5% (2004-07)		
Greene ⁷² 2005 16194711	CaPSURE	RP Cryosurgery BT EBRT Orchiectomy LHRH agonist LHRH antagonist Antiandrogen 5 α -RI WW				52% 2% 27% 13% 0% 3% 1% 1% 1% <1% 1% (1997-99)	58% 3% 21% 10% <1% 4% <1% 1% <1% 2% (2000-03)		P=0.011 (chi-square comparing 2 periods)	
Mettlin ⁷³ 1994 8062197	NCDB	TURP only RP RT		32.1% 11.1% 26.8%	20.4% 23.7% 28.0%				NR	

Author, year	Database	Treatment	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
		RP+RT		2.1%	2.4%					
		ADT		17.0%	16.0%					
		RT+ADT		5.0%	3.4%					
		RP+ADT		0.7%	1.3%					
		RP+RT+ADT		0.2%	0.2%					
		Other		5.0%	4.6%					
				(1985)	(1990)					
Mettlin ⁷⁴ 1996 8640686	NCDB	RP		12.4%	29.4%					
		RT		27.3%	30.6%					
		No Tx		38.0%	20.8%					
				(1987)	(1992)					
Mettlin ⁷⁵ 1995 8625214	NCDB	No Tx		39.1%	20.6%					Total cases = 52596 in 1987
		PT		11.4%	29.1%					
		RT		27.6%	31.0%					
		ADT		14.8%	11.4%					
		Combo & other		7.2%	7.8%					
				(1987)	(1992)					
Mettlin ⁷⁶ 1998 9781963	NCDB	RP			31.6%	34.1%			NR	
		EBRT			30.1%	26.3%				
		BT			1.4%	2.2%				
		ADT			12.0%	11.7%				
		Other			4.9%	4.1%				
		No treatment			20.0%	21.6%				
					(1992)	(1995)				
Hamilton ⁷⁸ 2011 20735387	POCS, NCI	BT (only)				8.5%	12.3%			
		BT+EBRT				6.4%	5.4%			
		EBRT (only)				19.0	20.1%			
		RP				45.8%	44.7%			
		PADT				7.6%	8.5%			
		WW				12.6%	9.0%			
						(1998)	(2002)			

Ordering of the studies follows Appendix Table C1.1.

5 α -RI = 5 α -reductase inhibitor; ADT = androgen deprivation therapy; AS = active surveillance; CAPRA = Cancer of the Prostate Risk Assessment; diff. = differentiated; OR = odds ratio; EM = expectant management; RP = radical prostatectomy; RT = radiation therapy; TURP = transurethral resection of the prostate; Tx = treatment; WW = watchful waiting.

Appendix Table C1.11. Trends in mortality rates (per 100,000 person-yr unless otherwise stated) or survival

Author, year	Database	Groups (yr)	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
Patient characteristics										
- Age										
Hankey ¹⁷ 1999 10379964	SEER	50-59	NA	0.7 (0.4, 1.0) (1969-89)	-2.4 (-4.8, -0.1) (1989-95)				Annual percentage changes calculated from joinpoint regression (95% CI).	Additional information is presented in Figure 2 of the paper.
		60-69	0.4 (0.1, 0.6) (1969-84)	1.9 (1.1, 2.7) (1984-91)	-4.2 (-5.7, -2.7) (1991-95)					
		70-79	0.3 (0.1, 0.4) (1969-85)	1.9 (1.2, 2.7) (1985-92)	-2.7 (-3.7, -1.7) (1992-95)					
		80-84	0.4 (0.1, 0.6) (1969-85)	2.6 (1.4, 3.9) (1985-91)	-1.4 (-2.9, 0.0) (1991-95)					
		≥85	1.7 (1.4, 1.9) (1969-88)	4.1 (2.1, 6.1) (1988-93)	-1.1 (-6.2, 4.3) (1993-95)					
		<i>Annual percentage change of the age-standardized (1970 US standard) mortality rates</i>								
Chu ¹⁸ 2003 12627516	SEER	50-59		7.3		5.4			-26% -27.9% -22.5% -11.9% +8.0% (Relative change %)	Additional information is presented in Figures 1-4 of the paper.
		60-69		51.3		37.0				
		70-79		188.9		146.4				
		80-84		404.9		356.7				
		≥85		612.4		661.3				
		<i>Age-adjusted (1990 US standard) mortality rates by age at death [White]</i>		(1986)		(1999)			P<0.001 (slope decreased of calendar period effects in 1991 based on APC analysis)	Data were not reported for other racial/ethnic groups.

Author, year	Database	Groups (yr)	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
	SEER	50-59 60-69 70-79 80-84 ≥85 <i>Age-adjusted (1990 US standard) mortality rates by age at death [Black]</i>		19.4 132.9 438.7 791.7 986.4 (1986)		17.7 115.1 393.6 818.8 1254.5 (1999)			-8.8 -13.4 -10.3 +3.4 +27.2 (Relative change %) P<0.001 (slope decreased of calendar period effects in 1991 based on APC analysis)	Additional information is presented in Figures 1-4 of the paper. Data were not reported for other racial/ethnic groups.
Merrill ²⁴ 2000 10792091	SEER	50-59 60-69 70-79 ≥80		Referent 0.63 (0.46, 0.87) 0.46 (0.34, 0.63) 0.34 (0.25, 0.47) (1988-89)	Referent 0.79 (0.57, 1.10) 0.57 (0.41, 0.78) 0.53 (0.39, 0.73) (1992-93)	Referent 0.76 (0.56, 1.04) 0.58 (0.43, 0.78) 0.49 (0.36, 0.66) (1994-95)			OR (95% CI) for death from prostate cancer vs. non-prostate cancer, stratified by age.	Data were reported only for White and Black patients.
McDavid ²⁸ 2004 15192905	SEER, NCHS	50-59 60-69 70-79 ≥80 <i>Annual percentage change of the mortality rate for each time period.</i>	NA 0.5 (1969-84) 0.2(1969-84) 1.2 (1969-87)	0.8 (1969-90) 1.8 (1984-92) 1.7 (1984-92) NA	NA NA NA 2.9 (1987-93)	-3.6 (1990-99) -5.6 (1992-99) -4.4 (1992-99) -3.4 (1993-99)			All results were significant with P<0.05.	The reporting of specific time intervals was determined by joint-point analysis. Additional information is

Author, year	Database	Groups (yr)	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
Jani ³⁰ 2008 18845997	SEER	40-49 ≥80 5-yr prostate-cancer specific mortality	36% 33% (1979-83)	18% 17% (1984-88)	1% 16% (1989-93)	2% 17% (1994-98)				presented in Figure 5 of the paper. Estimated from graph. Reported as survival. Also data for other age deciles.
Collin ³³ 2008 18424233	SEER	55-64 65-74 ≥75 Annual percentage change in age-adjusted (European Standard Population) mortality rates	0.47 (0.01, 0.93)* (1975-87) 0.41 (0.02, 0.80)* (1975-84) 1.06 (0.87, 1.24)* (1975-87)	4.27 (-3.56, 12.74) (1987-90) 1.71 (0.99, 2.45)* (1984-91) 2.80 (2.08, 3.52)* (1987-93)	-4.14 (-4.50, -3.79)* (1990-2004) -2.85 (-6.89, 1.36) (1991-94) -3.56 (-3.89, -3.24)* (1993-2002)	NA NA NA	NA -5.07 (-5.38, -4.76)* (1994-2004) -5.32 (-8.23, -2.32)* (2002-04)	Estimates (95% CI) from joinpoint regression; time intervals differ between age groups because they were determined from the regression * denotes P<0.05		
Devesa ³⁹ 1995 7707404	SEER	35-54 55-74 ≥75 Age-adjusted standardized (1970 US standard) mortality rate		1.2 56.1 392.6 (1987-91)					+0.1 (+9.1%) +6.2 (+12.4%) +51.5 (+15.1%) Absolute [relative] change in rate, compared to 1975-79	

Author, year	Database	Groups (yr)	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
Merrill ⁴⁰ 2000 10647666	SEER	50-59 60-69 70-79 ≥80 <i>Percentage of prostate cancer deaths out of all deaths observed among prostate cancer patients</i>		61% 50% 39% 30% (1988)	52% 51% 37% 30% (1992)	52% 41% 31% 26% (1995)				Excluded men younger than 50 yr for this analysis. Additional information is presented in Figure 2 of the paper.
Patient characteristics										
-										
Race/ethnicity										
Mebane ¹⁶ 1990 2258952	SEER	Black White <i>Age-adjusted (1970 US standard) mortality rate</i>	23.5 42.4 (1980)	21.9 45.8 (1985)						Data presented only for Black and White individuals.
Hankey ¹⁷ 1999 10379964	SEER	White Black Other <i>Annual percentage change of the age-standardized (1970 US standard) mortality rates</i>		0.7 (0.6, 0.8) (1969-87) 1.6 (1.4, 1.7) (1969-88) NA	3.1 (1.8, 4.4) (1987-91) 3.2 (1.3, 5.2) (1987-92) 2.6 (2.0, 3.3) (1973-92)	-1.9 (-2.6, -1.1) (1991-95) -1.7 (-3.5, 0.1) (1992-95) -1.8 (-8.0, 4.9) (1992-95)			Annual percentage changes calculated from joinpoint regression (95% CI).	Additional information is presented in Figure 1 of the paper.

Author, year	Database	Groups (yr)	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
Chu ¹⁸ 2003 12627516	SEER	White Black 1 yr survival rates of patients diagnosed with prostate cancer by year of diagnosis	96% 94% (1981-85)			98% 98 (1992-97)				
	SEER	White Black 3 yr survival rates of patients diagnosed with prostate cancer by year of diagnosis	85% 78% (1981-85)			94% 92% (1992-97)				
	SEER	White Black 5 yr survival rates of patients diagnosed with prostate cancer by year of diagnosis	76% 68% (1981-85)			91% 87% (1992-97)				
Brawley ¹⁹ 1997 9351560	SEER	White Black Age-adjusted standardized (1970 US standard) mortality rate	(1973)		(1994)				Change in mortality: +18.6% among White Americans; +41.4% among Black Americans	Additional information is provided in Figures 1 and 2 of the paper
	SEER	Proportion surviving 5 yr or longer after diagnosis	73.9% (1981) 61.0% (1973)	87.4% (1989)						
	SEER	White men only Age-adjusted standardized			All regions examined: 1991, 24.7;				All regions: decrease of 0.9 deaths	

Author, year	Database	Groups (yr)	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
		(1970 standard) mortality rate			1994, 23.8 (1991-94)				per 100,000 individuals per yr	
					Connecticut: 1991, 25.3; 1994, 23.0 (1991-94)				All regions: decrease of 2.3 deaths per 100,000 individuals per yr	
Merrill ²⁴ 2000 10792091	SEER	White Black		Referent 0.9 (0.8, 1.04) (1988-89)	Referent 1.11 (0.98, 1.27) (1992-93)	Referent 1.06 (0.94, 1.21) (1994-95)			OR (95% CI) for death from prostate cancer vs. non-prostate cancer, comparing White and Black men.	No data were reported for patients belonging to other racial/ethnic groups.
Stephenson ²⁶ 2002 12109343	SEER	Black <i>Age-adjusted mortality rate</i>		(1993)	(1997)			-10.9% relative change of mortality rate	Black men only. Additional information is provided in Figures 9-12 and 14 of the paper.	
Escobedo ²⁷ 2004 15542264	SEER-Connecticut	African American men only <i>Age-adjusted standardized (1970 standard) mortality rate</i>	78.2 (65.9-90.6) (1979-86)	81.2 (65.1-97.3) (1987-90)	93.1 (82.3-103.8) (1991-98)					

Author, year	Database	Groups (yr)	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
	SEER-Iowa	African American men only <i>Age-adjusted standardized (1970 standard) mortality rate</i>	79.5 (55.1-103.9) (1979-86)	111.1 (71.9, 105.3) (1987-90)	93.5 (69.1-117.9) (1991-98)					
	SEER-New Mexico	African American men only <i>Age-adjusted standardized (1970 standard) mortality rate</i>	104.7 (69.4-140.0) (1979-86)	62.1 (26.9-97.4) (1987-90)	47.6 (29.6-65.5) (1991-98)					
Sarma ³⁴ 2002 11828352	SEER	White Black <i>Age-adjusted (1970 US standard) mortality rate</i>	21.0 (1981) 45.8 (1981)		24.7 (1991) 56.2 (1993)	(peak values for each racial group)			Since 1993, Black individuals experienced a 3% annual decrease in age-adjusted mortality rate; White individuals experienced annual decreases in age-adjusted mortality rate of 1.4% during 1991-94 and 4.7% during 1994-98.	Additional information is presented in Figure 4 of the paper.
		White vs. Black 5-yr prostate cancer mortality		+14.1% (1983-87)	+14.6% (1988-93)				Average 5-yr relative survival of White vs. Black	Additional information is presented in Figure 5

Author, year	Database	Groups (yr)	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
Merrill ⁴⁰ 2000 10647666	SEER	White Black Other/unknown <i>Percentage of prostate cancer deaths out of all deaths observed among prostate cancer patients</i>		36% 41% 39% (1988)	35% 43% 34% (1992)	29% 34% 31% (1995)			patients	of the paper. Additional information is presented in Figure 3 of the paper.
Stewart ⁴⁴ 2004 15179359	SEER, NCHS	All races White White non-Hispanic White Hispanic Black American Indian/ Alaska native Asian/Pacific Islander Hispanic <i>Age-adjusted (2000 US standard) death rate</i>			38.6 35.7 34.6 24.0 78.0 19.8 16.7 23.6 (1990)		30.6 27.9 28.1 22.5 69.2 20.1 12.8 22.2 (2000)		-2.6% (P<0.05) -2.8% (P<0.05) - 2.5%(P<0.05) -1.1% - 1.4%(P<0.05) -1.5% - 3.4%(P<0.05) -1.0% (annual percentage change, P-values for the null hypothesis that there was no change)	
Demers ⁵¹ 2001 11745285	SEER- Detroit	White Black <i>Age-adjusted</i>		23.1 44.0 (1988)	25.4 49.5 (1992)	21.7 44.0 (1997)			P<0.001 (decreasing trend in	Additional information is

