Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

Methods used to estimate overdiagnosis and mean sojourn time.

We simulated a cohort of three million men aged 50-69 years and followed to death, calibrated against CAP data – prostate cancer incidence rate, and cancer-specific and all-other cause mortality rates (**eFigure 4**) and age at death (**eFigure 5**). We applied multistate survival model with parametric hazards and the following states: healthy, screen-detectable, screen-detected, clinically diagnosed, cancer-specific death, and all-other cause deaths, to estimate the natural history parameters and time to death after a cancer diagnosis (**eFigure 6**). The transition between healthy and screen-detectable states was assumed to follow the Weibull distribution, while other transitions were assumed to follow the Gompertz distribution. We estimated the transition hazards between the states and the misclassification of states (i.e., 1-episode sensitivity[1]) by maximising the likelihood functions.[2] We derived the mean sojourn time and overdiagnosis from microsimulation using the estimated transition parameters and one-off screening between ages 50 to 69 and assuming 85% of men with elevated PSA level undertake biopsy. We calculated the sojourn time as the length of time in the screen-detectable state given a transition to a clinically diagnosed state (i.e. the time by which diagnosis is advanced by screening [lead time]). We estimated overdiagnosed cases as the difference in cumulative prostate cancer incidence between screened and unscreened groups over lifetime. The probability of overdiagnosis was the fraction overdiagnosed among screen-detected cases.

Supplementary Tables

eTable 1: Prostate cancer-specific diagnoses and mortality and all-cause mortality at 10-years, 15-years and 18-years post-randomisation (and at 18 months for prostate cancer diagnoses) by random allocation and an as randomized estimate of the difference between groups.

	Intervention group *(n=189,326)*		**Control group** *(n=219,395)*		
	N	**Cumulative risk per 1000 men (95% CI)**	**N**	**Cumulative risk per 1000 men (95% CI)**	**Cumulative risk difference per 1000 men (95% CI)**
Prostate cancer mortality					
At 10-years	488	2.89 (2.65, 3.16)	575	2.95 (2.72, 3.21)	-0.06 (-0.41, 0.29)
At 15-years	1,018	6.90 (6.48, 7.34)	1,288	7.76 (7.34, 8.21)	-0.86 (-1.48, -0.25)
At 18-years	1,185	10.92 (10.14, 11.76)	1,440	12.09 (11.19, 13.07)	-1.17 (-2.41, 0.07)
All-cause mortality					
At 10-years	23,212	126.30 (124.79, 127.83)	26,581	125.37 (123.97, 126.79)	0.92 (-1.15, 3.00)
At 15-years	40,001	232.08 (230.06, 234.12)	46,073	232.75 (230.86, 234.65)	-0.68 (-3.46, 2.10)
At 18-years	44,747	316.15 (313.03, 319.29)	50,045	320.46 (316.91, 324.03)	-4.27 (-9.01, 0.47)
Prostate cancer diagnoses					
At 18-months	2,912	15.51 (14.96, 16.08)	711	3.28 (3.05, 3.53)	12.23 (11.63, 12.84)
At 10-years	7,558	42.92 (41.98, 43.88)	7,554	38.12 (37.28, 38.97)	4.80 (3.53, 6.07)
At 15-years	11,291	70.78 (69.51, 72.08)	12,368	69.40 (68.21, 70.62)	1.38 (-0.38, 3.14)
At 18-years	12,001	86.30 (84.53, 88.12)	12,938	85.44 (83.48, 87.44)	0.86 (-1.80, 3.53)

N is numbers of deaths and diagnoses as shown in the row headers. CI: Confidence interval. This table differs from Table 2, in that it reports cumulative risks at specific time points (10, 15 and 18 years), while Table 2 reports the data after a median 15 years of follow-up (range: 12.2 to 19.2 years).

eTable 2: Underlying causes of death[a] in intervention versus control groups at 15-year median follow-up (not including prostate cancer).

