

PROSTATE CANCER SCREENING

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RCT OF TREATMENT OF CLINICALLY LOCALIZED PROSTATE CANCER

Original Article

Radical Prostatectomy or Watchful Waiting in Early Prostate Cancer

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WHO? WHAT?

- The Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4)
 - Enrollment 1989-1999
 - An RCT of radical prostatectomy versus watchful waiting in men with localized prostate cancer diagnosed before the era of prostate-specific antigen (PSA) testing
 - Only 12% had non-palpable (T1C) cancers
 - Mean PSA 13 ng/ml

18 YEAR FOLLOW-UP: DEATH FROM PROSTATE CANCER

Table 1. Cumulative Incidence, Absolute Risk Reduction, and Relative Risk of Death from Any Cause, Death from Prostate Cancer, and Development of Distant Metastases at 18 Years of Follow-up.*

End Point	Cumulative Incidence				Absolute Risk Reduction with Radical Prostatectomy	Relative Risk with Radical Prostatectomy (95% CI)	P Value
	Radical Prostatectomy (N=347)		Watchful Waiting (N=348)				
	no. of events	% (95% CI)	no. of events	% (95% CI)	percentage points (95% CI)		
Death from prostate cancer							
All	63	17.7 (14.0 to 22.4)	99	28.7 (24.2 to 34.2)	11.0 (4.5 to 17.5)	0.56 (0.41 to 0.77)	0.001
Age							
<65 yr	31	18.3 (13.1 to 25.7)	58	34.1 (27.3 to 42.5)	15.8 (6.0 to 25.5)	0.45 (0.29 to 0.69)	0.002
≥65 yr	32	17.3 (12.5 to 24.0)	41	23.9 (18.2 to 31.5)	6.6 (−2.1 to 15.2)	0.75 (0.47 to 1.19)	0.19

DEATH FROM PROSTATE CANCER: AGE STRATIFIED

Table 1. Cumulative Incidence, Absolute Risk Reduction, and Relative Risk of Death from Any Cause, Death from Prostate Cancer, and Development of Distant Metastases at 18 Years of Follow-up.*

End Point	Cumulative Incidence				Absolute Risk Reduction with Radical Prostatectomy	Relative Risk with Radical Prostatectomy (95% CI)	P Value
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≥65 yr	32	17.3 (12.5 to 24.0)	41	23.9 (18.2 to 31.5)	6.6 (−2.1 to 15.2)	0.75 (0.47 to 1.19)	0.19

TUMOR RISK

- Low risk
 - $\text{PSA} < 10$ and Gleason score < 7
- High risk
 - $\text{PSA} \geq 20$ or a Gleason score > 7
- Intermediate risk – everyone else
 - Gleason 7 with $\text{PSA} < 20$
 - Gleason < 7 with $\text{PSA} 10\text{-}20$

DEATH FROM PROSTATE CANCER: TUMOR RISK STRATIFIED

Table 1. Cumulative Incidence, Absolute Risk Reduction, and Relative Risk of Death from Any Cause, Death from Prostate Cancer, and Development of Distant Metastases at 18 Years of Follow-up.*

End Point	Cumulative Incidence				Absolute Risk Reduction with Radical Prostatectomy	Relative Risk with Radical Prostatectomy (95% CI)	P Value
	Radical Prostatectomy (N=347)		Watchful Waiting (N=348)				
	no. of events	% (95% CI)	no. of events	% (95% CI)	percentage points (95% CI)		
Tumor risk							
Low	11	10.2 (5.8 to 18.0)	20	14.0 (9.1 to 21.5)	3.8 (−4.6 to 12.2)	0.54 (0.26 to 1.13)	0.17
Intermediate	24	15.1 (10.2 to 22.2)	50	39.3 (31.3 to 49.3)	24.2 (13.6 to 34.9)	0.38 (0.23 to 0.62)	<0.001
High	28	33.1 (24.0 to 45.7)	29	35.7 (26.3 to 48.5)	2.6 (−12.7 to 17.8)	0.87 (0.52 to 1.46)	0.84

But remember palpable cancers have a worse prognosis than non-palpable cancers

18 YEAR FOLLOW-UP: ALL-CAUSE MORTALITY

Table 1. Cumulative Incidence, Absolute Risk Reduction, and Relative Risk of Death from Any Cause, Death from Prostate Cancer, and Development of Distant Metastases at 18 Years of Follow-up.*

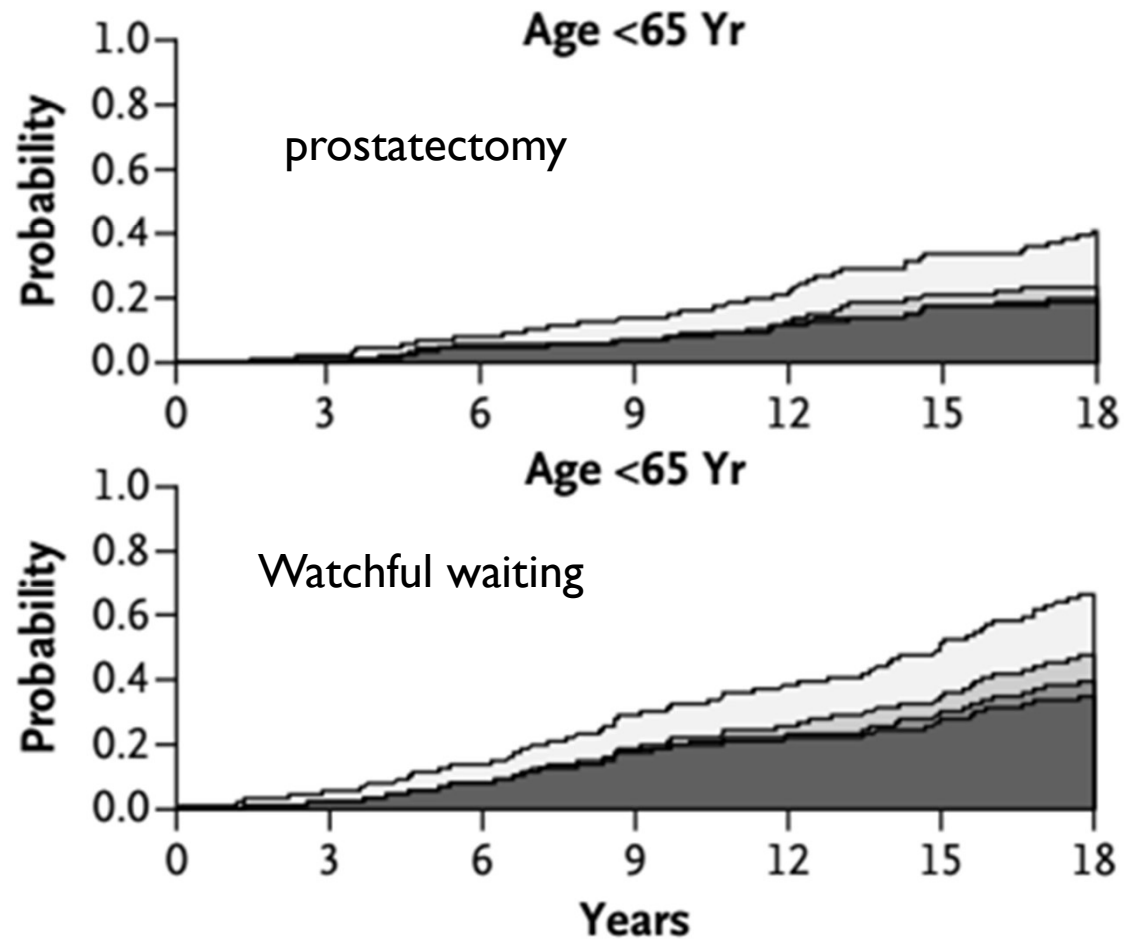
End Point	Cumulative Incidence				Absolute Risk Reduction with Radical Prostatectomy	Relative Risk with Radical Prostatectomy (95% CI)	P Value
	Radical Prostatectomy (N=347)		Watchful Waiting (N=348)				
	<i>no. of events</i>	<i>% (95% CI)</i>	<i>no. of events</i>	<i>% (95% CI)</i>			
Death from any cause					<i>percentage points (95% CI)</i>		
All	200	56.1 (50.9 to 62.0)	247	68.9 (63.8 to 74.3)	12.7 (5.1 to 20.3)	0.71 (0.59 to 0.86)	<0.001
Age							
<65 yr	69	40.0 (32.7 to 49.0)	112	65.6 (58.2 to 73.9)	25.5 (14.3 to 36.8)	0.50 (0.37 to 0.68)	<0.001
≥65 yr	131	69.8 (63.1 to 77.4)	135	71.7 (64.9 to 79.3)	1.9 (−8.2 to 12.0)	0.92 (0.73 to 1.18)	0.52

ALL-CAUSE MORTALITY: AGE STRATIFIED

Table 1. Cumulative Incidence, Absolute Risk Reduction, and Relative Risk of Death from Any Cause, Death from Prostate Cancer, and Development of Distant Metastases at 18 Years of Follow-up.*

End Point	Cumulative Incidence				Absolute Risk Reduction with Radical Prostatectomy	Relative Risk with Radical Prostatectomy (95% CI)	P Value
	Radical Prostatectomy (N=347)		Watchful Waiting (N=348)				
	<i>no. of events</i>	<i>% (95% CI)</i>	<i>no. of events</i>	<i>% (95% CI)</i>			
	<i>percentage points (95% CI)</i>						
Death from any cause							
All	200	56.1 (50.9 to 62.0)	247	68.9 (63.8 to 74.3)	12.7 (5.1 to 20.3)	0.71 (0.59 to 0.86)	<0.001
Age							
<65 yr	69	40.0 (32.7 to 49.0)	112	65.6 (58.2 to 73.9)	25.5 (14.3 to 36.8)	0.50 (0.37 to 0.68)	<0.001
≥65 yr	131	69.8 (63.1 to 77.4)	135	71.7 (64.9 to 79.3)	1.9 (−8.2 to 12.0)	0.92 (0.73 to 1.18)	0.52

No. at Risk 347 339 311 271 236 168 87



■ Death from prostate cancer ■ Other cause of death, with metastases ■ Other cause of death, with androgen-deprivation therapy ■ Other cause of death, without androgen-deprivation therapy

WHAT DO WE LEARN FROM SPCG-4?