Author, year	Database	Groups (yr)	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
		(1970 US standard) mortality rates							mortality rates, 1993-98)	presented in Figure 1 of the paper.
Godley ⁶⁰ 2003 14625261	SEER-Medicare	Non-Hispanic White Black Median survival time following diagnosis, yr		8.4 (8.3 to 8.7) 6.8 (6.3 to 7.2) (1986-88)	Not reached 7.8 (7.3 to 8.3) (1989-91)	Not reached Not reached (1992-96)			NR	
		Non-Hispanic White Black 5-yr survival rate following diagnosis		0.70 (0.69 to 0.71) 0.62 (0.59 to 0.65) (1986-88)	0.77 (0.76 to 0.78) 0.68 (0.65 to 0.70) (1989-91)	0.80 (0.79 to 0.81) 0.75 (0.73 to 0.77) (1992-96)			NR	
		Non-Hispanic White Black 10-yr survival rate following diagnosis		0.42 (0.41 to 0.43) 0.32 (0.29 to 0.34) (1986-88)	0.53 (0.51 to 0.54) 0.39 (0.35 to 0.43) (1989-91)	Not reached Not reached (1992-96)			NR	
		Non-Hispanic White Black Kaplan-Meir survival rate at 12 mo		0.97 (0.96 to 0.98) 0.95 (0.92 to 0.98) (1986-88)	0.98 (0.98 to 0.99) 0.93 (0.91 to 0.96) (1989-91)	0.99 (0.98 to 0.99) 0.97 (0.96 to 0.98) (1992-96)			P<0.001 (log-rank p-value comparing White with Black individuals)	
		Non-Hispanic White Black Kaplan-Meir survival rate at 60 mo		0.81 (0.80 to 0.83) 0.72 (0.66 to 0.79) (1986-88)	0.86 (0.85 to 0.87) 0.79 (0.75 to 0.82) (1989-91)	0.88 (0.87 to 0.89) 0.84 (0.82 to 0.87) (1992-96)			P<0.001 (log-rank p-value comparing White with Black individuals)	
		Non-Hispanic White Black		0.57 (0.55 to 0.59) 0.46 (0.39 to	0.67 (0.64 to 0.70) 0.56 (0.49 to	Not reached Not reached (1992-96)			P<0.001 (log-rank p-value comparing	

Author, year	Database	Groups (yr)	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
		<i>Kaplan-Meir survival rate at 120 mo</i>		0.53 (1986-88)	0.63 (1989-91)				White with Black individuals)	
Danley ⁷⁷ 1995 8580296	LAC/USC CSP	White – non Hispanic Black/African American Asian <i>Percent annual change in age-adjusted mortality rates (95% CI) using 1976 as the baseline</i>		0.5 (-0.2, 1.2) 0.3 (-1.8, 2.5) 1.6 (0.0, 3.2) 2.3 (-2.9, 7.80)					P>0.05 (difference between racial/ethnic groups for the linear trend over yr, 1976-88)	Additional information is presented in Figure 1 of the paper.
Patient characteristics										
–										
Comorbidities										
Merrill ²⁴ 2000 10792091	SEER	No Yes <i>Multiple primary cancers</i>		Referent 0.36 (0.32, 0.41) (1988-89)	Referent 0.38 (0.34, 0.43) (1992-93)	Referent 0.35 (0.32, 0.40) (1994-95)			OR (95% CI) for death from prostate cancer vs. non-prostate cancer, stratified by comorbidity status	Data were reported only for White and Black patients.
Tumor characteristics										
– stage										
Chu ¹⁸ 2003 12627516	SEER	Local/regional Distant Unstaged <i>1 yr survival rates of patients diagnosed with prostate cancer by year of</i>	98% 84% 96% (1981-85)			100% 81% 97% (1992-97)				

Author, year	Database	Groups (yr)	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
		<i>diagnosis</i> <i>[White]</i>								
	SEER	Local/regional Distant Unstaged <i>1 yr survival</i> <i>rates of patients</i> <i>diagnosed with</i> <i>prostate cancer</i> <i>by year of</i> <i>diagnosis</i> <i>[Black]</i>	98% 83% 97% (1981-85)			99% 81% 97% (1992-97)				
	SEER	Local/regional Distant Unstaged <i>3 yr survival</i> <i>rates of patients</i> <i>diagnosed with</i> <i>prostate cancer</i> <i>by year of</i> <i>diagnosis</i> <i>[White]</i>	93% 50% 84% (1981-85)			98% 49% 92% (1992-97)				
	SEER	Local/regional Distant Unstaged <i>3 yr survival</i> <i>rates of patients</i> <i>diagnosed with</i> <i>prostate cancer</i> <i>[Black]</i>	91% 47% 83% (1981-85)			97% 48% 90% (1992-97)				
	SEER	Local/regional Distant Unstaged <i>5 yr survival</i> <i>rates of patients</i> <i>diagnosed with</i> <i>prostate cancer</i> <i>[White]</i>	87% 33% 75% (1981-85)			96% 35% 87% (1992-97)				

Author, year	Database	Groups (yr)	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
	SEER	Local/regional Distant Unstaged 5 yr survival rates of patients diagnosed with prostate cancer [Black]	83% 30% 65% (1981-85)			93% 34% 84% (1992-97)				
Merrill ²⁴ 2000 10792091	SEER	Local Regional Distant Unknown		Referent 2.36 (2.02, 2.76) 5.21 (4.61, 5.89) 2.16 (1.85, 2.53) (1988-89)	Referent 2.49 (2.16, 2.89) 6.95 (6.14, 7.87) 2.13 (1.86, 2.43) (1992-93)	Referent 2.36 (2.05, 2.71) 6.35 (5.59, 7.21) 1.73 (1.52, 1.97) (1994-95)			OR (95% CI) for death from prostate cancer vs. non-prostate cancer, stratified by stage.	Data were reported only for White and Black patients.
Merrill ⁴⁰ 2000 10647666	SEER	Local Regional Distant Unknown <i>Percentage of prostate cancer deaths out of all deaths observed among prostate cancer patients</i>		22% 45% 64% 41% (1988)	22% 45% 67% 36% (1992)	19% 41% 63% 32% (1995)				Excluded in situ cancer cases for this analysis. Additional information is presented in Figure 4 of the paper.
Tumor characteristics – grade										
Merrill ²⁴ 2000 10792091	SEER	Well diff. Moderately diff. Poorly diff./undiff. Unknown		Referent 2.39 (2.04, 2.82) 4.09 (3.48, 4.82) 2.80 (2.35, 3.36) (1988-89)	Referent 2.03 (1.72, 2.39) 4.29 (3.63, 5.06) 2.81 (2.34, 3.38) (1992-93)	Referent 2.14 (1.80, 2.55) 4.84 (4.06, 5.78) 3.55 (2.92, 4.31) (1994-95)			OR (95% CI) for death from prostate cancer vs. non-prostate cancer, stratified by	Data were reported only for White and Black patients.

Author, year	Database	Groups (yr)	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
Merrill ⁴⁰ 2000 10647666	SEER	Well-diff. Moderately diff. Poorly diff./ undifferentiated <i>Percentage of prostate cancer deaths out of all deaths observed among prostate cancer patients</i>		16% 36% 55% 39% (1988)	16% 33% 55% 38% (1992)	12% 26% 48% 36% (1995)			grade.	Additional information is presented in Figure 5 of the paper.

Ordering of the studies follows Appendix Table C1.1.

APC = age-period-cohort; CI = confidence interval; Diff = differentiated; yr = year.

Appendix Table C.12. Trends in prostate cancer incidence rates (per 100,000 unless otherwise stated)

Author, year	Database	Groups	1980-84	1985-89	1990-94	1995-99	2000-04	2005-10	Statistical analysis	Notes
Patient characteristics										
– Age										
Hankey ¹⁷ 1999 10379964	SEER	50-59	NA	3.8 (2.7, 4.9) (1973-89)	32.7 (12.5, 56.4) (1989-92)	1.9 (-4.2, 8.5) (1992-95)			Annual percentage changes calculated from joinpoint regression (95% CI).	Additional information is presented in Figure 2 of the paper.
		60-69	2.3 (1.5, 3.1) (1973-84)	8.4 (6.1, 10.8) (1984-89)	24.2 (17.8, 30.9) (1989-92)	-9.0 (-11.2, -6.7) (1992-95)				
		70-79	NA	3.3 (2.5, 4.1) (1973-88)	16.5 (10.7, 22.7) (1988-92)	-16.9 (-21.1, -12.6) (1992-95)				
		≥80	NA	0.8 (-0.2, 1.9) (1973-85)	6.4 (3.6, 9.3) (1985-92)	-22.1 (-27.1, -16.8) (1992-95)				
		<i>Annual percentage change of the age-standardized (1970 US standard) incidence rates</i>								
Escobedo ²⁷ 2004 15542264	SEER- Connecticut	<54	3.8		13.7					African American men only
		55-54	210.3		567.2					
		65-74	721.5		1450.0					
		≥75	1157.3 (1973-88)		1495.2 (1989-98)					
		<i>Age-adjusted (1970 US standard) rates</i>								
	SEER-Iowa	<54	4.0		13.0					African American men only
		55-54	211.7		512.1					
		65-74	654.2		1253.6					
		≥75	1275.1 (1973-88)		1589.9 (1989-98)					
		<i>Age-adjusted (1970 US standard) rates</i>								
	SEER-New Mexico	<54	3.5		6.7					African American men only
		55-54	257.7		295.0					
		65-74	475.5		1093.7					
		≥75	1195.4 (1973-88)		978.3 (1989-98)					
		<i>Age-adjusted (1970 US standard) rates</i>								
McDavid ²⁸ 2004 15192905	SEER	50-59	NA	4.2* (1973-89)	29.6* (1989-92)	4.1* (1992-99)	NA		* Denotes P<0.05.	The reporting of specific
		60-69	3.3* (1973-85)	9.6* (1985-89)	23.88 (1989-92)	-7.9* (1992-95)	1.5* (1995-99)			
		70-79	2.6* (1973-86)	12.5* (1986-	-14.5* (1992-95)	0.6 (1995-99)	NA			

		≥80 <i>Annual percentage change for each time period.</i>	1.5* (1973-87)	92) 7.0* (1987-92)	-19.8* (1992-95)	-1.8 (1995-99)	NA	P-values were not provided for the other estimates.	time intervals was determined by joint- point analysis. Additional information is presented in Figure 3 of the paper.
Lu-Yao ³⁵ 1994 7905093	SEER	50-59 60-69 70-79 <i>Annual percent change in incidence</i>		+5.2%/yr +7.7%/yr +5.7%/yr (1983-89)				NR	
Welch ³⁸ 2009 19720969	SEER	<50 50-59 60-69 70-79 ≥80 <i>Incidence rate</i>		1.3 58.4 349.4 819.2 1146.5 (1986)			9.4 212.7 666.9 896.8 637.4 (2005)	7.23 (6.4-8.2) 3.64 (3.3-4.0) 1.91 (1.8-2.0) 1.09 (1.05- 1.14) 0.56 (0.53- 0.60) [RR (95% CI), comparing 1986 to 2005]	Additional information (1986-2005) is presented in Figure 1 of the paper.
Devesa ³⁹ 1995 7707404	SEER	35-54 55-74 ≥75 <i>Age-adjusted (1970 US standard) incidence rate</i>			13.2 459.7 1278.1 (1987-91)			+6.0 (+83.3%) +215.7 (+88.4%) +365.3 (+40%) Absolute [relative] change in rate, compared to 1975-79	
Merrill ⁴³ 1996 8931614	SEER	50-59 60-69 70-79			+4% -9% -20%				White males only (n=72,659)

		<i>standard) incidence rates</i>						
Hankey ¹⁷ 1999 10379964	SEER	Whites	2.4 (1.8, 3.1) (1973-85)	6.9 (2.5, 11.6) (1985-89)	18.4 (10.7, 26.6) (1989-92)	-12.8 (-15.7, -9.8) (1992-95)	Annual percentage changes calculated from joinpoint regression (95% CI).	Additional information is presented in Figure 1 of the paper.
		Black	NA	2.3 (1.8, 2.8) (1973-89)	17.0 (12.4, 21.8) (1989-93)	-14.0 (-20.2, -7.4) (1993-95)		
		Other	NA	1.5 (.3, 2.7) (1973-1987)	16.2 (10.8, 21.9) (1987-92)	-7.5 (-12.9, -1.7) (1992-95)		
		<i>Annual percentage change of the age-standardized (1970 US standard) incidence rates</i>						
Brawley ¹⁹ 1997 9351560	SEER	White					Change in incidence = +130% among White Americans, peak in 1992; +140% among Black Americans, peak in 1993	
		Black						
		<i>Age-adjusted incidence rate (standardized to 1970 values)</i>		(1973)	(1994)			
Farkas ²¹ 1998 9730458	SEER	Whites			Peak, +0.43 (1991) Start of decline, -0.28 (1991)			
		African- Americans			Peak, +0.73 (1992) Start of decline, -0.29 (1994)			
		<i>[Rate of increase in organ confined disease incidence per 100,000 persons]</i>						
Clegg ²⁵ 2002 12381706	SEER	White		-3.2 (2.7, 3.7) (1973-87)	20.7 (14.5-27.3) (1988-92)	2.2 (-2.8-7.4) (1995-98)	Estimates from joinpoint regression (95% CI)	The study did not report estimates for other
		<i>Estimated annual percentage change in age- adjusted (1970</i>			-13.5 (-23.4, - 2.3) (1993-94)			

		<i>US standard) incidence rates</i>					racial/ethnic groups.
	SEER	White <i>Estimated annual percentage change in age- adjusted (1970 US standard) reporting delay- adjusted incidence rates</i>	3.2 (2.7, 3.8) (1973-87)	19.9 (14.3, 25.8) (1988-94) -13.7 (-21.1, - 5.6) (1993-94)	-0.1 (-3.1, 2.9) (1995-98)	Estimates from joinpoint regression (95% CI)	The study did not report estimates for other racial/ethnic groups.
	SEER	Black <i>Estimated annual percentage change in age- adjusted (1970 US standard) incidence rates</i>	2.3 (1.8-2.8) (1973-87)	21.5 (16.7, 26.5) (1988-91) -14.5 (-14.5, - 0.9) (1991-93)	0.4 (-3.8, 4.8) (1994-98)	Estimates from joinpoint regression (95% CI)	Reporting delay data were available only after 1988.
	SEER	Black <i>Estimated annual percentage change in age- adjusted (1970 US standard) reporting delay- adjusted incidence rates</i>	2.2 (1.7-2.7) (1973-87)	20.7 (16.0, 25.6) (1988-91) -8.7 (-14.8, -2.3) (1991-93)	-2.1 (-5.6, 1.5) (1994-98)	Estimates from joinpoint regression (95% CI)	Reporting delay data were available only after 1988.
Merrill ³² 2002 11790678	SEER	White Black	(1989)	(1992)		+42% +35% Percentage increase of point prevalence corrected incidence	Additional information is presented in Figures 1-4 of the paper (1975-97).
Sarma ³⁴ 2002 11828352	SEER	White Black <i>Age-adjusted rates</i>	86 124 (1986)	179 (1992) 250 (1993)		+108% increase +102% increase	Also Figure 2 (1981-98)
	SEER	White Black		(1992)	(1998)	-5.7%/yr -4.0%/yr (annual change in incidence yr)	