Cause of death	Intervention n (%)	Control n (%)
Any (not incl. prostate cancer)	43,885 (100%)	48,885 (100%)
Other cancers	16,553(38%)	18,440 (38%)
Circulatory diseases	12,419 (28%)	13,662 (28%)
Respiratory disease	5,287 (12%)	5,796 (12%)
Digestive disease	2,316 (5%)	2,612 (5%)
Infectious disease	385 (1%)	402 (1%)
Genitourinary diseases	445 (1%)	503 (1%)
Blood, immune, endocrine	644 (1%)	736 (2%)
Nervous system disease	1,862 (4%)	2,217 (5%)
Accident	1,126 (3%)	1,278 (3%)
Other	2,705(6%)	3,074 (6%)
No ICD10 code	143 (<1%)	165 (<1%)

[a]*Underlying cause of death for non-prostate cancer deaths was determined by death certificate.*

There were 95,420 all-cause deaths in total, including 308 deaths without an ICD10 code and 2,650 prostate cancer deaths (N=92,462 non prostate cancer deaths with an ICD-10 code).

eTable 3. Effect of the CAP trial intervention on characteristics of prostate cancer cases at diagnosis[a]

		Intervention group			Controls
		Attended PSA clinic 75,694	Did not attend PSA clinic 113,632	All invited 189,326	219,395
Number of prostate cancers (%)[b]		6,554 (8.7%)	5,459 (4.8%)	12,013 (6.3%)	12,958 (5.9%)
Clinical characteristics at diagnosis					
Person-years of follow up		1,043,530	1,416,377	2,459,907	2,815,181
Rate per 1000-person years		6.28 (6.13, 6.43)	3.85 (3.75, 3.96)	4.88 (4.80, 4.97)	4.60 (4.52, 4.68)
Mean age (SD)		67.28 (6.54)	69.21 (5.91)	68.16 (6.33)	69.38 (5.90)
Median years between randomization and diagnosis (IQR)		5.90 (0.67, 11.26)	9.15 (5.25, 12.15)	7.84 (1.69, 11.76)	8.93 (5.29, 12.02)
Grade (%)					
	Grade recorded[c]	5,991 (91.4%)	4,769 (87.4%)	10,760 (89.6%)	11,501 (88.8%)
	≤6[b]	2,704 (3.6%)	1,407 (1.2%)	4,111 (2.2%)	3,482 (1.6%)
	7[b]	2,305 (3.0%)	2,097 (1.8%)	4,402 (2.3%)	5,082 (2.3%)
	3+4	*1,011 (1.3%)*	*1,074 (0.9%)*	*2,085 (1.1%)*	*2,708 (1.2%)*
	4+3	*468 (0.6%)*	*570 (0.5%)*	*1,038 (0.5%)*	*1,443 (0.7%)*
	Unknown[d]	*826 (1.1%)*	*453 (0.4%)*	*1,279 (0.7%)*	*931 (0.4%)*
	≥8[b]	982 (1.3%)	1,265 (1.1%)	2,247 (1.2%)	2,937 (1.3%)
Stage (%)					
	Stage recorded[c]	5,952 (90.8%)	4,933 (90.4%)	10,885 (90.6%)	11,945 (92.2%)
	T1/T2[b]	4,227 (5.6%)	2,647 (2.3%)	6,874 (3.6%)	6,746 (3.1%)
	T3[b]	1,160 (1.5%)	1,146 (1.0%)	2,306 (1.2%)	2,871 (1.3%)
	T4/N1/M1[b]	565 (0.7%)	1,140 (1.0%)	1,705 (0.9%)	2,328 (1.1%)

The intervention was a single invitation to PSA screening. The PSA clinic was the clinic men were invited to have the PSA test explained, consider having a PSA test and give written informed consent with a 24-hour period cooling off period.
IQR = interquartile range (25th percentile, 75th percentile). CI = confidence interval. [a]Diagnoses were collected from routine data sources, NHS England data were used in the first instance (n=23,415 cancers) and additional cases were included if present in data provided by Public Health Wales (n=930) or the National Disease Registration Service (NDRS, formerly Public Health England) (n=626). [b]Denominators are column header totals. [c]Denominators are N of prostate cancers in each column. [d]Missing primary and secondary Gleason grade to enable 3+4 and 4+3 subdivision.

eTable 4: Sensitivity analyses employing alternative definitions of prostate cancer deaths.