- Some men with prostate cancer will benefit from radical prostatectomy
 - Age < 65 yrs
 - Intermediate risk non-screen detected cancer
 - Almost all palpable
- Absolute mortality difference increases with time, especially after 10 years
- Difference does impact all-cause mortality
- Low risk prostate cancer - Even non-screen detected - has a good prognosis with watchful waiting:
 - 14% 18 year mortality

Original Article

Follow-up of Prostatectomy versus Observation for Early Prostate Cancer

Timothy J. Wilt, M.D., M.P.H., Karen M. Jones, M.S., Michael J. Barry, M.D., Gerald L. Andriole, M.D., Daniel Culkin, M.D., Thomas Wheeler, M.D., William J. Aronson, M.D., and Michael K. Brawer, M.D.

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DOI: 10.1056/NEJMoa1615869

WHO? WHAT?

- PIVOT trial was an RCT of radical prostatectomy vs observation in 731 men enrolled 1994-2002
 - Age < 75 yrs, median 67 yrs
 - Mean PSA 7.8 ng/ml
 - 50% T1C (screen detected)
- Clinically localized prostate cancer
 - stage T1-T2NxM0
- Minimum 12 maximum 19.5 years follow-up

FIGURE 1. KAPLAN–MEIER PLOT ALL-CAUSE MORTALITY

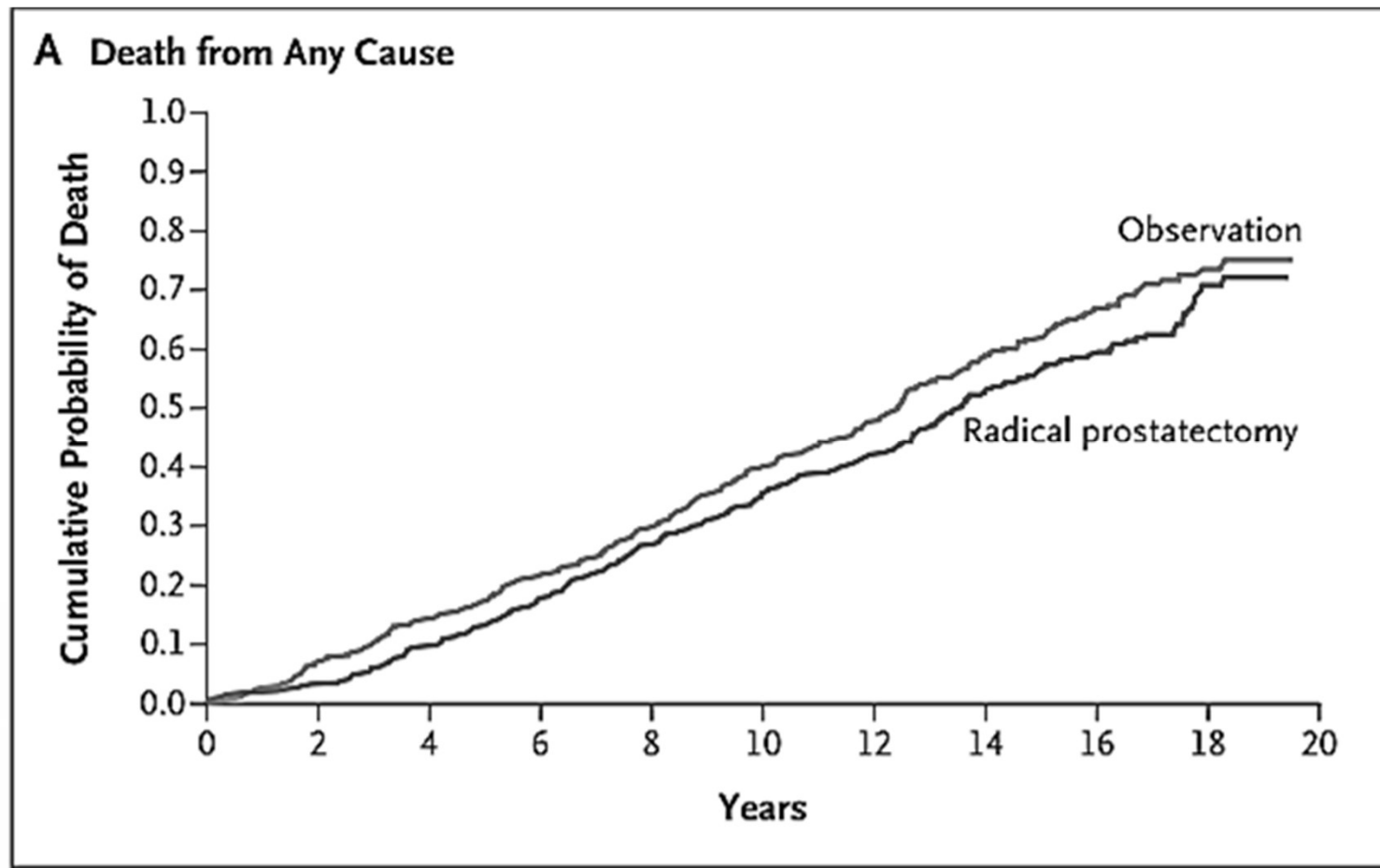


FIGURE 1. KAPLAN–MEIER PLOT PROSTATE CANCER MORTALITY

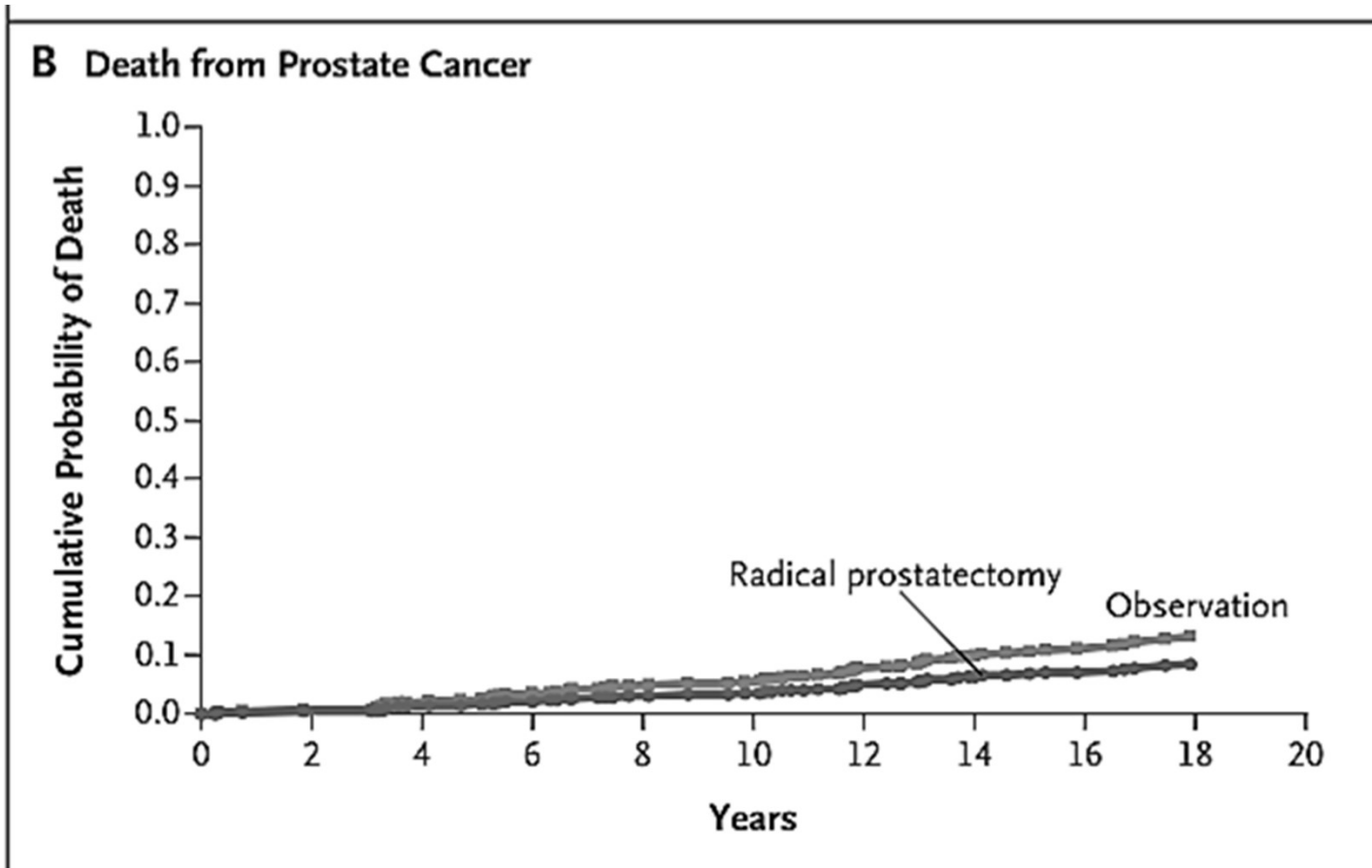


Table 1. Cumulative Incidence of Death from Any Cause through 19.5 Years.*

Variable	Radical Prostatectomy		Observation		Absolute Difference in Risk (95% CI)	Relative Risk (95% CI)
	No. of Events/ Total No.	% (95% CI)	No. of Events/ Total No.	% (95% CI)		
Overall	223/364	61.3 (56.2 to 66.1)	245/367	66.8 (61.8 to 71.4)	5.5 (−1.5 to 12.4)	0.92 (0.82 to 1.02)
Age at diagnosis					<i>percentage points</i>	
<65 yr	58/122	47.5 (38.9 to 56.3)	78/131	59.5 (51.0 to 67.6)	12.0 (−0.3 to 23.8)	0.80 (0.63 to 1.01)
≥65 yr	165/242	68.2 (62.1 to 73.7)	167/236	70.8 (64.7 to 76.2)	2.6 (−5.7 to 10.8)	0.96 (0.86 to 1.09)
Race†						
White	150/232	64.7 (58.3 to 70.5)	155/220	70.5 (64.1 to 76.1)	5.8 (−2.8 to 14.3)	0.92 (0.81 to 1.04)
Black	64/111	57.7 (48.4 to 66.4)	75/121	62.0 (53.1 to 70.1)	4.3 (−8.2 to 16.7)	0.93 (0.75 to 1.15)
PSA						
≤10 ng/ml	140/238	58.8 (52.5 to 64.9)	151/241	62.7 (56.4 to 68.5)	3.8 (−4.9 to 12.5)	0.94 (0.81 to 1.08)
>10 ng/ml	83/126	65.9 (57.2 to 73.6)	93/125	74.4 (66.1 to 81.2)	8.5 (−2.8 to 19.6)	0.89 (0.75 to 1.04)
Risk category‡						
Locally assessed						
Low	82/148	55.4 (47.4 to 63.2)	83/148	56.1 (48.0 to 63.8)	0.7 (−10.5 to 11.8)	0.99 (0.81 to 1.21)
Intermediate	77/129	59.7 (51.1 to 67.8)	89/120	74.2 (65.7 to 81.2)	14.5 (2.8 to 25.6)	0.80 (0.67 to 0.96)
High	55/77	71.4 (60.5 to 80.3)	59/80	73.8 (63.2 to 82.1)	2.3 (−11.5 to 16.1)	0.97 (0.80 to 1.17)
Centrally assessed						
Low	58/111	52.3 (43.0 to 61.3)	67/122	54.9 (46.1 to 63.5)	2.7 (−10.0 to 15.2)	0.95 (0.75 to 1.21)
Intermediate	97/155	62.6 (54.7 to 69.8)	99/139	71.2 (63.2 to 78.1)	8.6 (−2.2 to 19.1)	0.88 (0.75 to 1.03)