Shao ⁴² 2009 19713548	SEER	White Black <i>Incidence rate (SD)</i>	220.3 (1.5) 295.4 (6.3) (1988-89)	257.9 (1.5) 434.6 (6.7) (1996-97)	234.4 (1.3) 368.0 (5.3) (2004-05)	+14.1 (P<0.001) +72.6 (P<0.001)	[absolute change between 1988-89 and 2004-05 (p- values from ANOVA with linear contrast)]
Merrill ⁴³ 1996 8931614	SEER	White Black <i>Age-adjusted (1990 standard) incidence rate</i>	138.0 180.8 (1989)	221.6 298.5 (1992)		+61% (White) +65% (Black) [percent increase from 1989 to 1992]	-16% (White) +2% (Black) [percent change from 1992 to 1993]
Zhu ⁴⁵ 2009 19505907	SEER	White Black		1.25 (1.18, 1.31) 2.32 (2.07, 2.61) (1990-94)	2.63 (2.53, 2.72) 6.33 (5.95, 6.75) (2000-04)	2.11 (1.98, 2.25) 2.73 (2.39, 3.11)	No data were reported for other racial or ethnic groups. [IRR of 2000- 04 vs. 1990- 94 (95% CI)]
Polednak ⁴⁶ 2002 12477140	SEER	Non-Hispanic White Black		151.4 179.0 (1992)	122.1 183.5 (1997)	Age-adjusted incidence rates per 100,000 US 1990 standard population	Limited to locoregional prostate cancer. Data were not reported for patients of other racial/ethnic groups.
Demers ⁴⁹	SEER-	White	102	178		NR	Additional

1994 8203988	Detroit	Black <i>Age-adjusted (1970 US standard) incidence rates</i>	141 (1988)	218 (1991)			information is presented in Figure 1 of the paper.	
Potosky ⁶⁷ 1995 7530782	SEER- Medicare	White Black <i>Age-adjusted (1970 US standard) incidence rate</i>	840 1137 (1987)	1310 1848 (1991)			Men ≥65 yr old	
Danley ⁷⁷ 1995 8580296	LAC/USC CSP	White – non Hispanic Black/African American Asian <i>Percent annual change in age- adjusted incidence rates (95% CI) using 1976 as the baseline</i>	2.7 (2.3, 3.1) 0.7 (-0.1, 1.6) -0.7 (-2.8, 1.3) 0.2 (-0.8, 1.2) (1988)			P<0.001 (difference between racial/ethnic groups for the linear trend over 1976-88)	Additional information is presented in Figure 1 of the paper.	
Tumor characteristics – Stage								
Hankey ¹⁷ 1999 10379964	SEER	Localized/regional Distant Unstaged <i>Annual percentage change of the age-standardized (1970 US standard) incidence rates</i>	NA NA -15.3 (-20.1, - 9.3) (1973-80)	3.3 (2.4, 4.2) (1973-88) 1.4 (0.5, 2.3) (1977-86)	18.7 (10.6, 27.4) (1988-92) -1.3 (-4.1, 1.6) (1986-92) 17.9 (14.8, 21.0) (1980-92)	-9.8 (-15.5, -3.9) (1992-95) -17.9 (-20.8, - 14.9) (1991-95) -22.5 (-32.7, - 10.8) (1992-95)	Annual percentage changes calculated from joinpoint regression (95% CI).	Additional information is presented in Figure 3 of the paper.
Chu ¹⁸ 2003 12627516	SEER	50-59 60-69 70-79 80-84 ≥85	9.5 47.9 140.6 238.9 229.1	4.7 21.5 41.2 64.0 76.6		-50.5 -55.1 -70.7 -73.2 -66.6	Data were not reported for other racial/ethnic groups.	

		<i>Age-adjusted (1990 US standard) incidence rates of distant disease by age at diagnosis [White]</i>	(1986)	(1999)	(Relative change %)	
SEER	50-59		28.5	18.8	-34.0	Data were not reported for other racial/ethnic groups.
	60-69		117.6	50.1	-57.4	
	70-79		274.1	89.4	-67.4	
	80-84		260.4	147.2	-43.5	
	≥85		264.3	129.3	-51.5	
	<i>Age-adjusted (1990 US standard) incidence rates of distant disease by age at diagnosis [Black]</i>		(1986)	(1999)	(Relative change %)	
Dennis ²³ 2000 10679753	SEER	Localized	191.1	461.5	NR	
		Distant	50.3	42.0		
		Unknown	28.0	91.5		
		<i>Age-adjusted incidence rates</i>	(1985)	(1992)		
SEER	Localized	+3.2%	+14.3%	-6.2%	P<0.001	
	Distant	+2.5%	-1.7%	-15.9%		
	Unknown	-1.4%	+20.5%	-24.2%		
	<i>Annual relative percentage change in age- adjusted incidence rate</i>	(1973-85)	(1985-92)	(1992-1996)	(logistic regression with a linear term for time)	
SEER	Positive lymph nodes		12.7 53.0	15.5 146.4		
	Negative lymph nodes		265.3 (1988)	433.1 (1992)		
	Not examined					
	<i>Age-adjusted incidence rates</i>					
SEER	Positive lymph nodes	+9.7% (+45%) +33.6%		-23.2% (-65%) -8.2% (-29%)	P<0.001	
	Negative lymph nodes	(+219%) +14.2%		-9.2% (NR) (1992-1996)	(logistic regression with a linear	
	Not examined	(+70%)				

		<i>Annual relative percentage change in age-adjusted incidence rate (percentage change during the corresponding period)</i>				<i>(1988-92)</i>		<i>term for time)</i>	
Merrill ²⁰ 1997 9229202	SEER	Localized	53	62	110				White men only
		Regional	10	15	36				
		Distant	14	15	11				
		Unstaged	4	11	25				
		<i>Age-standardized (1970 US standard) rates [White]</i>	(1982)	(1987)	(1992)				
	SEER	Localized	77	78	138				Black men only
		Regional	13	17	37				
		Distant	35	34	32				
		Unstaged	6	18	43				
		<i>Age-standardized (1970 US standard) rates [Black]</i>	(1982)	(1987)	(1992)				
Stephenson ²⁶ 2002 12109343	SEER	Distant			16.2	6.3	-61%		Additional data are presented in Figures 1-5 and 14 of the paper.
		<i>Age-adjusted incidence rate</i>			(1990)	(1997)	(relative change in incidence rate of distant disease)		
Escobedo ²⁷ 2004 15542264	SEER-Connecticut	Localized/regional	63.0		158.1				African American men only
		Distant	36.0		26.1				
		Unstaged	10.9		23.5				
		<i>Incidence rates</i>	(1973-88)		(1989-98)				
	SEER-Iowa	Localized/regional	66.3		141.1				African American men only
		Distant	36.7		28.6				
		Unstaged	7.5		24.1				
		<i>Incidence rates</i>	(1973-88)		(1989-98)				
	SEER-New Mexico	Localized/regional	69.4		115.9				African American men only
		Distant	22.6		15.2				
		Unstaged	8.4		5.0				

		<i>Incidence rates</i>			
		(1973-88)	(1989-98)		
Sarma ³⁴ 2002 11828352	SEER	Localized disease <i>Rates among White individuals</i>	62.6 (1987)	117.7 (1998)	Additional data are presented in Figure 3 of the paper (1981-98). Numerical data for localized disease were reported separately for Black and White individuals.
	SEER	Localized disease <i>Rates among Black individuals</i>	78.8 (1987)	190.2 (1998)	Additional data are presented in Figure 3 of the paper (1981-98). Numerical data for localized disease were reported separately for Black and White individuals.
	SEER	Distant disease <i>Rates per 100,000 among White and Black individuals combined</i>	14.9 (1985)	6.6 (1995)	Additional data are presented in Figure 3 of the paper (1981-98). Numerical data for distant disease were

								reported in aggregate for Black and White individuals.
Lu-Yao ³⁵ 1994 7905093	SEER	Local Regional Distant <i>Annual percent change in incidence</i>		+5.9%/yr +10.6%/yr +0.4%/yr (1983-87)				NR
Shao ⁴² 2009 19713548	SEER	T stage 1 2 3 or 4 <i>Incidence rate per 100,000 (SD), age-adjusted to the 2000 US standard population in 5-yr age increments beginning at 25 yr.</i>		42.3 (0.6) 95.0 (1.0) 55.5 (0.7) (1988-89)	90.3 (0.9) 137.0 (1.1) 44.6 (0.6) (1996-97)	118.4 (0.9) 106.3 (0.9) 8.4 (0.2) (2004-05)	+76.1 (P<0.001) +11.2 (P<0.001) -47.1 (P<0.001)	[absolute change between 1988-1989 and 2004-05 (p-values from ANOVA with linear contrast)]
Severson ⁵⁰ 1995 7707440	SEER-Detroit	Local Regional Distant Unknown <i>Rate</i>	591.1 54.3 234.2 166.7 (1982)	715.7 76.1 225.6 187.6 (1987)	1435.1 129.4 176.6 424.5 (1992)			NR Age ≥75 yr Additional data (1973-92) are presented in Table 2 of the paper
Schwartz ⁵² 1999 10197854	SEER-Detroit	Local disease <i>Age-adjusted incidence rate</i>	56.5 (1982)		167.9 (1992)	129.6 (1996)		NR Additional information is provided in Figure 1 of the paper
Newcomer ⁵⁵ 9302136 1997	SEER, Seattle-Puget Sound	Localized Regional Distant Unknown	(1984)		(1991)		+120% +188% NR +120%	Additional information is presented in Figure 2

		Age-adjusted rate (1970 US standard)				Change in incidence rate, 1984 vs. 1991	of the paper.
	SEER, Seattle- Puget Sound	Distant Age-adjusted rate (1970 US standard)	42 (1986)	18 (1991)		P<0.001 (-60% change in incidence rate, 1986 vs. 1991)	Additional information is presented in Figure 2 of the paper.
Stephenson ⁵⁶ 1996 8608513	SEER-Utah	Distant Rate	14.0 (1984)	15.0 (1989)	9.3 (1993)	NR	Additional data are presented in Figure 2 of the paper (1984-93)
Tumor characteristics – Gleason score and histological grade							
Hankey ¹⁷ 1999 10379964	SEER	Well diff.	NA	3.2 (2.4, 4.0) (1973-92)	-20.4 (-27.3, - 12.9) (1992-95)	Annual percentage changes calculated from joinpoint regression (95% CI).	Additional information is presented in Figure 4 of the paper.
		Moderately diff.	9.1 (7.6, 10.6) (1973-88)	26.9 (19.7, 34.5) (1988-92)	-9.3 (-13.7, -4.7) (1992-95)		
		Poorly diff./undiff.	5.8 (5.3, 6.3) (1973-90)	18.3 (8.0, 29.6) (1990-92)	-14.7 (-17.8, - 11.4) (1992-95)		
		Unknown	-6.3 (-8.1, -4.5) (1973-88)	9.5 (-5.4, 26.7) (1988-92)	-13.4 (-25.2, 0.3) (1992-95)		
		<i>Annual percentage change of the age-standardized (1970 US standard) incidence rates</i>					
Farkas ²¹ 1998 9730458	SEER	White		Peak, +0.56 (1991) Start of decline, -0.20 (1993)			
		Black		Peak, +0.47 (1991)			
		<i>[Rate of increase</i>					

		<i>in moderately differentiated disease incidence per 100,000 persons]</i>				Start of decline, -0.15 (1994)		
Shao ⁴² 2009 19713548	SEER	2-4 5-7 8-10 <i>Per 100,000 (SD), age-adjusted to the 2000 US standard population in 5-yr age increments beginning at 25 yr.</i>	56.2 (0.7) 88.8 (0.9) 47.5 (0.7) (1988-89)		24.9 (0.5) 167.3 (1.2) 50.7 (0.7) (1996-97)	2.3 (0.1) 193.3 (1.2) 38.3 (0.5) (2004-05)	-53.9 (P<0.001) 104.5 (P<0.001) -9.2 (P<0.001)	[absolute change between 1988-1989 and 2004-05 (p-values from ANOVA with linear contrast)]
Schwartz ⁵² 1999 10197854	SEER-Detroit	Well diff. Moderately diff. Poorly diff. <i>Age-adjusted incidence rate</i>	28.2 22.8 NR (1982)		NR 122.9 NR (1993)	12.2 ~100 NR (1996)	NR	Additional information is provided in Figure 2 of the paper
Stephenson ⁵⁶ 1996 8608513	SEER-Utah	2-4 5-7 8-10 <i>Rate per 100,000</i>	32.7 30.2 21.4 (1984)	30.9 43.9 20.3 (1989)	36.0 96.5 30.4 (1993)		P = 0.0105 [rank-sum test comparing age-adjusted rates between 1990-94 and 1984-89 for all 3 groups of Gleason score] P<0.001 [ANCOVA comparing the age-adjusted rate and slope of Gleason 5-7 tumors vs. the	Additional information is provided in Figure 3 of the paper (1984-93)

				other groups, i.e. 2-4 and 8-10]	
Danley ⁷⁷ 1995 8580296	LAC/USC CSP	Localized Regional Metastatic Unstaged <i>Percent annual change of the stage-specific incidence rate [Non-Hispanic White]</i>	1.8 (1.4, 2.3) 11.3 (9.9, 12.6) 1.6 (0.7, 2.4) 3.2 (2.1, 4.4) (1976-88)	P<0.001 (for difference between stage groups for the linear trend over yr, 1976- 88)	Additional information is presented in Figure 2 of the paper.
	LAC/USC CSP	Localized Regional Metastatic Unstaged <i>Percent annual change of the stage-specific incidence rate [Hispanic White]</i>	-1.0 (-2.3, 0.4) 8.3 (4.3, 12.5) 0.4 (-1.9, 2.6) 1.7 (-1.8, 5.3) (1976-88)	P<0.001 (for difference between stage groups for the linear trend over yr, 1976- 88)	Additional information is presented in Figure 2 of the paper.
	LAC/USC CSP	Localized Regional Metastatic Unstaged <i>Percent annual change of the stage-specific incidence rate [Black]</i>	-0.5 (-1.6, 0.6) 7.7 (4.5, 10.9) 1.4 (-0.4, 3.1) 1.2 (-1.3, 3.8) (1976-88)	P<0.001 (for difference between stage groups for the linear trend over yr, 1976- 88)	Additional information is presented in Figure 2 of the paper.
	LAC/USC CSP	Localized Regional Metastatic Unstaged <i>Percent annual change of the stage-specific incidence rate [Asian]</i>	-1.7 (-4.2, 1) 8.9 (1.3, 11.7) -0.9 (-5.5, 4) -4.6 (-10.7, 2.0) (1976-88)	P<0.05 (for difference between stage groups for the linear trend over yr, 1976- 88)	Additional information is presented in Figure 2 of the paper.

Ordering of the studies follows Appendix Table C1.1.

ANOVA, analysis of variance; NA = not applicable; NR = not reported; RR = relative rate; SD = standard deviation; yr = years.