	Intervention group *(n=189,326)* Person years=2,543,298		**Control group** *(n=219,395)* Person years=2,885,418		**As randomized estimate**	
	Events	**Rate/1000 person years (95% CI)**	**Events**	**Rate/1000 person years (95% CI)**	**Rate ratio (95% CI)**	**P value[a]**
Including 'possible' prostate cancer death[d]	1230	0.48 (0.46, 0.51)	1498	0.52 (0.49, 0.55)	0.91 (0.85, 0.99)	P=0.020
Definite prostate cancer death only[e]	1028	0.40 (0.38, 0.43)	1254	0.43 (0.41, 0.46)	0.91 (0.84, 0.99)	P=0.030

[a]Likelihood ratio test of the null hypothesis "no difference in prostate cancer mortality between the groups", adjusted for randomisation cluster and age using a lexis diagram approach. [b]Defined as definite, probable or possible prostate cancer death or intervention related death by an independent cause of death committee. [c]Defined as definite prostate cancer death or intervention related death by an independent cause of death committee.

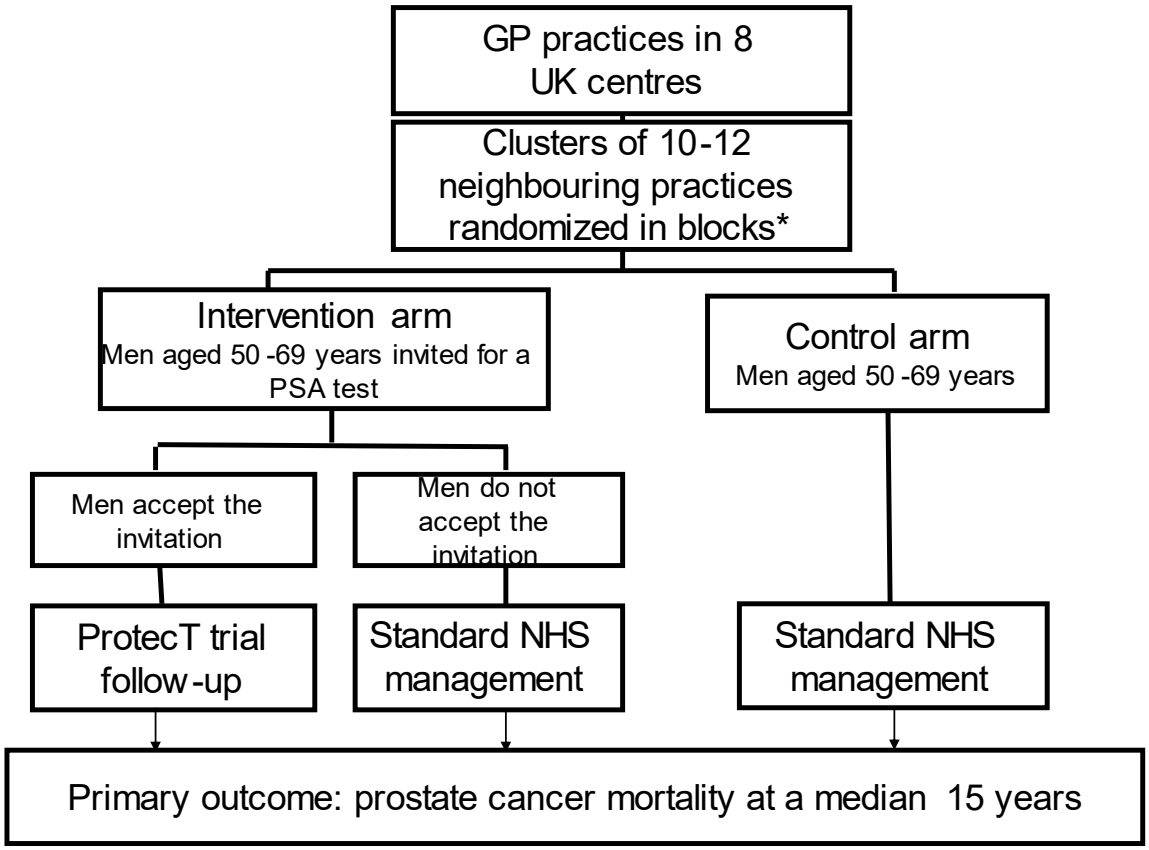
eTable 5: Estimated mean and median sojourn time and probability of overdiagnosis.