High	55/78	70.5 (59.6 to 79.5)	63/85	74.1 (63.9 to 82.2)	3.6 (−10.0 to 17.2)	0.95 (0.79 to 1.15)

* PSA denotes prostate-specific antigen.

† Race was reported by the participants.

‡ The risk category was determined according to the D'Amico risk score, which is based on tumor stage, histologic score, and PSA level.

Table 1. Cumulative Incidence of Death from Any Cause through 19.5 Years.*

Variable	Radical Prostatectomy		Observation		Absolute Difference in Risk (95% CI)	Relative Risk (95% CI)
	No. of Events/ Total No.	% (95% CI)	No. of Events/ Total No.	% (95% CI)		
					<i>percentage points</i>	
Overall	223/364	61.3 (56.2 to 66.1)	245/367	66.8 (61.8 to 71.4)	5.5 (−1.5 to 12.4)	0.92 (0.82 to 1.02)
Age at diagnosis						
<65 yr	58/122	47.5 (38.9 to 56.3)	78/131	59.5 (51.0 to 67.6)	12.0 (−0.3 to 23.8)	0.80 (0.63 to 1.01)
≥65 yr	165/242	68.2 (62.1 to 73.7)	167/236	70.8 (64.7 to 76.2)	2.6 (−5.7 to 10.8)	0.96 (0.86 to 1.09)
Race†						
White	150/232	64.7 (58.3 to 70.5)	155/220	70.5 (64.1 to 76.1)	5.8 (−2.8 to 14.3)	0.92 (0.81 to 1.04)
Black	64/111	57.7 (48.4 to 66.4)	75/121	62.0 (53.1 to 70.1)	4.3 (−8.2 to 16.7)	0.93 (0.75 to 1.15)
PSA						
≤10 ng/ml	140/238	58.8 (52.5 to 64.9)	151/241	62.7 (56.4 to 68.5)	3.8 (−4.9 to 12.5)	0.94 (0.81 to 1.08)
>10 ng/ml	83/126	65.9 (57.2 to 73.6)	93/125	74.4 (66.1 to 81.2)	8.5 (−2.8 to 19.6)	0.89 (0.75 to 1.04)
Risk category‡						
Locally assessed						
Low	82/148	55.4 (47.4 to 63.2)	83/148	56.1 (48.0 to 63.8)	0.7 (−10.5 to 11.8)	0.99 (0.81 to 1.21)
Intermediate	77/129	59.7 (51.1 to 67.8)	89/120	74.2 (65.7 to 81.2)	14.5 (2.8 to 25.6)	0.80 (0.67 to 0.96)
High	55/77	71.4 (60.5 to 80.3)	59/80	73.8 (63.2 to 82.1)	2.3 (−11.5 to 16.1)	0.97 (0.80 to 1.17)
Centrally assessed						
Low	58/111	52.3 (43.0 to 61.3)	67/122	54.9 (46.1 to 63.5)	2.7 (−10.0 to 15.2)	0.95 (0.75 to 1.21)
Intermediate	97/155	62.6 (54.7 to 69.8)	99/139	71.2 (63.2 to 78.1)	8.6 (−2.2 to 19.1)	0.88 (0.75 to 1.03)
High	55/78	70.5 (59.6 to 79.5)	63/85	74.1 (63.9 to 82.2)	3.6 (−10.0 to 17.2)	0.95 (0.79 to 1.15)

* PSA denotes prostate-specific antigen.

† Race was reported by the participants.

‡ The risk category was determined according to the D'Amico risk score, which is based on tumor stage, histologic score, and PSA level.

DEATH FROM PROSTATE CANCER

Table 2. Cumulative Incidence of Death from Prostate Cancer through 19.5 Years.

Variable	Radical Prostatectomy		Observation		Absolute Difference in Risk (95% CI)	Relative Risk (95% CI)
	No. of Events/ Total No.	% (95% CI)	No. of Events/ Total No.	% (95% CI)		
Overall	27/364	7.4 (5.2 to 10.6)	42/367	11.4 (8.6 to 15.1)	4.0 (–0.2 to 8.3)	0.65 (0.41 to 1.03)
Age at diagnosis						

percentage points

Recall in
SPCG-4 that
was 28.7%

Table 2. Cumulative Incidence of Death from Prostate Cancer through 19.5 Years.