Appendix Table C1.13. Gofrit 2007⁸⁵, systematic review of the effect of histopathologic grading changes

Author Year [UI]	Gofrit 2007 ⁸⁵ [17997434]		
Design	A systematic review of studies of the "Will Rogers" phenomenon		
Population	All urologic cancer patients (separate results reported for prostate cancer)		
Exposure	Histological reclassification (temporal change in guidelines or prevailing norms for diagnosing, staging or grading the histology of prostate cancer)		
Results	<p>Medline (15 cited studies)</p> <p>As reported by the authors:</p> <ol style="list-style-type: none"> 1. In prostate cancer the Will Rogers phenomenon is the result of the late 1990s acceptance that Gleason scores 2-4 should not be assigned on prostate biopsy. 2. Consequently grade inflation occurred and current readings are almost 1 Gleason grade higher compared to past readings of the same biopsy. 3. The result is an illusion of improvement in grade adjusted prognosis. 		
Comments	<p>As noted by the authors:</p> <ol style="list-style-type: none"> 1. Comparison of contemporary results to historical controls may be biased by the Will Rogers phenomenon. 2. Ignoring the possibility of stage or grade reclassification may lead to erroneous conclusions. 		
AMSTAR			
A priori design?	N	Study quality assessment performed?	N
Two independent reviewers?	N	Study quality appropriately used in analysis?	N
Comprehensive literature search?	N	Appropriate statistical synthesis?	NA
All publication types and languages included?	N	Publication bias assessed?	N
Included and excluded studies listed?	N	Conflicts of interest stated?	Y
Study characteristics provided?	N		

N = no; NA = not applicable; UI = Medline unique identifier.

Appendix Table C2.1: Eligibility criteria, follow-up protocols, triggers for intervention and definition of progression in cohorts of active surveillance/ watchful waiting/other observational management strategies

Center, Country [Pubmed ID] Enrollment year	Eligibility criteria	Followup or monitoring protocol	Triggers for intervention /active therapy	Definition of progression
Baylor College of Medicine and MSKCC, US ⁸⁹ [15017211] 1984-2001	Prostate cancer diagnosed by needle biopsy or transurethral resection and Gleason sum 7 or less. All patients were eligible for definitive therapy in the form of RP or RT. No patient had significant comorbidities. The decision for deferred therapy was made by the patient and treating physician together based on the likely presence of small volume cancer.	Pathological features of the biopsy results, clinical stage and/or PSA influenced the decision to proceed with the deferred therapy protocol. Prospectively designed protocol of deferred therapy: office evaluations every 3 mo first yr and every 6 mo thereafter. It included digital DRE and PSA. Repeat TRUS guided sextant biopsy was recommended at 6 mo or if the patient showed DRE/TRUS or PSA abnormalities consistent with disease progression. PSA velocity was calculated from 3 separate recorded values in a 12-mo period.	Definitive treatment when objective progression or patients' requests. Definitive treatment included RP and RT.	A point system for evaluating progression, including Gleason score increase, PSA velocity, DRE/TRUS, and biopsy specimen.
BCCA, Canada ¹³³ [9445192] NR	Patients who were placed onto a watchful waiting program. Patient who had received treatment (either hormones or PT) prior to the referral were excluded.	No fixed follow-up schedule; patients generally were seen every 3-6 mo as needed. PSA at diagnosis and all subsequent followup PSA were recorded.	NR	Clinical progression: an increase in palpable disease or T classification. Biochemical progression: PSA DT calculated by 2 methods.
Cleveland clinic, US ⁹⁹ [21256549] 2004-2009	Low-risk features by D'Amico criteria; a repeat (confirmation) prostate biopsy of ≥ 10 cores; favorable clinical and pathologic features at the diagnostic and repeat biopsy; absence of primary or secondary Gleason scores 4 or 5.	PSA every 6-12 mo, surveillance biopsy was usually performed every 2 yr or sooner.	Intervention was recommended to patients considering multiple parameters (PSA and PSA kinetics, changes in DRE, quantity of cancer in biopsy specimens, and biopsy Gleason score)	NR
Dana-Farber Cancer Institute, US ⁹⁸	Clinically localized disease (T1c-T2c), Gleason score 6 or less with no pattern 4, <3 cores positive for	PSA and DRE every 6 mo, and 20-core biopsy every 12 to 18 mo	Patients with progression were offered surgery or radiotherapy.	Progression criteria: 1) 3 or more positive cores, 2) increased grade (Gleason score 7 or greater)

Center, Country [Pubmed ID] Enrollment year	Eligibility criteria	Followup or monitoring protocol	Triggers for intervention /active therapy	Definition of progression
[21167525] 2000-2010	cancer and no more than 50% of cancer in any core. No age, PSA values or PSA density exclusion criteria was used.	Protocol with cure intent.		and/or 3) more than 50% of any core involved with cancer.
Erasmus Univ. hospital, Netherlands ¹²¹ [7544841] ≤1990; 1993-2006 ¹²²	Histologically confirmed cancer; Metastatic disease was excluded by a normal chest x-ray and a normal bone scan. The decision not to treat was made by the urologist in discussion with the patient and his family, with respect to patient age, general health, clinical stage and patient preference. All patients had estimated survival >1 yr. Men on AS who were detected within the screening program of the ERSPC. All men retrospectively met the following criteria: clinical stage T1c or T2, PSA ≤15 ng/mL, and Gleason score <8. The choice of initiating and continuing an AS was patient desire and/or physician advice. ¹²² ERSPC-screening protocol: Men aged 50–75 yr with PSA measurements (threshold 3.0 or 4.0 ng/ml), and/or TRUS, and/or DRE, at 2- or 4-yr intervals. Abnormal findings lead to sextant prostate biopsies, the Finnish centres have changed to 10 or 12 biopsy cores. Prostatic volume is measured by planimetric calculation during TRUS. After a PCA diagnosis, men are referred to the regular medical circuit (which may be the ERSPC centre), where	Usually followed clinically twice yearly (mean 2.7 annual visits, range 1.4 to 4.3) for physical exam including DRE and serum PSA and alkaline phosphatase levels. Bone scan and chest x-ray were repeated regularly and when clinically indicated. Follow-up regimens varied among local practices, data for this study were collected from chart reviews of medical history, DRE, dissemination studies, and PSA tests. ¹²²	Subjective progression, like obstructive micturition or pain, was considered for treatment decisions. ¹²¹ Note: The authors reported that of 13 patients with progression, 6 started treatment (5 for subjective symptoms; 1 for objective progression only). The authors also reported that PSA progression may serve as a trigger point to treatment. ¹²²	Local progression: symptomatic, increase in T category, increase in prostate size on DRE by 25%, or increase in ultrasound measured volume >40%. Metastatic progression: new bone lesion.

Center, Country [Pubmed ID] Enrollment year	Eligibility criteria	Followup or monitoring protocol	Triggers for intervention /active therapy	Definition of progression
	decisions on treatment are made. ¹²⁶			
Four tertiary care academic medical centers, ^a US ⁸⁶ [19233410] 1991-2007	Patients who would otherwise be considered for surgery or radiation due to a life expectancy >10 yr, and were defined as age ≤75 yr, clinical stage T1-T2a, PSA ≤10 ng/mL, ≤3 positive cores at diagnostic biopsy, Gleason score ≤6, no active treatment for a minimum of 6 mo after the second biopsy.	Office visits, review of general health and urinary symptoms, DRE and PSA every 6 to 12 mo, rebiopsies within 18 mo of starting AS and subsequently every 1 to 3 yr or prompted by a change in clinical status (e.g., significant and sustained PSA increase). MRI of the prostate was selectively used at diagnosis and every 1 to 3 yr after starting AS.	Criteria for recommending treatment were nonstandardized and physician specific.	NR
Freeman hospital, UK ¹¹⁸ [3191340] 1978-1985	Patients without symptoms after initial outflow tract surgery or biopsy.	Disease progression was monitored by history, physical exam, TRUS for T staging and prostate volume since 1983, serum acid and alkaline phosphatase and 6-monthly isotope bone scans.	No treatment until symptomatic progression.	NR
Hospitals in Manchester, UK ¹²⁷ [11711356] NR	"Localized" (bone scan-negative) prostate cancer patients treated by watchful-waiting. All patients had PSA level < 50 ng/mL	Patients were followed-up at 6- month intervals. All patients underwent "multiple bone scans" (all negative), and hormonal manipulation was demanded by the protocol when the PSA rose to 50 ng/mL. DRE not always performed in patient with long-standing, stable PSA values.	Hormonal manipulation was demanded by the protocol when the PSA rose to 50 ng/mL.	Bone scan for metastases; PSA levels.
Howard University College of Medicine, US ¹¹⁴ [1600492] 1967-1989	Stage A and B prostate cancer patients who were in a prospective expectant management program.	3-mo intervals for the first 5 yr, then at 4 to 6-mo intervals thereafter. Each visit assessment included DRE, pap and since 1985 a PSA was done.	Management plan of watchful waiting for most patients until signs and/or symptoms of disease activity occurred. Any progressive changes in enzymatic activity and/or signs or	NR

Center, Country [Pubmed ID] Enrollment year	Eligibility criteria	Followup or monitoring protocol	Triggers for intervention /active therapy	Definition of progression
		Bone scans were done initially and annually thereafter. CT of the pelvis was used infrequently, primarily in patients who elected not to have any form of surgical therapy.	symptoms of progression or metastasis (back pains or weight loss), or changes in rectal findings either by DRE or TRUS were treated despite evidence of a positive or progression of the bone scan.	
John Hopkins, US ⁹⁴ [20439642] 1994-2008	PSA density ≤ 0.15 ng/mL/cm ³ ; T1C; 12-core biopsy: Gleason ≤ 6 ; no Gleason pattern ≥ 4 ; ≤ 2 cores cancer positive; $\leq 50\%$ cancer in any single core (also included some men who did not meet these criteria due to personal preference or comorbidity)	Semiannual PSA and DRE; annual extended 12-core biopsy	Annual surveillance biopsy: Gleason ≥ 7 ; or Gleason pattern 4 or 5; or >2 cores cancer positive; or single core $>50\%$ cancer. Patient request or encouraged to seek curative treatment if perineural invasion on biopsy. ¹¹¹ PSA kinetics not used as a trigger for intervention.	Progression = unfavorable biopsy ²⁰⁷
Kagawa Medical Univ., Japan ¹²⁹ [10765093] 1990-1998	Japanese patients with nonpalpable prostate cancer, detected by elevated PSA. Diagnosed histopathologically by TRUS-guided six sextant biopsy: (1) Gleason score ≤ 6 ; (2) 1-2 positive cores per 6 sextant cores; and (3) $\leq 50\%$ involvement of any positive core	PSA doubling time based on 1 st PSA >1 mo after biopsy. ≥ 3 values at intervals ≥ 1 mo apart for >6 mo. Exponential slope fitted by regression.	NR	NR
Kagawa Medical Univ., Japan ⁸⁸ [18272471] 2002-2003	50-80 yr, initial PSA ≤ 20 ng/mL, 1-2 positive cores per 6-12 systematic biopsy cores, Gleason score ≤ 6 , $\leq 50\%$ cancer involvement in any core. Excluded if comorbidities: past stroke, unstable angina, DM uncontrollable with insulin, severe HTN, MI w/in 6 mo.	PSA every 2 mo for 6 mo, every 3 mo thereafter. Re-biopsy at 1 yr (no data beyond 1 yr)	PSADT ≤ 2 yr after 6 mo (based on all PSA or most recent 1 yr) Re-biopsy did not fit initial pathology criteria	NR
Kansas City VA, US ¹³⁴ [21172105]	Low-risk prostate cancer patients: stage T2 or less, Gleason ≤ 6 , PSA <20 ng/mL, and percent of total tissue on biopsy positive for cancer	PSA every 3 mo and a repeat TRUS guided prostate biopsy at 1 yr. All biopsies were performed using a standard 12-	NR	NR

Center, Country [Pubmed ID] Enrollment year	Eligibility criteria	Followup or monitoring protocol	Triggers for intervention /active therapy	Definition of progression
2004-2009	<20%	core biopsy scheme, however, an increased number of biopsies were taken for larger glands.		
Kitasato Univ. Hospital, Japan ¹³⁰ [11851612] 1991-2000	Biopsy-confirmed clinically localized prostate cancer	"a DRE", generally seen every 3-6 mo "as clinical circumstances dictated". Bone scintigraphy annually.	NR	Increase in T category, $\geq 25\%$ increase in prostate size on DRE, TRUS-measured volume increase $>50\%$, positive finding on a bone scan, a blastic lesion seen on skeletal radiograph or soft-tissue metastasis by biopsy. Not biochemical progression (though PSA DT calculated).
McGill Univ., Canada ¹⁰³ [18484590] 1987-2002	Patients with prostate adenocarcinoma with "favorable pathologic and biochemical parameters" ("clinically localized cancer" ²⁶) or patients who decline definitive treatment. The reasons for AS included patient choice, limited life expectancy because of advanced age or poor medical condition, and presumed insignificant prostate cancer.	PSA and DRE was done every 3-6 mo. TRUS guided biopsy was done annually or when there was a change in DRE or PSA.	The decision to treat was attributed to local pathologic disease progression and patient preference. The decision to undergo treatment was based on the suggestion of disease progression because of a rising PSA level or clinical progression on DRE or repeated sextant biopsy. ²⁶	Progression of T stage to T2b or more, progression shown in biopsy: 3 positive cores or more, $>50\%$ cancer in at least 1 core, or Gleason pattern of 4 Development of metastatic disease. ²⁶
Memorial Sloan-Kettering Cancer Center, US ⁹⁷ [21167529] 1997-2009	Low-risk prostate cancer patients who were eligible for AS; PSA <10 ng/mL, no prostate biopsy Gleason grade 4 or 5, clinical state T1-T2a, ≤ 3 positive biopsy cores (minimum 10), no biopsy core containing $>50\%$ cancer involvement and confirmatory biopsy to reassess eligibility before starting AS	Semiannually with DRE, free and total PSA measurements, and a review of general health and urinary symptoms. Biopsy was routinely recommended within 12 to 18 months of starting AS and subsequently repeated every 2 to 3 yr or as needed.	Treatment was recommended when the patient no longer met study eligibility criteria during followup.	NR
Northern Stockholm, Sweden ¹¹⁹ [17467883]	Patients with clinically localized prostate cancer, diagnosed by biopsies and cytological assessment, initially managed with	Followup was performed every 3 to 6 mo for the first 2 yr and every 6 to 12 months thereafter with DRE and PAP. Re-biopsies	Treatment was offered to the patients if clinical progression with symptoms occurred.	Clinical progression: positive bone scan or plain x-ray for the diagnosis of skeletal metastases.