Age group				
	Mean sojourn time (years)	**95% confidence interval (years)**	**Median sojourn time (years)**	**Interquartile range (years)**
50-54	12.1	12.1 – 12.2	10.6	5.0 – 17.5
55-59	13.2	13.1 – 13.2	11.9	5.5 – 19.3
60-64	14.2	14.2 – 14.3	13.0	5.9 – 21.4
65-69	15.3	15.2 – 15.3	13.8	6.2 – 23.4
50-69	**13.4**	**13.4 -13.4**	**12.0**	**5.5 -19.8**
	Mean overdiagnosis %	**95% confidence interval (%)**	**Median overdiagnosis %**	**Interquartile range %**
50-54	9.2	8.9 – 9.4	9.3	8.0 – 10.4
55-59	13.3	13.1 – 13.5	13.4	12.4 – 14.3
60-64	17.1	17.0 – 17.3	17.2	16.4 – 17.9
65-69	20.8	20.6 – 21.0	20.8	20.0 – 21.3
50-69	**15.0**	**14.4 – 15.5**	**14.8**	**13.6 – 15.8**

The sojourn time represents the duration of the preclinical screen-detectable period for each of the 3 million men who transition from screen-detectable to clinically diagnosed state. Sojourn time varies between individuals.
*****Overdiagnosis estimates are based on simulation of 200 cohorts of 3 million men aged 50 to 69 followed to death. The episode sensitivity[1] (the ability of the full diagnostic process – testing and biopsy – to find cancer in the detectable preclinical phase) increased from 50.0% to 85.3% for ages 50 to 69.