Variable	Radical Prostatectomy		Observation		Absolute Difference in Risk (95% CI)	Relative Risk (95% CI)
	No. of Events/ Total No.	% (95% CI)	No. of Events/ Total No.	% (95% CI)		
Overall	27/364	7.4 (5.2 to 10.6)	42/367	11.4 (8.6 to 15.1)	4.0 (−0.2 to 8.3)	0.65 (0.41 to 1.03)
Age at diagnosis					<i>percentage points</i>	
<65 yr	9/122	7.4 (3.9 to 13.4)	15/131	11.5 (7.1 to 18.0)	4.1 (−3.4 to 11.5)	0.64 (0.29 to 1.42)
≥65 yr	18/242	7.4 (4.8 to 11.5)	27/236	11.4 (8.0 to 16.1)	4.0 (−1.3 to 9.4)	0.65 (0.37 to 1.15)
Race						
White	17/232	7.3 (4.6 to 11.4)	28/220	12.7 (9.0 to 17.8)	5.4 (−0.2 to 11.1)	0.58 (0.32 to 1.02)
Black	8/111	7.2 (3.7 to 13.6)	11/121	9.1 (5.2 to 15.6)	1.9 (−5.6 to 9.2)	0.79 (0.33 to 1.90)
PSA						
≤10 ng/ml	16/238	6.7 (4.2 to 10.6)	23/241	9.5 (6.4 to 13.9)	2.8 (−2.2 to 7.9)	0.70 (0.38 to 1.30)
>10 ng/ml	11/126	8.7 (4.9 to 15.0)	19/125	15.2 (10.0 to 22.5)	6.5 (−1.7 to 14.7)	0.57 (0.29 to 1.16)
Risk category						
Locally assessed						
Low	6/148	4.1 (1.9 to 8.6)	8/148	5.4 (2.8 to 10.3)	1.4 (−3.9 to 6.7)	0.75 (0.27 to 2.11)
Intermediate	11/129	8.5 (4.8 to 14.6)	19/120	15.8 (10.4 to 23.4)	7.3 (−0.9 to 15.7)	0.54 (0.27 to 1.08)
High	10/77	13.0 (7.2 to 22.3)	15/80	18.8 (11.7 to 28.7)	5.8 (−5.9 to 17.2)	0.69 (0.33 to 1.45)
Centrally assessed						
Low	1/111	0.9 (0.2 to 4.9)	8/122	6.6 (3.4 to 12.4)	5.7 (0.5 to 11.6)	0.14 (0.02 to 1.08)
Intermediate	14/155	9.0 (5.5 to 14.6)	12/139	8.6 (5.0 to 14.5)	−0.4 (−7.0 to 6.5)	1.05 (0.50 to 2.18)
High	10/78	12.8 (7.1 to 22.0)	20/85	23.5 (15.8 to 33.6)	10.7 (−1.3 to 22.3)	0.54 (0.27 to 1.09)

Table 2. Cumulative Incidence of Death from Prostate Cancer through 19.5 Years.						
Variable	Radical Prostatectomy		Observation		Absolute Difference in Risk (95% CI)	Relative Risk (95% CI)
	No. of Events/ Total No.	% (95% CI)	No. of Events/ Total No.	% (95% CI)	<i>percentage points</i>	
Overall	27/364	7.4 (5.2 to 10.6)	42/367	11.4 (8.6 to 15.1)	4.0 (−0.2 to 8.3)	0.65 (0.41 to 1.03)
Age at diagnosis						
<65 yr	9/122	7.4 (3.9 to 13.4)	15/131	11.5 (7.1 to 18.0)	4.1 (−3.4 to 11.5)	0.64 (0.29 to 1.42)
≥65 yr	18/242	7.4 (4.8 to 11.5)	27/236	11.4 (8.0 to 16.1)	4.0 (−1.3 to 9.4)	0.65 (0.37 to 1.15)
Race						
White	17/232	7.3 (4.6 to 11.4)	28/220	12.7 (9.0 to 17.8)	5.4 (−0.2 to 11.1)	0.58 (0.32 to 1.02)
Black	8/111	7.2 (3.7 to 13.6)	11/121	9.1 (5.2 to 15.6)	1.9 (−5.6 to 9.2)	0.79 (0.33 to 1.90)
PSA						
≤10 ng/ml	16/238	6.7 (4.2 to 10.6)	23/241	9.5 (6.4 to 13.9)	2.8 (−2.2 to 7.9)	0.70 (0.38 to 1.30)
>10 ng/ml	11/126	8.7 (4.9 to 15.0)	19/125	15.2 (10.0 to 22.5)	6.5 (−1.7 to 14.7)	0.57 (0.29 to 1.16)
Risk category						
Locally assessed						
Low	6/148	4.1 (1.9 to 8.6)	8/148	5.4 (2.8 to 10.3)	1.4 (−3.9 to 6.7)	0.75 (0.27 to 2.11)
Intermediate	11/129	8.5 (4.8 to 14.6)	19/120	15.8 (10.4 to 23.4)	7.3 (−0.9 to 15.7)	0.54 (0.27 to 1.08)
High	10/77	13.0 (7.2 to 22.3)	15/80	18.8 (11.7 to 28.7)	5.8 (−5.9 to 17.2)	0.69 (0.33 to 1.45)
Centrally assessed						
Low	1/111	0.9 (0.2 to 4.9)	8/122	6.6 (3.4 to 12.4)	5.7 (0.5 to 11.6)	0.14 (0.02 to 1.08)
Intermediate	14/155	9.0 (5.5 to 14.6)	12/139	8.6 (5.0 to 14.5)	−0.4 (−7.0 to 6.5)	1.05 (0.50 to 2.18)
High	10/78	12.8 (7.1 to 22.0)	20/85	23.5 (15.8 to 33.6)	10.7 (−1.3 to 22.3)	0.54 (0.27 to 1.09)

Table 3. Disease Progression and Treatment for Disease Progression or Adverse Events (Original Follow-up).

Variable	Radical Prostatectomy (N=364) <i>number (percent)</i>	Observation (N=367)	Absolute Difference (95% CI) <i>percentage points</i>	Hazard Ratio (95% CI)
Treatment for disease progression†				
For any reason	122 (33.5)	219 (59.7)	26.2 (19.0 to 32.9)	0.45 (0.36 to 0.56)
For increasing or persistently elevated PSA value	74 (20.3)	139 (37.9)	17.5 (11.0 to 23.9)	0.46 (0.34 to 0.61)
For local progression	45 (12.4)	93 (25.3)	13.0 (7.3 to 18.5)	0.44 (0.31 to 0.63)
For regional progression	2 (0.5)	3 (0.8)	0.3 (−1.3 to 1.9)	0.64 (0.11 to 3.82)
For systemic progression	17 (4.7)	32 (8.7)	4.0 (0.4 to 7.8)	0.49 (0.27 to 0.88)
Adverse events requiring treatment‡				
Erectile dysfunction	53 (14.6)	20 (5.4)	−9.1 (−13.5 to −4.8)	2.77 (1.65 to 4.63)
Incontinence	63 (17.3)	16 (4.4)	−12.9 (−17.5 to −8.6)	4.22 (2.44 to 7.30)
Other	45 (12.4)	41 (11.2)	−1.2 (−5.9 to 3.5)	1.08 (0.71 to 1.65)

WHAT DO WE LEARN FROM PIVOT?

- After almost 20 years, prostatectomy did not have a statistically significant effect on all-cause mortality
- Surgery was associated with a higher frequency of adverse events than observation but a lower frequency of treatment for disease progression, mostly for asymptomatic, local, or biochemical progression

Original Article

10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer

F.C. Hamdy, J.L. Donovan, J.A. Lane, M. Mason, C. Metcalfe, P. Holding, M. Davis, T.J. Peters, E.L. Turner, R.M. Martin, J. Oxley, M. Robinson, J. Staffurth, E. Walsh, P. Bollina, J. Catto, A. Doble, A. Doherty, D. Gillatt, R. Kockelbergh, H. Kynaston, A. Paul, P. Powell, S. Prescott, D.J. Rosario, E. Rowe, and D.E. Neal, for the ProtecT Study Group*.

n engl j med 375;15 nejm.org October 13, 2016

WHO? WHAT?

- The ongoing Comparison Arm for ProtecT (CAP) cluster RCT evaluates prostate cancer screening effectiveness
- Primary care centers allocated to a round of PSA testing (intervention) or standard clinical care. Over 550 centres (around 450,000 men) were randomised in eight United Kingdom areas (2002–2008).
- Intervention group participants were also eligible for the ProtecT RCT

WHO? WHAT?

- ProtecT RCT evaluated active monitoring, radiotherapy and radical prostatectomy treatments for localised prostate cancer
- Between 1999 and 2009, a total of 82,429 men 50 to 69 years of age received a PSA test:
 - 2664 received a diagnosis of *localized prostate cancer*
 - 1643 agreed to undergo randomization to active monitoring (545), surgery (553), or radiotherapy (545)

WHO?

- Median age 62 years (range, 50 to 69)
- Median PSA level at the prostate-check clinic was 4.6 ng per milliliter (range, 3.0 to 19.9)
- 77% had tumors with a Gleason score of 6, ~20% Gleason 7.
- 76% had stage T1c disease (PSA detected, non-palpable)
 - Remainder T2 – confined within the gland, present in one or both lobes by needle biopsy, and palpable by digital rectal examination or visible by imaging