Center, Country [Pubmed ID] Enrollment year	Eligibility criteria	Followup or monitoring protocol	Triggers for intervention /active therapy	Definition of progression
1978-1982	WW. Patients with palpable tumors (71% T1-2 and 29% with T3) were included in a prospective surveillance protocol with close follow-up. Bone scan and PAP were normal in all patients.	were done every year during the first 4 yr, and a bone scan was repeated every 12 to 18 mo.		
Orebro Medical Center, Sweden ¹¹⁵ [7933233] 1977-1984	Patients were given no initial treatment if the tumor was localized to the prostate gland without penetration of the capsule on DRE (stages T0 to T2) and there was no evidence of distant metastases. However, several restrictions were applied to those with a palpable tumor (stages T1 to T2). From March 1978 to Feb. 1979, patients >75 yr were not given any initial treatment (deferred treatment).	Every 6 to 12 mo, patients were followed with clinical exam, lab tests including PAP and bone scans. PSA was only performed during the last few yr.	Patients were treated hormonally if disease progressed for they had symptoms of progression.	NR
PIVOT, US ¹²⁰ [18783735] 1994-2002	Biopsy proven T1-T2/Nx/M0 prostate cancer of any histologic grade, diagnosed within 12 mo, PSA≤50 ng/mL, ≤75 yr, bone scan negative for metastatic disease, estimated life expectancy >10 yr, medically and surgically fit for RP	Office visit & PSA every 6 mo Bone scan every 5 yr	Discouraged treatment for asymptomatic progression (eg, per PSA)	NR
PRIAS, Netherlands ¹⁰⁰ [19817747] 2006 – ongoing	Originating from the ERSPC. ¹²⁶ Histologically proven adenocarcinoma of the prostate; fit for curative treatment; PSA-level at diagnosis ≤ 10 ng/mL; PSA density ≤ 0.2 ng/ml/ml; clinical stage T1c or T2; adequate biopsy sampling according to biopsy protocol; Gleason score ≤3+3=6; maximal 2 biopsy cores invaded with prostate cancer; willing to attend the follow-up visits.	PSA at 3 mo, DRE at 6 mo and standard rebiopsy after 1 yr.	PSA DT 0 to 3 yr, T state >2 or rebiopsy findings exceed study inclusion thresholds	NR

Center, Country [Pubmed ID] Enrollment year	Eligibility criteria	Followup or monitoring protocol	Triggers for intervention /active therapy	Definition of progression
Princess Margaret hospital, Canada ¹³² [21211899] 1995-2010	PSA <10 ng/ml, clinical stage T1c-T2a, Gleason score <6, and ≤3 positive biopsy cores (<50% of a core involved at initial diagnostic biopsy)	PSA was measured every 3mo for 2 yr and every 6 mo in stable patients. DRE was performed every 6 mo. A confirmatory biopsy was typically performed 12 mo after the initial biopsy and then every 2–3 yr until the patient reached 80 yr of age or refused treatment. All biopsies were performed by one of three dedicated uroradiologists using a standardized approach that did not depend on prostate volume Fist-time biopsies consisted of 6 cores before 2001 and 11 cores after 2001. Repeat biopsies consisted of 10 cores before 2001 and 15-16 cores after 2001.	NR	Pathologic progression: increased grade, increased number of cores to more than 3 or any core involvement >50%
ProtecT, UK ¹⁰⁵ [19603015] 2000-2008	Clinically localized prostate cancer. Patients agreed to participate in RCT and were allocated to active monitoring group, or refused to be randomly allocated to groups and chose to be managed by monitoring.	PSA every 3 mo in yr 1, and every 6 mo thereafter; referred to biopsy if a PSA ≥3 ng/mL; rebiopsy was not routine	The aim of active monitoring is “to identify developing cancers early enough to allow treatment with surgery or radiotherapy” ^b “Test results were reviewed annually, and patient and clinician decided whether to continue with monitoring” ¹²⁸ (implied using PSA level or change and/or rebiopsy results as triggers).	NR
Royal Marsden Hospital, UK ⁹² [15839912] 1993-2002	AS: Fitness for RP, T1-2, N0/X, M0/X, PSA≤20 ng/mL, Gleason ≤7. “Favorable prognostic characteristics and according to patient preference.” WW: localized prostate cancer (any T stage, N0/X, M0/X, any PSA, Gleason score ≤7). Unsuitable for	WW: PSA and DRE every 6 mo AS: PSA and DRE every 3-6 mo for 2 yr, then every 6 mo. Repeat Bx not routine. Repeat imaging only if clinically indicated.	WW: Symptomatic prostate cancer progression AS: Rate of rise of PSA, according to judgment of each patient and clinician.	NR

Center, Country [Pubmed ID] Enrollment year	Eligibility criteria	Followup or monitoring protocol	Triggers for intervention /active therapy	Definition of progression
	RP typically because advanced age or comorbidities.			
Royal Marsden Hospital, UK ⁹³ [17850368] ≥2002	T1/2a, N0/X, Mo/X, PSA<15 ng/mL, Gleason ≤7 (primary Gleason ≤3), cancer in ≤50% of biopsy cores. (Patients were 50-80 yo). Fit for RP, Elected AS for initial treatment	PSA monthly in yr 1, every 3 mo in yr 2, and every 6 mo thereafter. DRE every 3 mo for 2 yr. TRUS-guided octant biopsy at 18-24 mo	PSA DT<4 yr, histologic progression (see Definition of progression), or patient preference, or PSA velocity >1 ng/mL/yr ¹⁰⁹	Gleason score >7, primary Gleason ≥4, (initial Gleason 3+3, upgraded to Gleason ≥3+4) ¹¹⁰ or ≥50% biopsy cores positive.
SPCG-4, Finland, Sweden, and Iceland ¹²⁴ [12226148] 1989-1999	Patients with newly diagnosed localized prostate cancer, < 75 yr, with life expectancy of >10 yr, T stage of T0d, T1 or T2, eligible for radical prostatectomy, well differentiated to moderately well differentiated tumor, negative bone scan, PSA level < 50 ng/mL. After 1994, men with T1c tumors — according to the revised 1987 International Union against Cancer classification — were also eligible. Men with a poorly differentiated tumor were not eligible. Patients whose condition was diagnosed with an extended biopsy protocol were accepted if <25% of the tumor was Gleason grade 4 and <5% grade 5.	Followup was done every 6 mo in the first 2 yr, then every 1 yr. Followup included: a clinical examination, measurement of hemoglobin, creatinine, PSA, and alkaline phosphatase levels. A bone scan and chest radiograph were obtained every 1 yr after start of the study. After 1996, chest x-ray films were obtained annually for the first 2 yr. Rebiopsy was not routinely undertaken. ¹²⁸	Adjuvant local or systemic treatment was not given. TURP was recommended as a treatment for local progression.	Local progression: a transcapsular tumor growth was palpable; symptoms of obstruction of the flow of urine that necessitated intervention, or both.
Taichung Veterans hospital, Taiwan ¹¹⁷ [12854876] 1983-1996	Men undergoing TURP for clinically benign hyperplasia of prostate with stage T1a prostate cancer.	After the introduction of serum PSA in 1990, 3-6 monthly PSA and DRE were used to detect the disease progression.	No treatment until there was evidence of cancer progression.	Abnormal DRE and/or progressive elevation of PSA “proved” by transrectal needle biopsy, or appearance of metastatic disease.
Toronto-SRCC, Canada ⁹⁵ [11395227] 1995-2002 as a	Histologic diagnosis of adenocarcinoma of the prostate within 12 mo of enrollment; no previous treatment for prostate carcinoma; clinical stage T1b-T2b	Every 3 mo for the first 2 yr and every 6 mo thereafter	Clinical, histologic or PSA progression triggered the offer of treatment based on age, extent of disease and comorbidities. Specific treatment protocol was not	Clinical progression = at least one of the following: >2 times of the product of the maximum perpendicular diameters of the primary lesion as measured

Center, Country [Pubmed ID]	Eligibility criteria	Followup or monitoring protocol	Triggers for intervention /active therapy	Definition of progression
<p>phase II trial</p> <p>2003-ongoing as an observational open prospective cohort</p>	<p>N0 M0 (1997 TNM classification); PSA \leq15ng/ml; Gleason score \leq7.</p> <p>Protocol changes in inclusion criteria and additional information regarding the original criteria, reported in Klotz 2010:⁹⁶ Between 1995 and 1999, study was offered to low-risk patients (Gleason \leq6 or less, PSA \leq10 ng/ml) and to patients older than 70 yr old with PSA <15 ng/ml or Gleason \leq3+4. Since January 2000, the study was restricted to low-risk patients only.</p>		<p>reported.</p> <p>Protocol changes in PSA DT assessment, reported in Klotz 2010:⁹⁶ For the first 4 yr of the study, PSA DT <2y was used as a trigger. This criterion identified 10% of patients as high-risk and was considered overly stringent. In 1999 the cut-off was increased to 3 yr.</p> <p>Protocol changes in PSA DT calculation, reported in Loblaw 2010:¹¹³ From 1995 to 2002 PSA DT was calculated by a statistician using linear regression of all PSA values after the patient left the clinic and the 95% upper bound confidence limit of PSA DT had to be <3 yr. Later PSA DT was calculated by physicians who used PSA fluctuations to determine whether PSA DT was “truly” <3 yr. In 2005 the group developed a general linear mixed model as a clinical decision making aid.^c</p>	<p>digitally; symptoms requiring TURP; development of ureteric obstruction; radiological or clinical evidence of distant metastasis.</p> <p>Histologic progression = Gleason score upgraded to 8 or greater in the rebiopsy of the prostate at 18 mo post enrollment.</p> <p>PSA progression = when all the following were satisfied: PSA DT <2 yr, based on at least 3 separate measurements over a minimum of 6 mo; final PSA >8 ng/ml; p-value <0.05 from regression of ln(PSA) on time.</p> <p>Additional information on biopsy frequency during followup, reported in Klotz 2010⁹⁶ and Krakowsky 2010:¹¹² Subsequent biopsies were performed every 3-4 yr to identify biologic progression. Patients with borderline PSA DT underwent biopsies more frequently. Between 1995 and 2000 sextant biopsies were used; since 2000, 10 to 14-core biopsies were performed using the Vienna nomogram.</p>
<p>UCSF, US¹⁰¹ [18433013]</p> <p>>1991</p>	<p>Prostate cancer diagnosis, no prior therapy at another institution, primary therapy AS or no primary therapy (surgery, radiation, brachytherapy, androgen ablation) within 6 mo of diagnosis</p> <p>Patients selectively were offered AS if they met the following diagnostic criteria: PSA <10 ng/mL, Gleason</p>	<p>Office visit w/DRE every 3 mo, PSA every 3 mo (usually), TRUS every 6-12 mo.</p> <p>\geq2003: prostate biopsy every 12-24 mo</p> <p>\geq2002: “regular” nurse practitioner contact to ensure surveillance compliance and address concerns and anxiety</p>	<p>Implied that there was not a specific protocol for intervention; active treatment based on disease progression</p>	<p>Increase in Gleason or PSA velocity >0.75 ng/mL/yr (also analyzed PSA velocity >2 ng/mL/yr and PSA DT<2 yr.</p> <p>Ultrasonography not used (too much inter-observer variability in lesion size)</p> <p>Gleason upgrade to \geq4 (if \leq6 at diagnosis) or \geq4+3 (if 3+4 at</p>

Center, Country [PubMed ID] Enrollment year	Eligibility criteria	Followup or monitoring protocol	Triggers for intervention /active therapy	Definition of progression
	sum ≤ 6 , absence of Gleason grade 4 or 5, cancer involvement of $< 33\%$ of biopsy cores, and clinical T1/T2a tumor			diagnosis); PSADT ≤ 2 or 3 yr ¹⁰⁶ Gleason ≥ 7 or $\geq 33\%$ of cores or $> 50\%$ of any core ¹⁰⁷
Univ. of Connecticut Health Center, US ¹⁰⁴ [18707696] 1990-2006	Patients who elected WW or AS program. Men on WW were generally older with localized prostate cancer who did not desire aggressive intervention. Men on AS were generally younger with low-risk disease.	WW: no additional information. Patients on AS were followed with PSA on an average of every 6 mo. If PSA trending upward, the checks increased to every 3 mo depending on initial presentation and PSA trend. Rebiopsies recommended 2 yr after initial biopsy or if an increased in PSA > 0.75 ng/dl, a change in DRE or at patient request.	Increase in tumor volume (increased number or percent of cores positive), progression in Gleason score, onset of urinary symptoms, change in DRE or patient request for definitive treatment due to anxiety related to increasing PSA trend.	NR
Univ. of Florida, US ¹²³ [18263992] 2003-2006	Low-stage, low-grade disease (minimal disease on biopsy), severe medical condition with a life expectancy of < 10 yr, and patient's desire.	Patients are followed every 3 mo with PSA and DRE annually. Repeat biopsy about 6 mo after the initial diagnosis.	Cancer progresses or symptoms become imminent.	NR
Univ. of Miami, US ⁹⁰ [17850361] 1991-2007	Patients with clinically localized prostate cancer who elected for watchful waiting and to be treated only when disease progressed. ¹⁰⁸ No strict guidelines for accruing patients on the AS protocol in the early yr. Generally, patients with a Gleason score ≤ 7 and stage $\leq T2b$ were offered AS. Over the yr the inclusion criteria became narrower, i.e. Gleason score ≤ 6 , PSA ≤ 15 ng/mL, stage $\leq T2$ and low-volume disease ($\leq 50\%$ of two biopsy cores). Slightly changes in eligibility criteria,	DRE and PSA every 3-4 mo for 2 yr and every 6 mo subsequently. After 2000, a laterally directed and peripherally targeted TRUS biopsy of 10-12 cores was performed 9-12 mo after the first rebiopsy, and then every yr or earlier if there was a dramatic rise in PSA or a change on DRE.	Disease progression ⁹⁰ Treatment is encouraged at an increase in tumor volume, Gleason score ≥ 7 , or the presence of > 2 positive cores.	Local stage progression detected by DRE and/or biochemical progression (PSA increase 25-50 %/yr) or systemic progression when metastases detected. ⁹⁰

Center, Country [Pubmed ID] Enrollment year	Eligibility criteria	Followup or monitoring protocol	Triggers for intervention /active therapy	Definition of progression
	reported in Soloway 2010 ⁹¹ and Gorin 2011. ⁸⁷ AS is offered to prostate cancer patients with PSA ≤ 10 ng/mL, Gleason score ≤ 6 , ≤ 2 positive biopsy cores with tumor $\leq 20\%$ in each core, stage $\leq T2$ and age ≤ 80 yr.			
Univ. of North Carolina, US ¹³¹ 1991-1996	Patients with stage T1c prostate cancer who chose to be on expectant management. All patients had DRE enzymatic PAP values obtained prior to or at least 4 wk after prostatic biopsy, radionuclide bone scan, and the absence of a visible lesion upon transrectal US that was proven malignant histologically.	PSA was monitored at 3 mo, then every 6 mo. Hematocrit and creatinine were measured every 6 mo.	NR	Development of palpable disease in DER, gross hematuria, urinary tract infection, bothersome symptoms due to bladder outlet obstruction, metastatic disease as shown in physical examination or radiographic examination, PSA level increase in 3 consecutive measurements and the total increase was > 5 ng/ml.
Watchful Waiting Study, US ¹²⁵ [14501381] 1998-2003	Age < 85 yr, biopsy proven prostate cancer within 48 mo, PSA < 50 ng/mL, have not received any therapy including surgery, radiation, hormone or chemotherapy, have not been diagnosed with metastatic disease, at least 3-yr life expectancy, no history of any type of malignancy within the past 5 yr with the exception of non-melanoma skin cancer, liver and kidney function within 1.5 x upper range of normal, not taking > 50 ug selenium/day as supplement, Gleason score < 8 .	PSA every 3 mo.	Developing progressive disease or electing to initiate cancer therapy	NR
Western General Hospital, UK ¹¹⁶ [8343901] 1978-1990	Early cancer as either incidental (T0/stage A) or localized *T1/stage B1/B2), non-metastatic (M0) disease with normal serum PAP.	Every 3 mo for clinical assessment, routine blood tests and measurement of serum markers. Chest X-rays, skeletal X-rays and bone scans were performed every 6 mo. Urinary	Progression of disease and/or development of symptoms.	Development of metastases (M1) or elevation of PAP to more than 2 u/l.