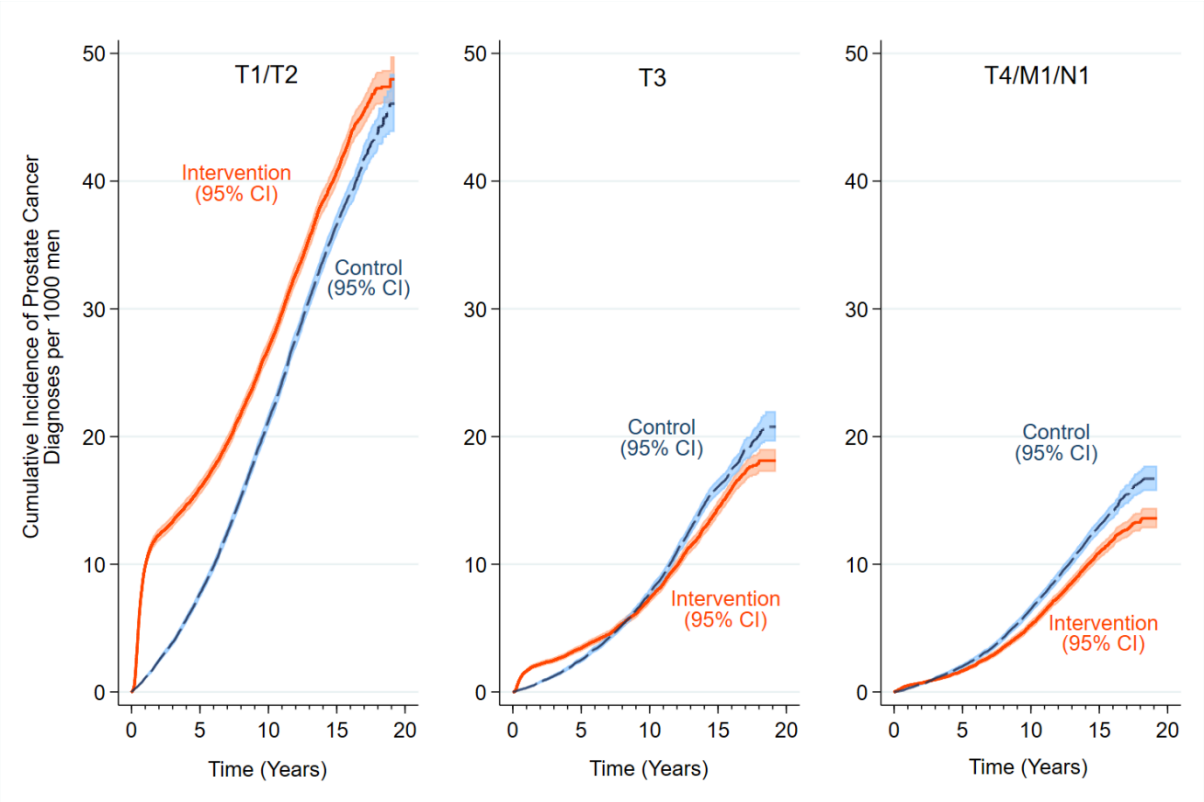
Supplementary Figures

eFigure 1: CAP trial design.



CAP is a UK-wide cluster RCT in which 573 GP practices in 8 UK centres (Sheffield, Newcastle, Bristol, Birmingham, Cardiff, Leeds, Cambridge, Leicester) were randomised and consented to either PSA testing and prostate cancer diagnosis (ProtecT trial) or the routine-practice comparison arm. Pre-specified Prostate cancer mortality outcomes were collected at a median 10-years (reached 31st March 2016) and 15-years (reached 31st March 2021) follow-up.

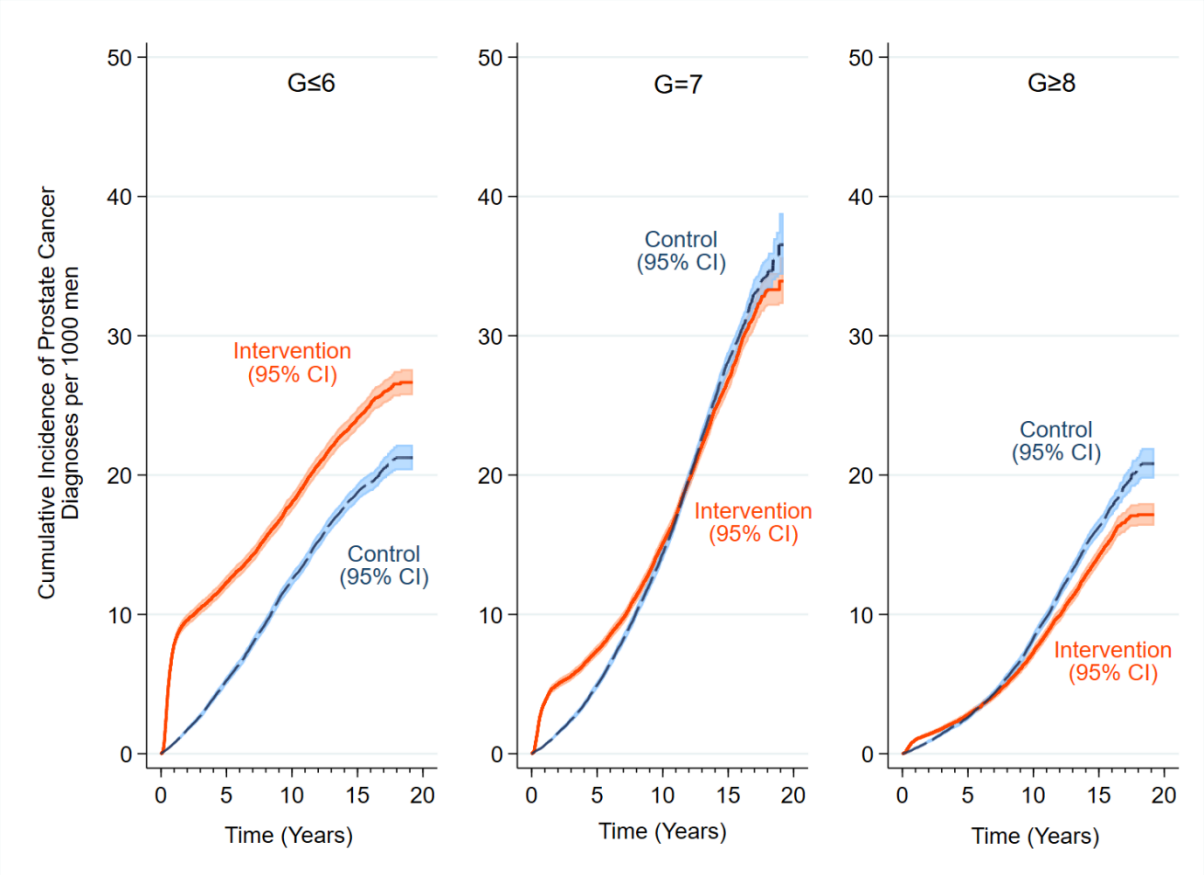
eFigure 2: Cumulative incidence of prostate cancer by TNM stage at diagnosis.