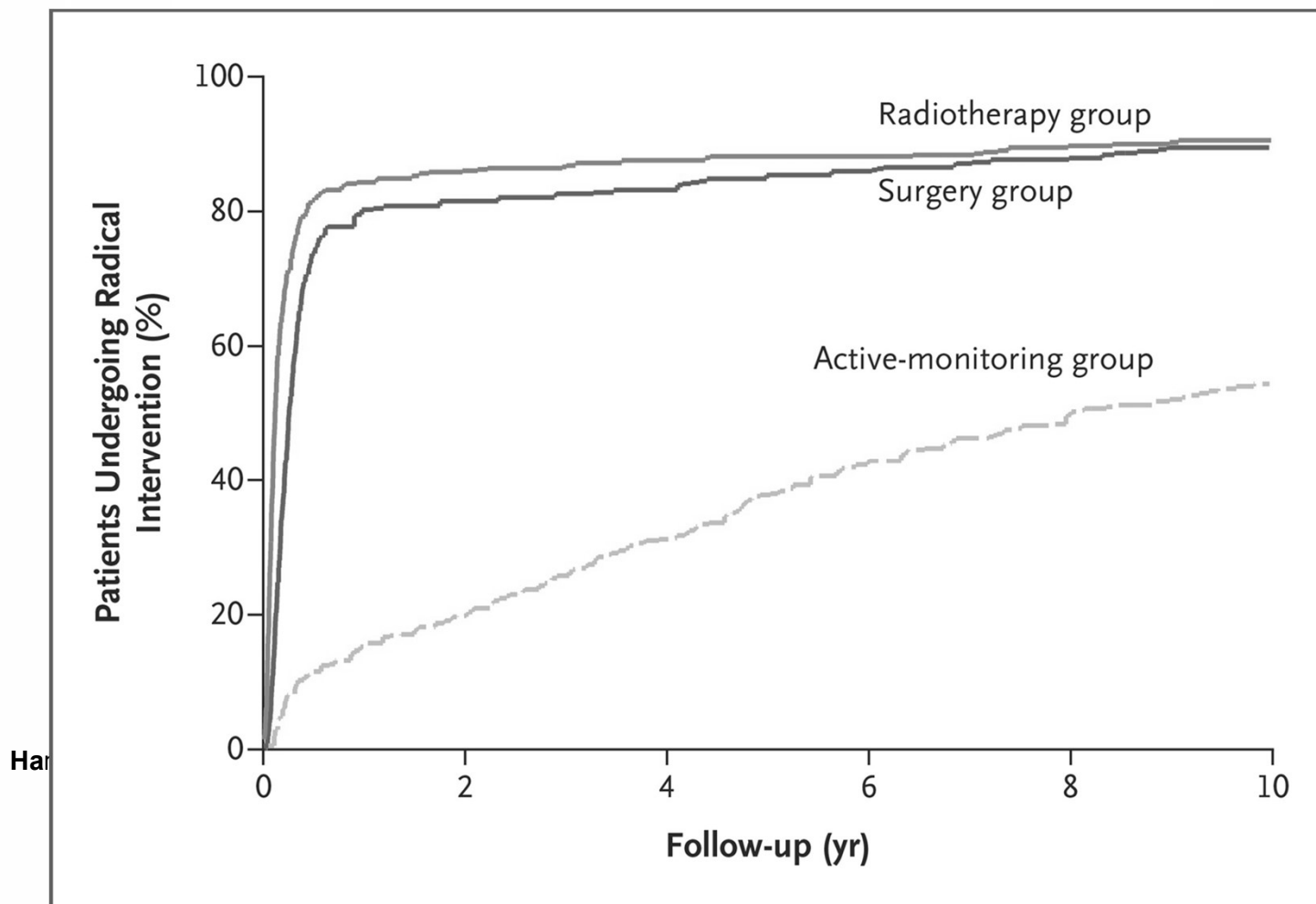
ACTIVE MONITORING

- Serum PSA levels
 - Every 3 months in the first year and every 6 to 12 months thereafter.
 - An increase of at least 50% during the previous 12 months triggered a review
- SPCG-4 and PIVOT used watchful waiting
- “Active surveillance” in U.S. usually includes DRE and periodic biopsy

WHO? WHAT?

- ProtecT RCT chose prostate cancer specific mortality as primary end point
- Secondary end points
 - All-cause mortality
 - Rates of metastases, clinical progression, primary treatment failure, and treatment complications.
 - Metastatic disease was defined as bony, visceral, or lymph-node metastases on imaging or PSA levels above 100 ng per milliliter.

Kaplan–Meier Estimates of the Cumulative Probability of Undergoing Radical Intervention during the Follow-up Period, According to Treatment Group.



PROSTATE CANCER MORTALITY

Variable	Active Monitoring (N=545)	Surgery (N=553)	Radiotherapy (N=545)	P Value*
Prostate-cancer mortality				
Total person-yr in follow-up	5393	5422	5339	
No. of deaths due to prostate cancer†	8	5	4	
Prostate-cancer-specific survival — % (95% CI)†				
At 5 yr	99.4 (98.3–99.8)	100	100	
At 10 yr	98.8 (97.4–99.5)	99.0 (97.2–99.6)	99.6 (98.4–99.9)	
Prostate-cancer deaths per 1000 person-yr (95% CI)†	1.5 (0.7–3.0)	0.9 (0.4–2.2)	0.7 (0.3–2.0)	0.48

OUTCOMES

Variable	Active Monitoring (N=545)	Surgery (N=553)	Radiotherapy (N=545)	P Value*
Incidence of clinical progression‡				
Person-yr of follow-up free of clinical progression	4893	5174	5138	
No. of men with clinical progression	112	46	46	
Clinical progression per 1000 person-yr (95% CI)	22.9 (19.0–27.5)	8.9 (6.7–11.9)	9.0 (6.7–12.0)	<0.001
Incidence of metastatic disease				
Person-yr of follow-up free of metastatic disease	5268	5377	5286	
No. of men with metastatic disease	33	13	16	
Metastatic disease per 1000 person-yr (95% CI)	6.3 (4.5–8.8)	2.4 (1.4–4.2)	3.0 (1.9–4.9)	0.004

OUTCOMES

Variable	Active Monitoring (N=545)	Surgery (N=553)	Radiotherapy (N=545)	P Value*
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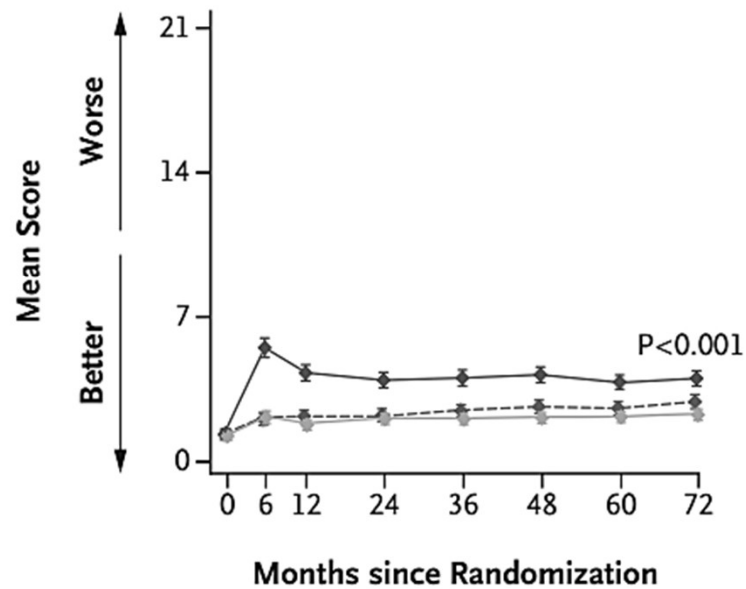
ALL-CAUSE MORTALITY

Variable	Active Monitoring (N=545)	Surgery (N=553)	Radiotherapy (N=545)	P Value*
All-cause mortality				
Total person-yr in follow-up	5393	5422	5339	
No. of deaths due to any cause	59	55	55	
All-cause deaths per 1000 person-yr (95% CI)	10.9 (8.5–14.1)	10.1 (7.8–13.2)	10.3 (7.9–13.4)	0.87

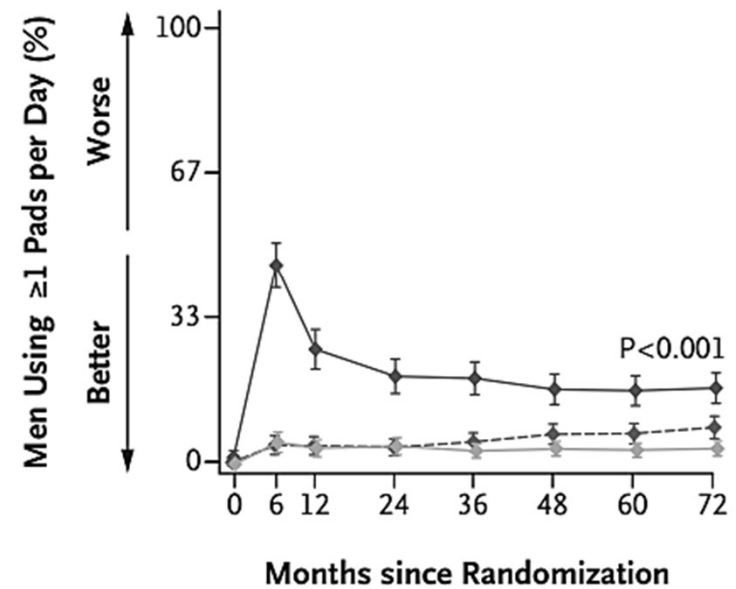
PIVOT at 10 years
all-cause mortality
approaching 40%