Center, Country [PubMed ID]	Eligibility criteria	Followup or monitoring protocol	Triggers for intervention /active therapy	Definition of progression
Enrollment year		flow rates and residual volumes were assessed if outflow obstruction was suspected.		

NR = not reported; DT = doubling time; PSA = prostate-specific antigen; TNM = tumor-node-metastasis system; TURP = transurethral resection of the prostate; yr = yr(s); wk = wk(s); mo = mo(s); SRCC = Sunnybrook Regional Cancer Center; BCCA = the British Columbia Cancer Agency; DRE = digital rectal examination; WW = watchful waiting; AS = active surveillance; EM = expectant management; PAP = prostate acid phosphatase; PSA = prostate specific antigen; TRUS = Trans-rectal ultrasound; CT = computerized tomography; PSA = prostate-specific antigen; TNM = tumor-node-metastasis system; SRCC = Sunnybrook Regional Cancer Center; BCCA = the British Columbia Cancer Agency; ED = erectile dysfunction; PRIAS = Prostate cancer Research International; ProtecT = Prostate testing for cancer and Treatment; SPCG-4 = Scandinavian Prostate Cancer Group Study Number 4; UCSF=University of California at San Francisco; European Randomized Study of Screening for Prostate Cancer = ERSPC; VA = Veterans Affairs; MSKCC = Memorial Sloan-Kettering Cancer Center

^a Cleveland Clinic Foundation, Memorial Sloan-Kettering Cancer Center, University of British Columbia and University of Miami

^b Source: <http://www.epi.bris.ac.uk/protect/>

^c The model generates 2 reclassification curves (high and low risk) which, when overlaid over PSA data of each patient, defines 3 risk zones of high, intermediate and low risk of reclassification. A patient with a PSA consistently in the high risk zone is recommended to undergo treatment.

Appendix Table C3.1 Studies on offer, acceptance, and adherence of active surveillance

Factors examined	Author Year Pubmed ID	Study approach	AS/WW definitions	Findings	Issues
<ul style="list-style-type: none"> physicians factors affecting offer 	Crawford 1997 ¹⁶⁶ 9301699	survey of 780 men in the prostate cancer support group (US TOO) and 200 urologists	WW (not explicitly provided)	<ul style="list-style-type: none"> 83% patients and 76% urologists preferred aggressive therapy treatment options for men with localized disease and few comorbidities, urologists on the average would prefer RP (67%), RT (29%), WW (4%) different perspectives on whether treatment options were discussed: 20% patients felt treatment options were not discussed while 1% urologists felt treatment options were not discussed 	<ul style="list-style-type: none"> 200/335 urologists and 780/1000 patients responded to the survey urologists in this survey were not necessarily the urologists who took care of the patients in the survey
<ul style="list-style-type: none"> patient factors affecting acceptance 	Berry 2003 ¹⁶⁴ 12856636	content analysis of 13 men in focus groups and 31 men in individual unstructured interviews; men were within 6 mo dx of localized prostate cancer	WW (not explicitly provided)	<ul style="list-style-type: none"> 20/44 men who relied on influential others (an individual whose illness experience and/or story had explicit influence on the participant's treatment decision) to make a treatment decision, 1 broadened the horizon to consider WW, 1 moved away from considering WW 	<ul style="list-style-type: none"> small sample size
<ul style="list-style-type: none"> patient factors affecting acceptance 	Chapple 2002 ¹⁶² 12133062	interview 50 men from UK with all stages of prostate cancer, 4 of whom chose WW	WW = no active treatment	<ul style="list-style-type: none"> few men who chose WW had consulted the Internet, concerned about the side-effects and uncertain treatment outcomes, and found physicians who were supportive of their decision 	<ul style="list-style-type: none"> men with all stages of disease in UK small sample size
<ul style="list-style-type: none"> patient factors affecting acceptance 	Davison 2009 ¹⁵⁶ 19136342	qualitative description of interviews of 25 of 45 eligible men with low-risk prostate cancer on AS	implied; details not provided (patients from 2 large tertiary care centers that support AS)	<ul style="list-style-type: none"> MD description of prostate cancer affects patient perception of the seriousness of the condition and affects treatment choice MD recommendation most influential on patient decision to select AS concerns about impotency and incontinence affects treatment choice 	<ul style="list-style-type: none"> small sample size limited applicability
<ul style="list-style-type: none"> patient factors affecting offer 	Demark-Wahnefried 1998 ¹⁶³ 9669815	survey of 231 men (50% Black) with prostate cancer in N. Carolina	WW (not explicitly provided)	<ul style="list-style-type: none"> WW discussed \geq high school vs. <high school education 59.5% v. 43.7% (P<0.05) MD recommendation most influential in treatment decision (57%) (no differences between Blacks and Whites (no numerical data); urban vs. rural (62.3% vs. 43.9%, P=0.004)) 	<ul style="list-style-type: none"> no statistical adjustment

Factors examined	Author Year Pubmed ID	Study approach	AS/WW definitions	Findings	Issues
				<ul style="list-style-type: none"> differences NS in WW options discussed between rural and urban residents (53.7% vs. 51.9%) differences NS in WW options discussed between Blacks and Whites (48.7% vs. 56.1%) 	
<ul style="list-style-type: none"> patient and physician factors affecting acceptance 	Diefenbach 2002 ¹⁵⁸ 11828358	survey of 654 men (77% RT; 17% RP; 6% WW) with early stage disease recruited by either a urologist or radiation oncologist	WW (not explicitly provided)	<ul style="list-style-type: none"> most influential in reaching a treatment decision: physician recommendation (51%), advice from family and friends (19%), information from books and journals (18%), Internet (7%), disease and treatment factors (3%) patients who chose RP over RT or WW perceived prostate cancer as a significantly more serious disease (P <0.001) 	<ul style="list-style-type: none"> unclear if WW was actively offered by urologists or radiation oncologists to patients since only 6% opted for WW
<ul style="list-style-type: none"> Expected life expectancy (what MD would offer) 	Durham 2003 ¹⁵⁷ 12835804	Survey (of screening behaviors, with case vignettes, piloted for understandability and face validity on 10 GPs) of GPs (in New Zealand), equalized urban vs. rural. 201 urban, 180 rural GPs responded.	WW: not defined (non-curative)	<ul style="list-style-type: none"> For men with localized prostate cancer, GPs responded that If life expectancy <10 yr, WW would be suggested treatment (45%), followed by hormone (23%), RT (13%), prostatectomy (8%), other combinations (6%) If life expectancy >10 yr, WW suggested 3%; prostatectomy 53%, other combination 17%, RT 14%, hormone 8% 	<ul style="list-style-type: none"> Survey of GPs given theoretical cases (vignettes) No data urban vs. rural Survey response rate 66%
<ul style="list-style-type: none"> offer of WW by MD 	Fowler 2000 ¹⁶¹ 10866869	Survey ("pretested") of 1063 urologists (504) and radiation oncologists (559)	WW = "expectant management"	<ul style="list-style-type: none"> ~10-20% of urologists and radiation oncologists would recommend WW if PSA ~5 ng/mL and Gleason score 4 or 5 (Scenario was for a 65 yr man in good health, with negative DRE and no evidence of nonlocalized disease). Almost no (0-1%) would recommend WW for those with higher PSA or Gleason scores. No difference between urologists and radiation oncologists. 	<ul style="list-style-type: none"> Surveys sent to urologists and radiation oncologists were somewhat different Survey response rate 64% (urologists) & 76% (radiation oncologists)
<ul style="list-style-type: none"> offer of AS by MD Acceptance of AS by patient 	Gorin 2011 ⁸⁷ 21215429	survey of 185 men already on AS (unclear selection procedure)	DRE + PSA q 3-4 mo for the first 2 yr, then q 6 mo; annual bx; sooner if significant rise in PSA or change in DRE; treatment	<ul style="list-style-type: none"> AS offered by the MD who had made the initial dx in 38/105 (36%) MD influence had the greatest impact on choosing AS (73%) 	<ul style="list-style-type: none"> non-validated survey instrument population already decided to enroll in AS

Factors examined	Author Year Pubmed ID	Study approach	AS/WW definitions	Findings	Issues
<ul style="list-style-type: none"> patient factors affecting acceptance 	Holmboe 2000 ¹⁶⁰ 11089712	open-ended interview of 102 men with localized disease who had made a treatment decision but had not yet received the treatment (88% RP, RT or ADT; 12% WW)	encouraged for ↑ tumor volume, Gleason ≥7 or >2 positive cores WW (not explicitly provided)	<ul style="list-style-type: none"> concerns for incontinence (48%) and erectile dysfunction (44%) also reasons for choosing AS 30% men stated that physician recommendation influenced their treatment decision 59% of patients discussed WW (presumably with their physicians) fear of consequences most common reason (64%) for not selecting WW; some of the others were perceived elevated risk because of ↑ PSA or Gleason (12%); physician (12%) and/or family (4%) against WW 	<ul style="list-style-type: none"> had been on AS varying times (some >2 yrs) survey response rate 57% small sample size unclear details concerning WW
<ul style="list-style-type: none"> patient and physician factors affecting acceptance 	O'Rourke 1999 ¹⁶⁷ 10370363	qualitative description of interviews of 18 men with prostate cancer (dx'd within 6 wk; stage I or II; undecided choice of treatment) and their wives; they were referred by their urologists	WW (not explicitly defined)	<ul style="list-style-type: none"> "The process of reaching a treatment decision was influenced by the urologists; second opinions [mostly concurrence between primary care physician and the urologist in this sample], and comparisons of self with others." "Couples ruled out options based on formal and informal information, although sometimes inaccurate, personal and vicarious cancer experiences, and beliefs about cancer that were intricately tied to emotions and fears." "Couples considered both their own individual histories and concerns and their shared life experiences." "'Doing nothing' was ultimately rejected for the certainty they perceived to be associated with it: certain death, feared to be slow and painful." 	<ul style="list-style-type: none"> small sample size
<ul style="list-style-type: none"> physician factors affecting offer 	Ramsey 2011 ¹⁵⁵ 20959991	survey of 238 men (multi-center) with newly dx'd localized T1-3 disease and 25 urologists concerning their office encounters (initial consultation vs. second opinion)	AS (not explicitly provided)	<ul style="list-style-type: none"> urologists recommended 0.52 more treatment options (SE 0.19, P <0.001) in initial consultation than in second opinion visit for low-risk disease, 25% urologists recommended AS, 77% recommended RP in initial consultation; 16% urologists recommended AS, 91% 	<ul style="list-style-type: none"> cannot establish causality for more RP recommended by urologists; plausible that patients sought out urologists for a second opinion because the patients were more interested in RP applicability limited to patients/urologists in academic

Factors examined	Author Year Pubmed ID	Study approach	AS/WW definitions	Findings	Issues
				recommended RP in second opinion visit <ul style="list-style-type: none"> discrepancy between what physicians recommended and what patients heard physicians recommended: in patients for whom urologists recommended RP, 67% patients heard the recommendation; in patients for whom urologists recommended RT or ADT, ~25% patients heard the recommendation 	centers
<ul style="list-style-type: none"> physician factors affecting offer 	Steginga 2002 ¹⁶⁵ 11856106	interview of 108 men with newly dx'd localized prostate cancer from 2 hospital clinics and 4 urology practices in Australia	WW (not explicitly provided)	<ul style="list-style-type: none"> unprompted recall of their urological consultation: 71% of the physicians discussed WW; 92% discussed RP, and 87% discussed RT 	<ul style="list-style-type: none"> limited applicability to US
<ul style="list-style-type: none"> ~Adherence to AS (actually receiving active treatment) ~Clinical factors (perception of physician advice) 	Zietman 2001 ¹⁵⁹ 11586206	Survey ("8-point telephone questionnaire) of 53 men receiving surveillance who ultimately received treatment (of 198 who were being followed with WW). (10 additional men did not respond because they had died, were too infirm or too elderly)	Surveillance/WW: no primary treatment with radiation, prostatectomy or androgen deprivation; DRE & PSA q4-6 mo (Retrospective study)	<ul style="list-style-type: none"> 81% believed that treatment was desired by the physicians, which was the primary cause of the change in plan. In contrast, MD notes revealed that for only 24% was there documentation that MDs advocated therapy due to clinical or biochemical evidence of tumor progression. <ul style="list-style-type: none"> 71% had PSA increase only and 11% had no progression evidence Physicians more often perceived that treatment was initiated by patients (in abstract conclusions only) 	<ul style="list-style-type: none"> Nonvalidated telephone survey (not described) Retrospective definition of WW Only surveyed those who received therapy Survey response rate 84% Did not report on full survey results, including the intended purposes of influences that affected decision

DRE = digital rectal examination; bx = biopsy ; dx = diagnosis

Appendix Table C3.2. KQ3 multivariable analyses

Author yr Pubmed ID	Factors	Data source	Duration	Analyzed sample	Population characteristics	WW/AS definitions	Methods	Results as described in paper
<i>Receipt of AS/WW versus alternative treatments</i>								
Harlan 2003 ⁶⁷ 14532780	clinical, social, insurance	CaPSURE	1989- 2000	5365	localized prostate ca	no active treatment	logistic regression predicts WW vs. active treatment	1. low vs. high risk (D'Amico), OR=5.1 (CI 3.8, 6.9) 2. >75 vs. <65, OR=14.3 (CI 9.1, 22.5) 3. comorbidity score >1 vs. 0-1, OR=1.43 (CI 1.1, 1.8) 4. private ins. vs. Medicare, OR=0.7 (CI 0.5, 1.0) NS: academic vs. community; black vs. white; education; income; in relationship
Latini 2006 ¹⁴⁶ 16400651	clinical	CaPSURE	1989- 2004	5643	Biopsy-confirmed prostate cancer patients. Analysis of treatment choice was limited to men with localized disease (clinical stage T1 to T3a).	Not explicitly provided	Multinomial logistic regression RP vs. BT vs. EBRT vs. ADT vs. WW	No differences between Latino and non-Latino White men in primary treatment after adjusting for other variables (clinical risk, age, education, marital status, type of insurance, comorbidities, dx yr, and study site; P-value or estimates not reported). No other information reported for the association of ethnicity with WW as compared to other treatments.
Marr 2006 ¹⁴¹ 16515991	clinical	CaPSURE	1995- 2003	5149	Men with localized prostate cancer (T3a or less with no evidence of lymph or distant metastases)	Not explicitly provided	multinomial logistic regression predicting WW vs. RP	1. Heart disease vs. none OR=3.0 (2.2, 4.2) 2. Stroke vs. none OR=1.2 (0.7, 2.2) 3. Urinary conditions vs. none OR=1.4 (1.0, 2.1) 4. comorbidities: 1-2 other comorbidities vs. none OR=1.0 (0.7, 1.6) 3 other comorbidities vs. none OR=1.6 (0.9, 2.7) 6 or more other comorbidities vs. none OR=5.2 (1.8, 15.1) (results were not reported for other comorbidity groups) Estimates were adjusted for study site, dx yr, clinical risk, age, education, relationship status and BMI. Regression estimates or p-values were not provided for these variables.
Sadetsky 2008 ¹³⁹ 17893700	delivery system	CaPSURE	1995- 2006	2507	Newly diagnosed localized prostate cancer, >65 yr.	Not explicitly provided	Multinomial logistic regression EM vs. EBRT vs. ADT vs. BT vs. RP	Using RP as the baseline: Insurance status, insurance provider for predicting EM, - HMO vs. not, OR=0.62 (CI 0.29, 1.33) - PPO vs. not, OR=0.95 (CI 0.36, 2.51) - VA vs. not, OR=4.74 (CI 1.94, 11.55) - Medicate + supplement vs. not, OR=0.88 (CI 0.57, 1.37)