Number at risk at the start of each two-year period (number of prostate cancer diagnoses in that period)												
Time (year)	**Median (IQR) follow up**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**
A: Clinical stage T1/T2												
Intervention	14.20 (11.42, 16.04)	189,326 (2302)	180,957 (418)	174,289 (514)	167,024 (697)	158,876 (805)	149,145 (868)	139,138 (763)	103,163 (386)	48,427 (119)	12,794 (2)	0 (0)
Control	14.35 (11.09, 15.67)	219,395 (531)	212,352 (665)	204,203 (844)	194,558 (1,044)	184,887 (1,083)	172,125 (1079)	158,863 (936)	119,810 (459)	38,396 (94)	9,687 (11)	0 (0)
B: Clinical stage T3												
Intervention	14.20 (11.42, 16.04)	189,326 (404)	180,957 (136)	174,289 (183)	167,024 (220)	158,876 (302)	149,145 (374)	139,138 (388)	103,163 (230)	48,427 (68)	12,794 (1)	0 (0)
Control	14.35 (11.09, 15.67)	219,395 (168)	212,352 (223)	204,203 (300)	194,558 (357)	184,887 (447)	172,125 (547)	158,863 (541)	119,810 (230)	38,396 (52)	9,687 (6)	0 (0)
C: Clinical stage T4/M1/N1[a]												
Intervention	14.20 (11.42, 16.04)	189,326 (131)	180,957 (97)	174,289 (152)	167,024 (223)	158,876 (266)	149,145 (316)	139,138 (309)	103,163 (161)	48,427 (46)	12,794 (4)	0 (0)
Control	14.35 (11.09, 15.67)	219,395 (133)	212,352 (181)	204,203 (227)	194,558 (314)	184,887 (397)	172,125 (417)	158,863 (402)	119,810 (207)	38,396 (47)	9,787 (3)	0 (0)

CI: confidence interval, IQR: interquartile range, [a]If any of these conditions were satisfied patients were categorized as T4, e.g. a patient with T3, N0 and M1 would be categorized as T4/N1/M1.