URINARY OUTCOMES

A ICIQ Incontinence Score

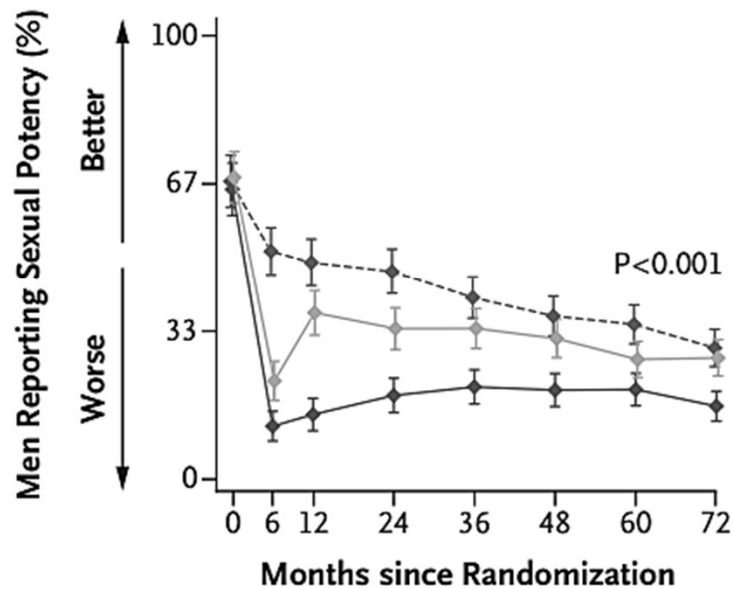


B EPIC Item: ≥ 1 Pad per Day

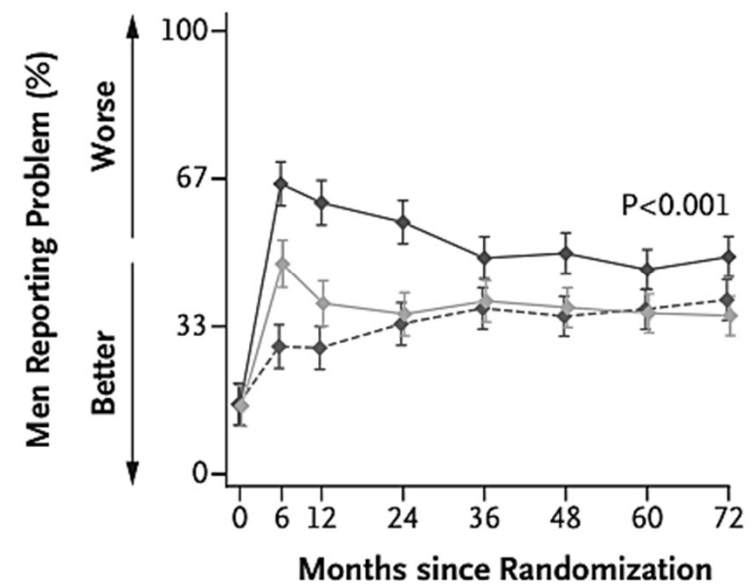


SEXUAL OUTCOMES

A EPIC Item: Erection Firmness

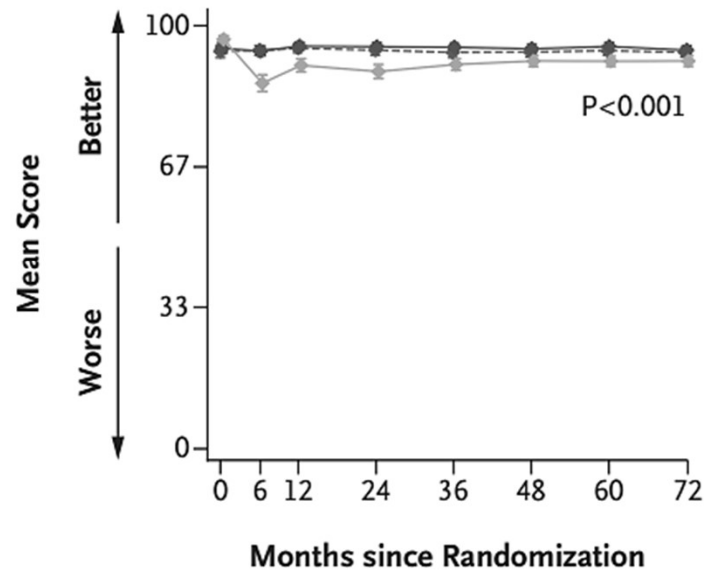


B EPIC Problem with Erectile Dysfunction

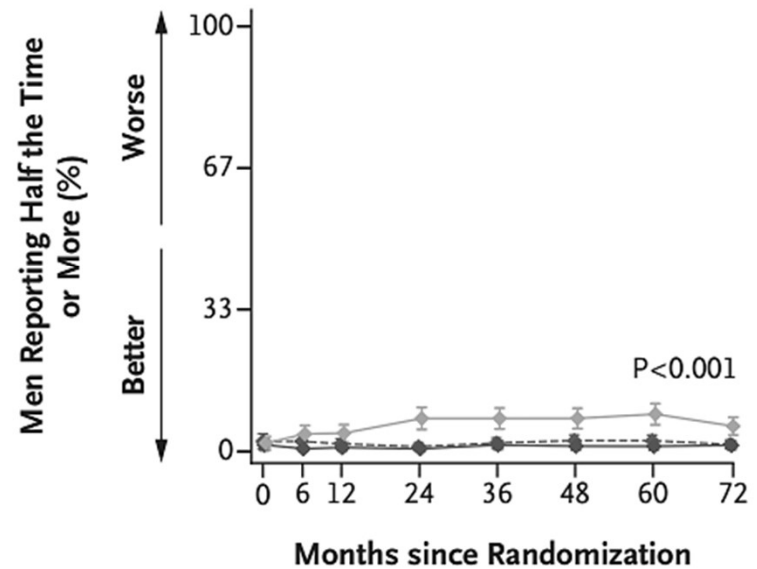


BOWEL OUTCOMES

B EPIC Bowel Bother Score



E EPIC Item: Bloody Stools



391 PROSTATECTOMIES

- No deaths related to surgery
- 9 men had thromboembolic or cardiovascular events
- 14 required transfusion of more than 3 units of blood,
- 1 had a rectal injury
- 9 required intervention for anastomotic problems.

WHAT DO WE LEARN FROM PROTECT?

- Treatment of clinically localized low risk prostate cancer does not make it less likely that men will die of prostate cancer in 10 years when compared to active monitoring with PSA levels
- ~50% with active monitoring will remain untreated at 10 years (may not be comparable to “active surveillance”)
- Side effects dependent upon treatment

RCT OF SCREENING FOR PROSTATE CANCER

NEW TRIALS?

- No new trials
- Updated results from PLCO and ERSPC
- Awaiting CAP-ProtecT

ASSESSMENT OF BENEFITS

- USPSTF and others focused heavily on results of the two major RCTs
 - ERSPC
 - PLCO
- Remaining 4 trials not of sufficient quality

Extended mortality results for prostate cancer screening in the PLCO trial with median follow-up of 15 years

Paul F. Pinsky PhD, Philip C. Prorok PhD, Kelly Yu PhD, Barnett S. Kramer MD, MPH, Amanda Black PhD, John K. Gohagan PhD, E. David Crawford MD, Robert L. Grubb MD, Gerald L. Andriole MD

Cancer, 123: 592–599. doi:10.1002/cncr.30474

PLCO

- Large U.S. trial of screening
- Community based Rx rather than a specific treatment protocol – so treatment differential between screened and control groups should be reduced or eliminated
- Median follow-up 14.8 years

PLCO: MAJOR CRITIQUE

CROSSOVER

Appendix E Table 1. Use of PSA by Study Arm During the Screening Phase of the PLCO Trial

Time period of latest test	Study Arm		
	Control*		Screening [†]
	Routine Screening PSA, %	PSA for Any Purpose, %	Routine Screening, %
<1 year	46	52	78
1-2 years	14	16	8
2-3 years	5	6	3
>3 years	4	4	2
Never tested for any reason	21		9

Note: table adapted from Pinsky et al (2010)

*Based on annual surveys of control arm subjects during years 0 to 5 of the trial (N=2225; range per study year 181-435)

†Based on adherence to trial screening protocol

“It was estimated that 86% of the men in the control arm and 99% of the men in the intervention arm received any PSA testing during the trial, and the estimated yearly screening-phase PSA testing rates were 46% and 84%, respectively.”