Author yr Pubmed ID	Factors	Data source	Duration	Analyzed sample	Population characteristics	WW/AS definitions	Methods	Results as described in paper
								<ul style="list-style-type: none"> - Medicare + FFS vs. not, OR=0.35 (CI 0.16, 0.78) - Medicare + HMO vs. not, OR=0.75 (CI 0.26, 2.13) - Medicare + PPO vs. not, OR=0.33 (CI 0.14, 0.77) <p>Estimates were adjusted for education level, risk category, age at dx, income, relationship status, race/ethnicity, and yr of dx. No estimates or p-values were reported for these variables.</p>
Dall'Era ¹³⁶ 2009 19230923	Clinical, social	CaPSURE	1995- 2007	5939	Patients with prostate cancer Patients undergoing cryotherapy were excluded.	Not explicitly provided	Binary logistic regression active treatment vs. WW/AS	<p>Among patients with low-risk:</p> <ol style="list-style-type: none"> 1. social support, in permanent relationship vs. not, OR=1.82 (CI 1.13, 2.94) 2. insurance status, Medicare (with or without supplement) vs. private or VA, OR=0.49 (CI 0.34, 0.71) <p>Overall cohort: Insurance status, Medicare vs. no Medicare, OR=0.53 (CI 0.35, 0.79)</p> <p>Multivariable models included: age at dx, race/ethnicity, education, relationship/marital status and insurance coverage. Results were only reported for relationship/marital status and insurance status; no estimates or p-values were reported for the other variables.</p>
Moses 2010 ¹⁴⁵ 20100957		CaPSURE	1995- July 2008	4284	Men with biopsy- proven prostate cancer, who reported a health- related quality of life questionnaire within 12 mo before selecting primary treatment by 2007	Not explicitly provided	Multinomial logistic regression with all variables significantly associated with receipt of treatment (AS vs. RP vs. RT, ADT vs. cryotherapy vs. TUMT) in a univariate test	<p>AS vs. RP</p> <ul style="list-style-type: none"> - White vs. African American: OR=0.52 (CI 0.22, 1.25); P=0.15 - Other vs. African American: OR=0.69 (CI 0.16, 2.97); P=0.62 - Other vs. White: OR=1.32 (CI 0.34, 4.64); P=0.15 <p>Estimates were adjusted for risk (D'Amico level), age, health perception, number of comorbidities, education level, and type of insurance. Estimates or p-values were not reported for these variables.</p>
Barocas 2008 ¹³⁷ 18707731	Clinical, social	CaPSURE	1999- 2004	1421	Localized prostate cancer.	No treatment within 6 mo after dx	Binary logistic regression AS	<ol style="list-style-type: none"> 1. age at dx, >74y vs. ≤74y, OR=7.30 (CI 4.39, 12.21) 2. risk of disease (modified D'Amico), low vs. not low, OR=3.40 (CI 1.91, 6.04) 3. education level, high school or less vs. some or more college, OR=0.86 (CI 0.53, 1.41)

Author yr Pubmed ID	Factors	Data source	Duration	Analyzed sample	Population characteristics	WW/AS definitions	Methods	Results as described in paper
Konety 2008 ¹³⁸ 18343440	clinical	CaPSURE	NR	11,261	Biopsy-proven prostate cancer	Not explicitly provided	Multinomial logistic regression WW vs. any other primary therapy	<p>“Low-risk” = PSA<10ng/ml, stage T1 or T2a, PSA density <0.15, < 1/3 positive cores, and no Gleason pattern 4 and 5. The OR for patients who met all 4 criteria for low-risk was 2.7 (CI 1.9, 3.8) vs. all other patients.</p> <p>Model stratified for disease risk category (see paper for other risk categories):</p> <p>low-risk patients, using WW as the baseline,</p> <ul style="list-style-type: none"> - BT: ≥75 yr vs. <75 yr, OR=0.234 (CI 0.161, 0.339) - BT + EBRT: ≥75 yr vs. <75 yr, OR=0.109 (CI 0.025, 0.473) - EBRT: ≥75 yr vs. <75 yr, OR=0.430 (CI 0.288, 0.641) - PADT: ≥75 yr vs. <75 yr, OR=0.744 (CI 0.507, 1.090) - RP: ≥75 yr vs. <75 yr, OR=0.014 (CI 0.008, 0.025) <p>Results were adjusted for demographics and the number of comorbidities at dx. There was no significant interaction between age and comorbidity level.</p> <p>Model stratified by number of comorbidities: no comorbidities, using WW as the baseline,</p> <ul style="list-style-type: none"> - BT: ≥75 yr vs. <75 yr, OR=0.165 (CI 0.068, 0.400) - BT + EBRT: ≥75 yr vs. <75 yr, OR=0.139 (CI 0.038, 0.516) - EBRT: ≥75 yr vs. <75 yr, OR=0.400 (CI 0.178, 0.898) - PADT: ≥75 yr vs. <75 yr, OR=0.385 (CI 0.171, 0.866) - RP: ≥75 yr vs. <75 yr, OR= 0.004 (CI 0.001, 0.015) <p>See paper for other comorbidity categories Results were adjusted for demographic and risk covariates, and accruing site.</p>
Shavers ¹⁴² 2004 15009794	clinical, social, delivery system	SEER-Medicare	1994-1996	24,974	Black, Hispanic or White men with prostate cancer, ≥65 yr, with continuous Medicare Part A & B coverage for ≥1 yr prior to dx	No RP, RT, or ADT within 6 mo of dx	Binomial logistic regression predicts WW as initial therapy vs. all other treatments	<ol style="list-style-type: none"> 1. Race/ethnic group, <ul style="list-style-type: none"> - Black vs. White, OR=1.3 (CI 1.1, 1.4) - Hispanic vs. White, OR=1.2 (CI 1.03, 1.4) 2. Stage, SEER historical stage, <ul style="list-style-type: none"> - in situ vs. local (1994), OR=8.8 (CI 3.5, 21.7) - regional vs. local (1994), OR=0.4 (CI 0.3, 0.4) - distant vs. local (1994), OR=0.2 (CI 0.1, 0.2) - local + regional (1995 to 1996) vs. local (1994), OR=0.9 (CI 0.8, 0.98)

Author yr Pubmed ID	Factors	Data source	Duration	Analyzed sample	Population characteristics	WW/AS definitions	Methods	Results as described in paper
								<ul style="list-style-type: none"> - unstaged/unknown, vs. local (1994), OR=1.2 (CI 1.1, 1.3) 3. grade, differentiation, <ul style="list-style-type: none"> - moderate vs. well differentiated, OR=0.3 (CI 0.2, 0.3) - poorly/undifferentiated vs. well differentiated, OR=0.1 (CI 0.1, 0.12) - unknown vs. well differentiated, OR=0.4 (CI 0.4, 0.5) 4. life expectancy, <10 yr vs. ≥10y, OR=1.4 (CI 1.3-1.6) 5. age at dx, per yr, OR=1.1 (CI 1.07, 1.09) 6. comorbidity, specific conditions, <ul style="list-style-type: none"> - CHF vs. not, OR=1.4 (CI 1.2, 1.6) - COPD vs. not, OR=1.4 (CI 1.2, 1.5) - dementia vs. not, OR=2.0 (CI 1.4, 3.0) 7. mean inpatient comorbidity index, per unit, OR=1.9 (CI 1.5, 2.4) 8. mean outpatient comorbidity index, per unit, OR=1.3 (CI 1.0, 1.6) 9. marital status, <ul style="list-style-type: none"> - single vs. married, OR=1.5 (CI 1.4, 1.4) - 10. income, median census tract income per yr, <ul style="list-style-type: none"> - <30,000 vs. ≥40,000, OR=1.1 (CI 1.03, 1.2) - 30,000 to 39,000 vs. ≥40,000, OR=1.1 (CI 1.03, 1.2) 11. education, % of residents in census tract with less than high school education, <ul style="list-style-type: none"> - 20-29.99 vs. <20, OR=1.1 (CI 1.1, 1.2) - ≥30 vs. <20, OR=1.2 (CI 1.1, 1.3)
Snyder 2010 ¹³⁵ 20734396	clinical, social	SEER- Medicare	2000	13,769	Clinically localized prostate cancer, ≥66 yr, survived ≥9 mo, on Medicare (not managed care)	No treatment within 9 mo of dx	logistic regression predicts treatment vs. WW	<p>Using WW as the reference treatment: compared to RP:</p> <ul style="list-style-type: none"> 1. age, per year, RR=0.73 (0.72, 0.75); P<0.001 2. race, <ul style="list-style-type: none"> - black vs. white, RR=0.34 (CI 0.27, 0.44); P<0.001 - other vs. White, RR=1.52 (CI 1.13, 2.04) 3. urban vs. rural, RR=1.54 (CI 1.20, 1.96) 4. SES highest vs. lowest quintile, RR=1.77 (CI 1.43, 2.19) 5. Ca grade poor vs. well differentiated, RR=13.38 (CI 9.26, 19.35) 6. Comorbidity, <ul style="list-style-type: none"> - 1 vs. 0, RR=0.84 (CI 0.71, 0.99) - ≥2 vs. 0, RR=0.67 (CI 0.54, 0.83) <p>compared to RT:</p>

Author yr Pubmed ID	Factors	Data source	Duration	Analyzed sample	Population characteristics	WW/AS definitions	Methods	Results as described in paper
								<p>1. age, 2. black vs. white, RR=0.39 (CI 0.31-0.50) 3. urban vs. rural, RR=1.48 (CI 1.18-1.85) 4. SES highest vs. lowest quintile, RR=1.52 (CI 1.26-1.84) 5. Ca grade poor vs. well differentiated, RR=2.34 (CI 1.78-3.08) 6. Comorbidity 2+ vs. 0, RR=0.80 (CI 0.67-0.96) 7. Comorbidity, - 1 vs. 0, RR=1.11 (CI 0.96, 1.28) - ≥ 2 vs. 0, RR=0.67 (CI 0.54, 0.83)</p> <p>compared to RT + ADT 1. age, 0.90 (CI 0.90-0.91); P<0.001 2. black vs. white, RR 0.39 (CI 0.31-0.50) 3. urban vs. rural, RT RR 1.48 (CI 1.18-1.85) 4. SES highest vs lowest quintile, RT RR=1.52 (CI 1.26-1.84) 5. Ca grade poor vs. well differentiated, RT RR=2.34 (CI 1.78-3.08) 6. Comorbidity 2+ vs. 0, RR=0.80 (CI 0.67-0.96) 7. Comorbidity, - 1 vs. 0, RR=1.11 (CI 0.96, 1.28) - ≥ 2 vs. 0, RR=0.67 (CI 0.54, 0.83)</p> <p>Additional information is provided in Table 2 of the paper for the comparison of ADT monotherapy vs. WW.</p> <p>All estimates were adjusted for SEER region.</p>
Hamilton ⁷⁸ 2011 20735387	clinical; geographic	SEER	2002	1139	clinically localized	No therapy within 4 mo of dx	multivariate logistic regression predicts WW vs. any other treatment	<p>1. Age ≥ 75 vs. <60 OR=8.8 (CI 2.9, 26.76), P=0.008 (trend) 2. Not married vs. married OR=2.19 (1.03, 4.66), P=0.04 2. New Jersey vs. California OR=3.56 (CI 1.15, 11.03) 3. PSA ≥ 20 vs. ≤ 4.0 OR=0.18 (CI 0.04, 0.78), P=0.003 4. Gleason 8-10 vs. <6 OR=0.04 (CI 0.00, 0.32), P=0.03 5. Comorbidities ≥ 1 vs. 0 OR=0.26 (CI 0.08, 0.89), P=0.03</p> <p>NS: race</p>
Yan 2000 ¹⁵³ 10699903	Clinical	Survey of men diagnosed with prostate	1989- 1998	1809	Screen-detected, clinically localized prostate cancer	Not explicitly provided	Multinomial logistic regression (WW vs. RP vs.	<p>1. Non-Black more likely (than Black) to choose RP than WW [OR=4.3 (1.7, 10.9)] or (nonsignificantly) RT than WW [OR=2.6 (0.86, 7.7)] 2. Clinical stage T2 more likely (than T1) to choose RP</p>

Author yr Pubmed ID	Factors	Data source	Duration	Analyzed sample	Population characteristics	WW/AS definitions	Methods	Results as described in paper
		cancer (through an earlier research screening study)					RT)	than WW [OR=3.0 (1.8, 4.8)] or RT than WW [OR=2.8 (1.6, 4.7)] 3. No urinary dysfunction more likely (than yes) to choose RP than WW [OR=1.8 (1.13, 2.8)] but NS RT vs. WW [OR=1.08 (0.66-1.8)] 4. No sexual dysfunction NS RP vs. WW [OR=0.83 (0.5, 1.3)] but less likely to choose RT than WW [OR=0.52 (0.30, 0.84)] 5. PSA level, for every 1 ng/mL increase (at dx) RP more likely than WW [OR=1.12 (1.04, 1.20)] and RT than WW [OR=1.15 (1.07, 1.23)] 6. Age, for every 5-yr increase RP less likely than WW [OR=0.21 (0.17, 0.27)] and RT less likely than WW [OR=0.49 (0.39, 0.63)] NS: marital status, education, income, indication for biopsy, and a Charlson-like comorbidity score.
Wolters 2010 ¹⁴⁷ 19739124	clinical	post hoc analysis of ERSPC	1993- 2006	8010 (completed data set)	low, intermediate and high risk cancer	Not explicitly provided	polytomous logistic regression predicts AS compared to RP	1. Age OR=1.19 (CI 1.17, 1.21) 2. PSA OR=0.30 (0.23, 0.39) 3. T2 vs. T1 =OR 0.33 (CI 0.28, 0.39) 4. PSA 50+ vs. ≤4.0 OR=1.73 (CI 1.02, 2.94) 5. Gleason ≥8 vs. ≤6 OR=0.20 (CI 0.13, 0.32) NS: study arm; lymph node involvement
Sommers 2008 ¹⁵⁴ 18704993	patient preference	survey of men newly dx'd localized cancer	2004- 2007	167	T1, T2N0M0, not yet treated	Not explicitly provided	logistic regression predicts choice of WW vs. other treatments or undecided	1. desire to avoid side effects main predictor of choice of WW (logistic regression coefficients not provided, P<0.05) 2. "current bowel problem" was also a predictor of choice of WW (logistic regression coefficients not provided, P<0.05)
Adherence to AS/WW								
Carter 2003 ¹⁶⁶⁸ /id 14581423	clinical	DOD CPDR database	1991- 2002	313	≤70 yr, Gleason ≤6 (no pattern 4), ≤3 positive cores, ≤T2, PSA ≤ 20 ng/mL	Not explicitly provided	multivariate Cox proportional hazard predicts definitive 2° treatment	1. T2c vs. T1a/b HR 16.4 (CI 3.16, 85.16), P=0.0009 2. PSA doubling time 2-5 yr vs. <2 yr HR 0.32 (CI 0.20, 0.52), P<0.0001 Median f/u 3.8 yr NS: age; PSA at dx; Gleason, race; FH; comorbidities
Latini ¹⁴⁰ 2007	clinical, social,	CaPSURE	1997- 2002	105	Patients with biopsy-proven	No treatment for ≥6 mo	Cox proportional	PSA velocity, ng/ml/yr, - -0.51-0.50 vs. <0.51, HR=0.402 (CI 0.092, 1.754);