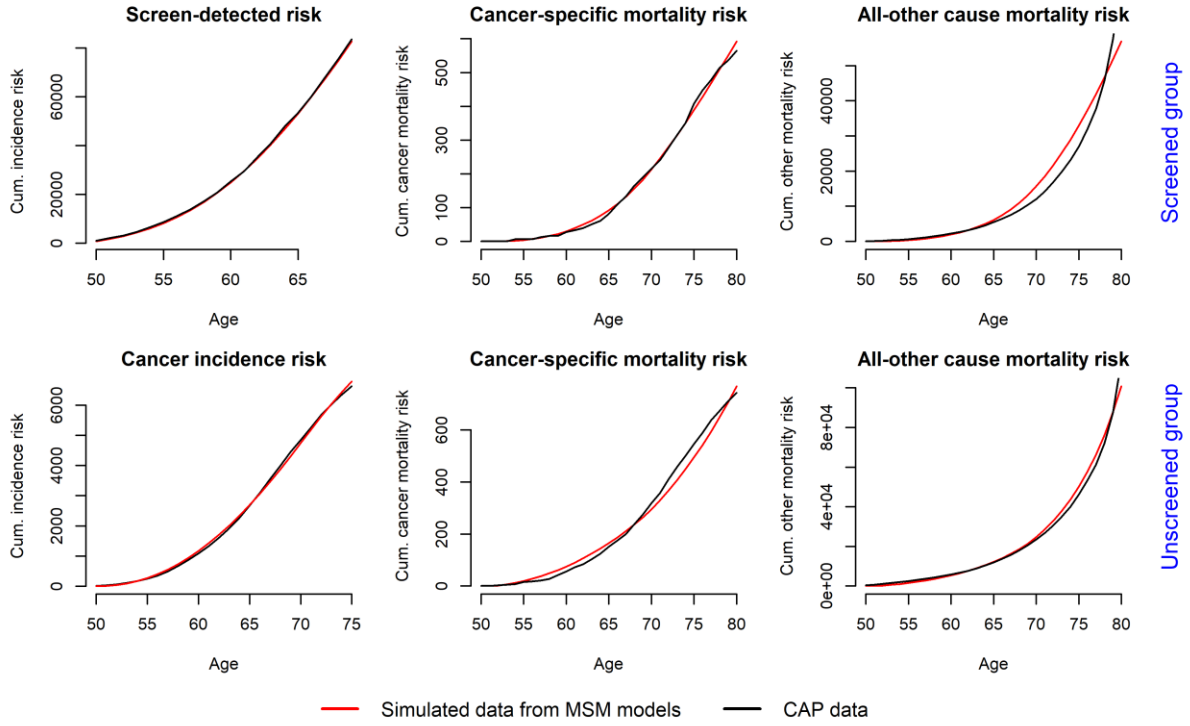
eFigure 3: Cumulative incidence of prostate cancer by Gleason score at diagnosis.