PLCO: SUMMARY 2016

Screened group

- n=38,343
- 255 prostate cancer deaths
- 47.8 per 10^5 person years

Control group

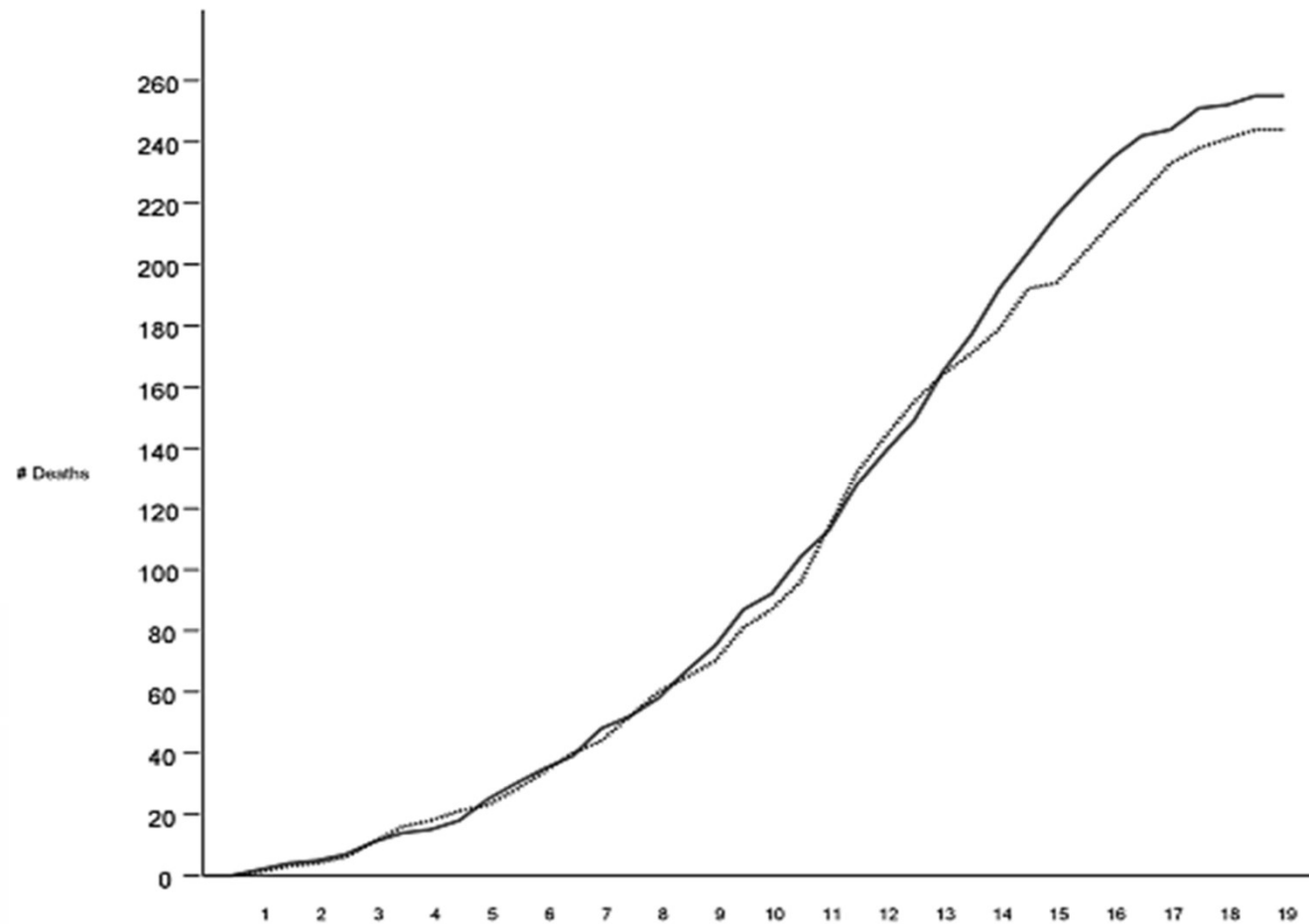
- n=38,350
- 244 prostate cancer deaths
- 46.0 per 10^5 person-years

Active treatment (surgery, radiation, hormonal)

89% of screening group

90% of control group

DEATHS FROM PROSTATE CANCER BY ARM AND YEARS FROM RANDOMIZATION (PER 10⁵ PERSON -YRS).



WHAT DO WE LEARN FROM PLCO?

- Safe conclusion: Systematic screening for prostate cancer did not lower prostate cancer mortality after 15 years when compared to opportunistic screening

Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up

Fritz H Schröder, Jonas Hugosson, Monique J Roobol, Teuvo L J Tammela, Marco Zappa, Vera Nelen, Maciej Kwiatkowski, Marcos Lujan, Liisa Määttänen, Hans Lilja, Louis J Denis, Franz Recker, Alvaro Paez, Chris H Bangma, Sigrid Carlsson, Donella Puliti, Arnaud Villers, Xavier Rebillard, Matti Hakama, Ulf-Hakan Stenman, Paula Kujala, Kimmo Taari, Gunnar Aus, Andreas Huber, Theo H van der Kwast, Ron H N van Schaik, Harry J de Koning, Sue M Moss, Anssi Auvinen, for the ERSPC Investigators*

Lancet 2014; 384: 2027–35

EUROPEAN TRIAL (ERSPC)

- Actually seven different studies (plus Portugal and France)

- Finland
- Netherlands
- Italy
- Switzerland
- Belgium
- Sweden
- Spain

Variations across study centers included:

Randomization/consent procedures

Screening intervals (2-7 years)

PSA cutpoints (2.5 – 4.0)

RESULTS: ERSPC AGE 55-69

- Initial treatment
 - 69% surgery or radiation
 - 13% hormonal tx
 - 18% active surveillance

UPDATED ERSPC RESULTS (2014)

- Reported data for age 55-69 years subgroup
- Analysis truncated at 13 years
- Rate ratio for prostate cancer mortality
 - 0.85 (0.70, 1.03) after 9 years
 - 0.78 (0.66, 0.91) after 11 years
 - 0.79 (0.69, 0.91) at 13 years

UPDATED ERSPC RESULTS (2014)

- Absolute risk reduction of death from prostate cancer at 13 years
 - 0.11 per 1000 person-years or 1.28 per 1000 men randomized,
 - One prostate cancer death averted per 781 (95% CI 490–1929) men invited for screening

Cumulative Hazard of Death from Prostate Cancer among Men 55 to 69 Years of Age.

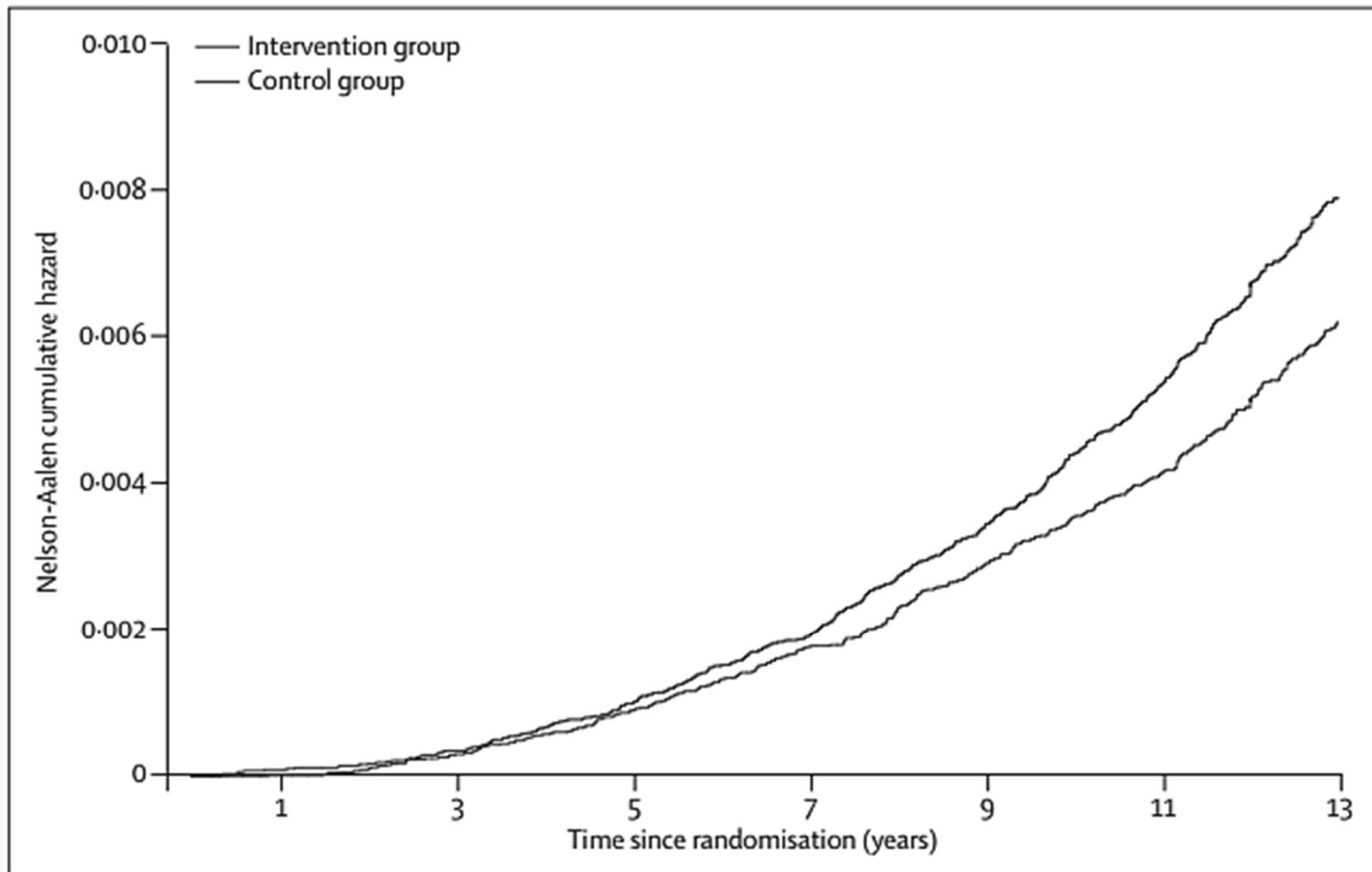


Figure 2: Nelson-Aalen estimates of cumulative prostate cancer mortality (all centres, excluding France)

MULTI-CENTERED STUDY

- An analysis of prostate cancer mortality in the intervention and control groups in the core age group of individual centers showed significant RRs only for:
 - Sweden: 0.62 (0.41, 0.92)
 - Netherlands: 0.67 (0.51, 0.88)

OVERDIAGNOSIS REMAINS A PROBLEM

	Intervention group			Control group			Rate ratio* (95% CI)	Rate difference per 1000 person-years* (95% CI)	Rate difference per 1000 men*
	Prostate cancer (n)	Person- years	Rate per 1000 person- years	Prostate cancer (n)	Person- years	Rate per 1000 person- years			
Years 1–9 including France	7902	835 353	9.46	5726	984 993	5.81	1.64 (1.58–1.69)	3.69 (3.42–3.95)	26.5
Years 1–9	6147	585 627	10.50	4127	736 688	5.60	1.91 (1.83–1.99)	5.00 (4.68–5.32)	39.0
Years 1–11	6797	692 186	9.82	5262	873 415	6.02	1.66 (1.60–1.73)	3.90 (3.61–4.20)	35.5
Years 1–13	7408	775 527	9.55	6107	980 474	6.23	1.57 (1.51–1.62)	3.44 (3.16–3.72)	34.8

*Control group for Finland weighted by 1:1.5.