Author yr Pubmed ID	Factors	Data source	Duration	Analyzed sample	Population characteristics	WW/AS definitions	Methods	Results as described in paper
17632144	delivery system				localized prostate cancer, who elected AS.	after dx	hazards regression time-to-active treatment/ AS interruption	<p>P=0.23 - 0.51-1.50 vs. <-0.51, HR=1.518 (CI 0.425, 5.419);</p> <p>P=0.52 - \geq1.51 vs. <-0.51, HR=3.181 (CI 1.122, 9.016); P=0.03</p> <p>P=0.01 Cancer anxiety change rate, HR=1.019 (CI 1.004, 1.035); P=0.01</p> <p>The following NS variables were also considered in the model (HR estimates not provided): relationship; clinical risk group, D'Amico classification; BMI ; race; education; number of comorbidities; insurance; age at dx; PSA velocity x CA change rate (interaction).</p>
Meng 2003 ¹⁴³ 14634396	social, clinical, delivery system	CaPSURE	1989- 2001	457	Men with localized prostate cancer who chose WW as the initial treatment within 9 mo of the dx, no active treatment within 6 months of initiating WW and >6 months of study followup	Not explicitly provided	Cox proportional hazards models with backward stepwise regression (stay criteria p<0.1) for active treatment (WW interruption)	<p>Of the 457 men initially treated with WW, 188 (41%) received subsequent active treatment at a median of 1.7 yr.</p> <p>1. disease risk (D'Amico), - High vs. low risk of prostate cancer: HR=2.75 (CI 1.84, 4.12); P<.0001 - Intermediate vs. low risk of prostate cancer: HR=1.51 (CI 1.05, 2.07); P=.028</p> <p>2. age, - 65-74 vs. <65, HR=0.70 (CI 0.41, 1.18); P=0.18 - \geq75 vs. <65. HR=0.57 (CI 0.33, 0.96); P=0.035</p> <p>3. education level, - not college graduate vs. college graduate, HR=0.66 (CI 0.46, 0.94); P=0.021 - unknown vs. college graduate, HR=0.68 (CI 0.42, 1.10); P=0.11</p>
Koppie 2000 ¹⁴⁴ 10840429	clinical	CaPSURE	NR	329	Men with biopsy- confirmed prostate cancer who elected WW as their initial treatment.	No therapy within 9 mo of dx	Cox proportional hazards regression, including an analysis of time-dependent predictors time-to-active treatment/ WW interruption	<p>Cox regression using only baseline variables:</p> <p>1. age, - 65-74 yr vs. <65 yr, HR=0.374 (CI 0.179, 0.784); P=0.009 - \geq65 yr vs. <65 yr, HR=0.336 (CI 0.166, 0.679); P=0.002</p> <p>2. clinical T stage at dx, - T2 vs. T1, HR =1.833 (CI 1.123, 2.992); P=0.015 - T3-T4 vs. T1, HR=1.149 (CI 0.440, 3.002); P=0.777</p> <p>3. PSA at dx, ng/ml - 4.1-10.0 vs. 0-4.0, HR=3.064 (CI 1.352, 6.944); P=0.007</p>

Author yr Pubmed ID	Factors	Data source	Duration	Analyzed sample	Population characteristics	WW/AS definitions	Methods	Results as described in paper
								<p>- 10.1-20.0 vs. 0-4.0, HR=3.680 (CI 1.544, 8.769); P=0.003</p> <p>- \geq20.1 vs. 0-4.0, HR=6.864 (CI 2.587, 18.202); P<0.001</p> <p>4. Gleason score at dx, - 7 vs. 2-6, HR=1.082 (CI 0.570, 2.053); P=0.809 - 8-10 vs. 2-6, HR=1.179 (CI 0.395, 3.515); P=0.7681</p> <p>5. Disease risk, - intermediate vs. low, HR=NR; P=NR - high vs. low, HR=NR; P=NR</p> <p>6. Race/ethnicity, Black vs. White, HR=1.220 (CI 0.451, 3.302); P=0.695</p> <p>Cox regression using time-dependent covariates: change in serum PSA vs. baseline, per unit, HR=1.99 (CI 1.18, 3.35).</p> <p>Results from models using changes in stage or PSA before treatment as time-dependent covariates were not reported.</p> <p>Estimates were adjusted for age, race, PSA at dx, clinical T stage, total Gleason score.</p>
Wu 2004 ¹⁵¹ 14767282	clinical	DOD CPDR database	1990-2001	1158	No metastases	No active treatment within 9 mo of dx	multivariate Cox proportional hazard predicts 2° treatment (RP, RT, ADT) vs. staying on WW	<p>1. Age at dx, per yr, HR=0.96 (CI 0.95, 0.98), P<0.001</p> <p>2. Log(PSA), per unit, HR=1.43 (CI, 1.28, 1.60); P<0.001</p> <p>3. Clinical stage: - T2 vs. T1, HR=1.32 (CI 1.04, 1.66), P=0.021 - T3+T4 vs. T1, HR=1.62 (CI 0.99, 2.63); P=0.054</p> <p>NS: highest Gleason sum ; FH; comorbidity; dead or alive</p>
van As 2008 ¹⁴⁸ 18342430	clinical	Royal Marsden Hospital, UK	2202-2006	326	localized disease	PSA q 1 mo yr1, q 3 mo yr 2, then q 6 mo; Bx at 18 mo – 2 yr Treat if PSA velocity >1 ng/mL/yr; Gleason \geq 4+3 or >50% positive	multivariate Cox regression with respect to radical treatment for patients who elected AS	<p>free/total PSA ratio (P<0.001) and T stage (P=0.006) were independent predictors of time to radical treatment in patients on AS</p> <p>NS: initial PSA; PSA density; Gleason; % positive core; Number of positive cores; prostate volume</p> <p>median f/u of 22 mo</p>

Author yr Pubmed ID	Factors	Data source	Duration	Analyzed sample	Population characteristics	WW/AS definitions	Methods	Results as described in paper
El-Geneidy 2004 ¹⁵⁰ 15008720	clinical	Portland VA	1993- 2000	175	T1-2 on WW	cores Not explicitly provided	stepwise multivariate Cox regression predicts curative treatment	1. Age 66-74 vs. >75 yr HR=5.0 (CI 1.13, 22.17), P=0.034 2. PSA doubling time <3 yr vs. >10 yr HR=2.73 (CI 1.19, 6.24), P=0.018 3. 34%-50% vs. <34% positive biopsies HR=2.47 (CI 1.14, 5.35), P=0.022 NS (univariate) : PSA ≥4 vs. <4; Gleason ≥6 vs. <5; T2 vs. T1; ≥34% positive bx vs. <34% ; PSA density Median f/u 3.3 yr (range 0.1-8.6 yr).
Chose AS vs. randomization to available treatments								
Mills 2006 ¹⁴⁹ 16774847	patient personal preferences	comparison of 180 men who refused randomization but selected AS with 138 men randomized to AS (from ProtecT study)	2001- 2004	318	not reported	regular PSA	multivariate logistic regression predicting "selecting AS" vs. "randomized to AS"	1. SES and baseline anxiety associated with selecting treatment: per decrease in SES from I to V, OR=0.68 (CI 0.49, 0.96); P=0.03. 2. baseline anxiety (per unit increase on HAD scale) OR=0.93 (CI 0.87, 0.99); P=0.04 adjusted for baseline score, study center, age (further adjustment for marital status, SES had little impact (data not shown)) Applicability limited to predominantly white married, middle class men 50-69 yrs healthy for clinic testing.

Estimates are provided with 95% confidence intervals and p-values when available.

AS = active surveillance; BMI = body mass index; CI = confidence interval; DOD CPDR = Department of Defense Center for Prostate Disease Research; dx = diagnosis; ERSPC = European Randomized Study of Screening for Prostate Cancer; FH = family history; HAD = Hospital Anxiety and Depression scale; NS = non-statistically significant; OR = odds ratio; PCOS = Prostate Cancer Outcomes Study; ProtecT = Prostate Testing for Cancer and Treatment study; PSA = prostate-specific antigen; TUMT = transurethral microwave thermotherapy of the prostate; UI = PubMed unique identifier; VA = Veterans Affairs; WW = watchful waiting; yr = year.

Appendix Table C3.3. Lin 2009,¹⁶⁸ systematic review of patient decision aids

Author Year [PMID]	Lin 2009 ¹⁶⁸ [19841280]
Design	A systematic review of patient decision aids for prostate cancer treatment
Population	Men with low-risk prostate cancer who had the option of RP, RT, or WW
Intervention (Exposure)	Various decision aids (written information package, consultation with nurse or urologist, generic video, interactive computer program/CD-ROM decision aid, personalized multidisciplinary consultation, either stand-alone or in combinations)
Results	<p>Medline, CINAHL, Web of Science, and Cochrane Library initial search yielded 219 articles. 13 (3 RCTs (1 poor and 2 good per Jadad rating) and 10 nonrandomized trials) met eligibility criteria (inception through 3/2009).</p> <p>Key findings</p> <ol style="list-style-type: none"> 1. Majority of DAs were developed de novo 2. The participants in general found the DAs to be informative. 3. One RCT reported a decrease in anxiety in participants in the intervention arm (written information package with discussion, a list of questions they could ask their physician, and an audiotape of the medical consultation) versus written information alone.¹⁷⁵ 4. One RCT found that there was no difference in satisfaction with treatment choice between those who received individualized DAs and those using a generic DA.¹⁷⁴ 5. One RCT found that the men in the DA arm selected their physician's treatment choice less often than those who received usual care.¹⁷³ 6. The nonrandomized studies reported that DAs appeared to increase patients' knowledge concerning prostate cancer and its treatments.
Comments	As noted by the systematic review authors: few high quality trials, heterogeneous outcome measures, and the quality of the information provided in the DAs themselves were not assessed and therefore whether these DAs met the quality standards set by the International Patient Decision Aids Standards Collaboration could not be determined. ¹⁷⁶
AMSTAR	
A priori design?	yr Study quality assessment performed? yr
Two independent reviewers?	yr Study quality appropriately used in analysis? yr
Comprehensive literature search?	yr Appropriate statistical synthesis? yr
All publication types and languages included?	n Publication bias assessed? n
Included and excluded studies listed?	n Conflicts of interest stated? yr
Study characteristics provided?	yr

DA = decision aid; RCT = randomized controlled trial.

Appendix Table C4.1: Cost comparisons of WW or AS with active treatments

Author year UI	Design	Data source	Years	N Population characteristics	Methods	Costs	WW (95% CI)	RP (95% CI)	RT (95% CI)	Notes
Snyder ¹³⁵ 2010 20734396	Retrospective cohort study (also includes a comparison with a non-cancer control group)	SEER-Medicare	2000, followed for 5 yr	WW = 2805 RP monotherapy = 2200 RT monotherapy = 2582 Total N = 13,769 (included 3992 patients receiving hormonal therapy + RT or medical pADT) ≥65 yr; lived in SEER regions, clinically localized prostate cancer Control group (n=13,769; matched for age, sex, race, region, comorbidity, survival)	Costs from Medicare adjusted for inflation to 2007 dollars and geographic region; discounted 3% per yr after 1 st yr; grouping based on treatment received 1 st 9 mo; estimates were derived from IPTW analysis using a propensity score accounting for age, race, comorbidity, SEER region, urban/rural location, socioeconomic status and grade	Incremental costs vs. control: Yr 1 Total over 5 yr	\$ 3936 (3078-4794)	\$ 15,556 (14,835-16,277)	\$ 12,319 (11,419-13,219)	Required patients to have survived at least 9 mo post diagnosis; total costs were only calculated for years during which the patient survived.
Andersson ²⁰¹ 2011 21265595	Substudy of RCT	SPCG-4	Recruitment, 1989-99; followed through July 2007	WW = 105 RP = 107 <75 years, life expectancy >10 years, T0d-T2 disease, WHO well/moderately differentiated, PSA <50ng/ml, no evidence of skeletal metastases on bone scan; patients from the trial were included	Medical records were retrospectively reviewed; a healthcare provider perspective was adopted (costs generated from care outside the hospital were not considered); resource use was measured in physical units and then multiplied by the unit cost (based on 2007 Swedish prices converted to €).	Total mean cost after median followup of 11.8 yr for the WW group and 12.2. for the RP group	€ 18,124 (NR)	€ 24,247 (NR)	NA	No patient was lost to follow-up P<0.01 for the absolute difference between groups, unadjusted analysis; in multivariable analysis P=0.003 (adjusted for age, PSA and

Author year UI	Design	Data source	Years	N Population characteristics	Methods	Costs	WW (95% CI)	RP (95% CI)	RT (95% CI)	Notes
				if they resided in the counties where the two centers that randomized most patients were located (Örebro and Uppsala).						Gleason score).
Penson ²⁰⁰ 2001 11248628	Retrospective cohort study	CaPSURE	1990-97	WW = 37 Active Tx = 198 [RP monotherapy, RP + neoadjuvant hormone therapy; RT monotherapy, RT + neoadjuvant hormonal therapy; medical pADT, orchiectomy, medical pADT followed by orchiectomy]	Direct costs of prostate cancer treatment (outpatient visits, laboratory tests and procedures, prescribed medications, surgical treatments and hospitalizations), adjusted to 1996 values; outpatient costs were calculated using 1996 Medicare Physician and Laboratory Fee Schedule; outpatient facility costs per unit were obtained from average Medicare service costs (1992); total costs were calculated by multiplying the frequency of each service by the unit cost; hospitalization costs were obtained from Medicare (1994); drug costs were obtained from the 1996 Red Book	Average first year cost	\$ 484 (NR)	\$ 7320 (NR)	\$ 7430 (NR)	P <0.001 for the treatment effect (ANCOVA, adjusted for stage, Gleason sum, serum PSA at diagnosis, insurance status, comorbidities, age); cost estimates are unadjusted means.