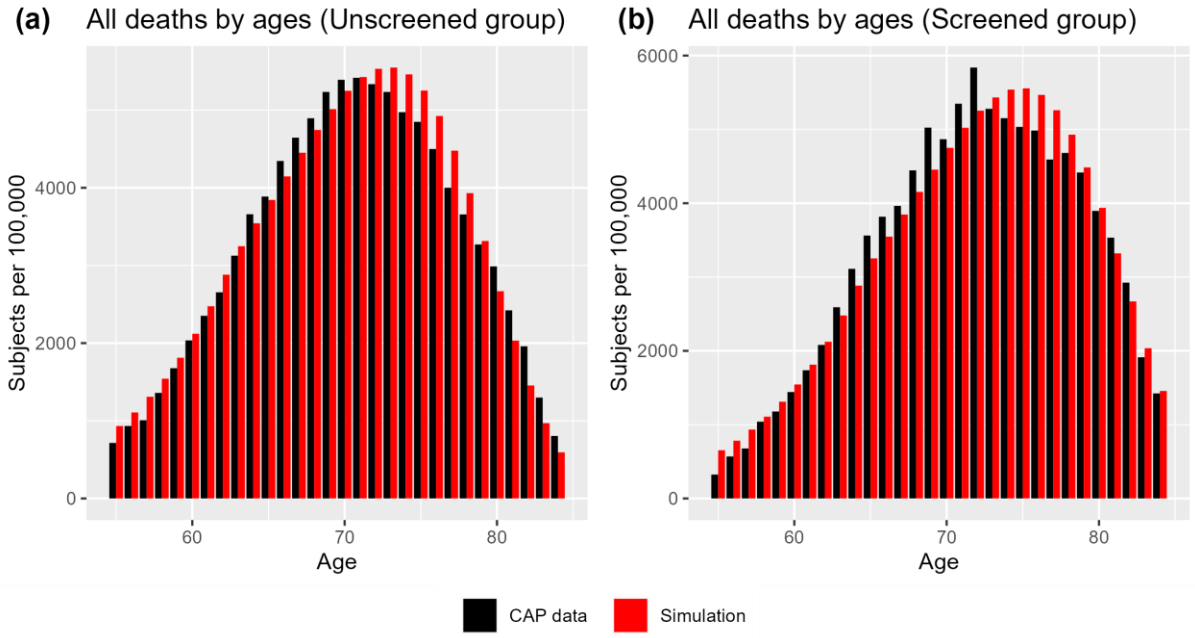
Number at risk at the start of each two-year period (number of prostate cancer diagnoses in that period)												
Time (year)	**Median (IQR) follow up**	**0[b]**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**
A: Gleason≤6												
Intervention	14.20 (11.42, 16.04)	189,326 (1790)	180,957 (313)	174,289 (330)	167,024 (378)	158,876 (390)	149,145 (402)	139,138 (307)	103,163 (153)	48,427 (47)	12,794 (1)	0 (0)
Control	14.35 (11.09, 15.67)	219,395 (374)	212,352 (458)	204,203 (503)	194,558 (565)	184,887 (556)	172,125 (463)	158,863 (373)	119,810 (157)	38,396 (33)	9,687 (0)	0 (0)
B: Gleason 7												
Intervention	14.20 (11.42, 16.04)	189,326 (930)	180,957 (256)	174,289 (366)	167,024 (460)	158,876 (578)	149,145 (664)	139,138 (676)	103,163 (352)	48,427 (118)	12,794 (2)	0 (0)
Control	14.35 (11.09, 15.67)	219,395 (317)	212,352 (432)	204,203 (593)	194,558 (705)	184,887 (754)	172,125 (899)	158,863 (863)	119,810 (426)	38,396 (84)	9,687 (9)	0 (0)
C: Gleason≥8												
Intervention	14.20 (11.42, 16.04)	189,326 (257)	180,957 (155)	174,289 (198)	167,024 (266)	158,876 (342)	149,145 (389)	139,138 (375)	103,163 (208)	48,427 (57)	12,794 (0)	0 (0)
Control	14.35 (11.09, 15.67)	219,395 (193)	212,352 (288)	204,203 (288)	194,558 (391)	184,887 (503)	172,125 (539)	158,863 (502)	119,810 (236)	38,396 (52)	9,687 (5)	0 (0)

CI: confidence interval, IQR: interquartile range

eFigure 4: Comparing simulated data to empirical data for the cumulative prostate cancer incidence and cancer-specific and all-other cause mortality risk among the screened men and the unscreened group. Average of 200 simulations of three million men aged 50-69 years with one-off screening in the screened group.

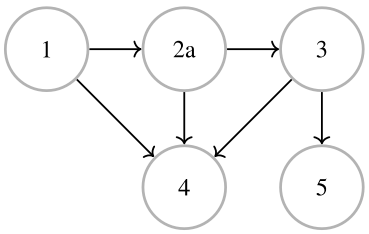


eFigure 5: Comparison number of subjects per 100, 000 cohorts at death from all causes by ages between simulated data and CAP data. Average of 200 simulations of three million men aged 50-69 years with one-off screening in the screened group.

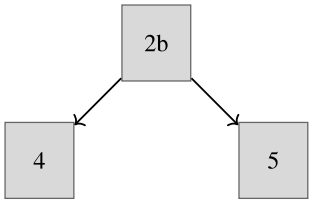


eFigure 6: Transition diagram for multi-state survival models a. Natural history model with states 1-Healthy, 2a – Screen-detectable, 3-clinically diagnosed, 4-all-other cause death, 5-cancer-specific death; b. survival model for screen-detected cancers with states 2b-screen-detected, 4-all-other cause death, 5-cancer-specific death.

Model a.



Model b.



Supplementary Material References

1. Hakama M, Auvinen A, Day NE, Miller AB. Sensitivity in cancer screening. *Journal of Medical Screening* 2007; **14**(4): 174-7.
2. Bhatt R, van den Hout A, Pashayan N. A multistate survival model of the natural history of cancer using data from screened and unscreened population. *Stat Med* 2021; **40**(16): 3791-807.