Table 2: Prostate cancer incidence in the intervention and control groups during three time periods truncated (all centres, core age group, France excluded except for years 1–9)

One prostate cancer death averted per 27
additional prostate cancers detected

NO DIFFERENCE IN ALL-CAUSE MORTALITY

	Intervention group			Control group			Rate ratio (95% CI)	p value
	Deaths (n)	Person-years	Rate per 1000 person-years	Deaths (n)	Person-years	Rate per 1000 person-years		
All-cause mortality								
Core age group	15369	825018	18.6	19108	1011192	18.9	1.00 (0.98–1.02)	0.82
All ages	18251	935185	19.5	21992	1120432	19.6	1.00 (0.98–1.02)	0.98

WHAT ABOUT MORBIDITY?

- ERSPC reported metastatic disease rates from four of seven centers.
- 30% relative reduction (3.1 per 1000 randomized)
- Metastatic disease includes disease diagnosed by imaging or high PSA – impact on non-treatment related morbidity or longer-term mortality uncertain

WHAT DO WE LEARN FROM ERSPC?

- Screening *may* reduce mortality from prostate cancer
 - Benefit is small
 - Benefit is delayed 5-10 years
 - Overdiagnosis and thus overtreatment remain vexing problems
- At 13 years, men are not more likely to be alive if screened than if not screened

ERSPC INVESTIGATORS CONCLUSION:

“Greater absolute benefit from PSA screening at 13 years of follow-up in the ERSPC trial not sufficient to justify population-based screening”

ERSPC INVESTIGATORS

CONCLUSION

- In the present situation, early diagnosis cannot be refused to men who are well informed and request to be tested.
- Information must concentrate on the occurrence of overdiagnosis, which is also the main target of future research. Multiparametric MRI and the developments of new markers are the hope for the future.
- In the meantime available instruments with multivariate risk stratification must be applied.

BENEFIT OF SCREENING – PENDING CAP RESULTS

- Yogi Berra
 - “It's tough to make predictions, especially about the future.”
- I predict the CAP screening trial will show no benefit or smaller benefit than ERSPC

BUT WHY NOT SCREEN?

**WHAT HARM FROM A SIMPLE BLOOD
TEST?**

HARMS OF DIAGNOSIS

- 80% false positive rate, i.e. 80% of elevated PSA values do not result in dx of cancer
 - Further increase in testing
 - Anxiety

HARMS OF DIAGNOSIS

- Biopsy
 - About 1/3 of men who have a biopsy experience pain, fever, bleeding, infection, transient urinary difficulties or other issues that are considered a moderate or major problem
 - 4% will be hospitalized with complications

HARMS OF TREATMENT: OVERDIAGNOSIS

- Men who are screened are more likely to be diagnosed with and treated for cancer than men who are not screened
- Although men who are not screened will also experience treatment complications, they will occur in fewer men, later in life

HOW OFTEN IS EACH TREATMENT USED?

- I don't know – some evidence for increasing use of active surveillance

PRIMARY CARE RESPONSIBILITY

- Should you offer PSA screening on a population level? If yes, limit by age?
- If not, how to handle requests?
- How to reduce screening intensity?
- Who should be referred for biopsy? Is there a role for pre-biopsy calculator? Other markers? MRI?
- What is our role in selection of treatment?

Prostate Cancer Screening: Time to Question How to Optimize the Ratio of Benefits and Harms

Andrew J. Vickers, PhD

Vickers AJ. Prostate Cancer Screening: Time to Question How to Optimize the Ratio of Benefits and Harms. *Ann Intern Med*. [Epub ahead of print 5 September 2017] doi: 10.7326/M17-2012

MINIMIZING HARMS

- Shared decision making should be encouraged
- Stop screening those with little to gain – specifically men over age 70
- Biopsy only those at high risk for aggressive disease
- Don't treat those unlikely to benefit
- Effective treatment should be used

SAME AUTHOR – SHARED DECISION MAKING

Table. Decision Tool for Prostate Cancer Screening

Key facts about prostate cancer and screening

Prostate cancer is common; most men will develop it if they live long enough.

Although only a small proportion of men with prostate cancer die of the disease, the best evidence shows that screening reduces the risk for prostate cancer death.

Screening detects many low-risk or “indolent” cancer cases.

In the United States, most low-risk cancer is treated and the treatment itself can lead to complications, such as incontinence, erectile dysfunction, and bowel problems.

SAME AUTHOR – SHARED DECISION MAKING

Table. Decision Tool for Prostate Cancer Screening

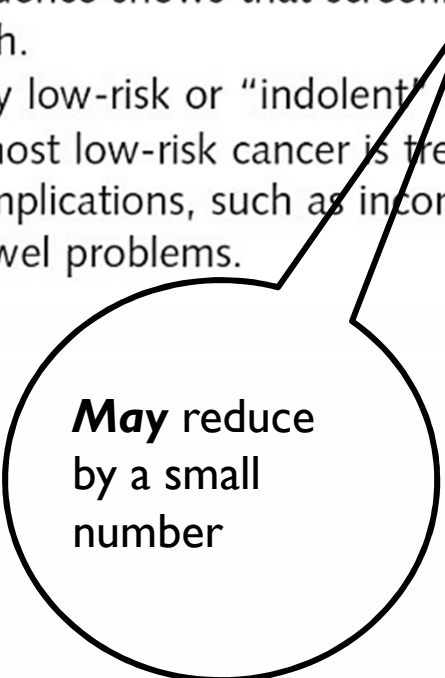
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May reduce
by a small
number

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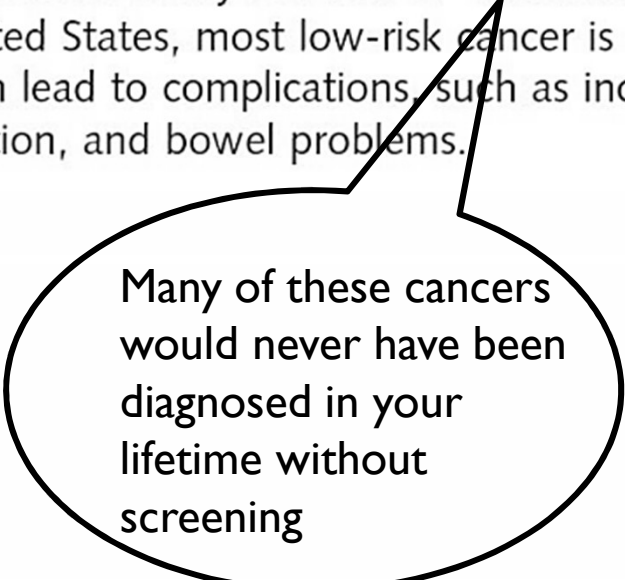
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Many of these cancers
would never have been
diagnosed in your
lifetime without
screening

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In the United States, most low-risk cancer is treated and the treatment itself can lead to complications, such as incontinence, erectile dysfunction, and bowel problems.



Or death

SAME AUTHOR – SHARED DECISION MAKING

Table. Decision Tool for Prostate Cancer Screening

Key take-home messages

The goal of screening is to find aggressive prostate cancer early and cure it before it spreads beyond the prostate.

Most cancer cases found by screening do not need to be treated and can be safely managed by a program of careful monitoring known as “active surveillance.”

If you choose to be screened, there is a good chance that you will be diagnosed with low-risk cancer and you may face pressure from your physicians or family to treat it.

SAME AUTHOR – SHARED DECISION MAKING

Table. Decision Tool for Prostate Cancer Screening

Discrete decision

If you are concerned that you would be uncomfortable knowing that you have cancer and not treating it, screening may not be for you.

If you are confident that you would only accept treatment for aggressive cancer and would not be unduly worried about living with a diagnosis of low-risk disease, you are probably a good candidate for screening.

LEFEVREM@HEALTH.MISSOURI.EDU

QUESTIONS?