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Statin use and reduced cancer-related mortality

Journal Club 24/11/12

Presenter: Anas Sarhan

Moderator: Prof. Ronan Conroy

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The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Statin Use and Reduced Cancer-Related Mortality

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Introduction

- University of Copenhagen
- Aim: is statin use begun before a cancer diagnosis a/w reduced ca.-related mortality?
- Background:
  - ↓ cholesterol may ↓ cell proliferation
  - Statin-associated ↓ in mevalonate pathway products a/w ↓ ca. recurrence
  - Statins linked to arresting cell cycle progression

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Introduction

- Previous large-scale trials of statin use in CVD patients w/o cancer failed to demonstrate influence of statins on incidence of cancer or ca.-related mortality.
- Design:
  - Retrospective cohort; entire Danish ca. population
  - 1/1/95 – 31/12/07 (f/u until 31/12/09)
  - Pts using statins prior to Dx v. pts never used

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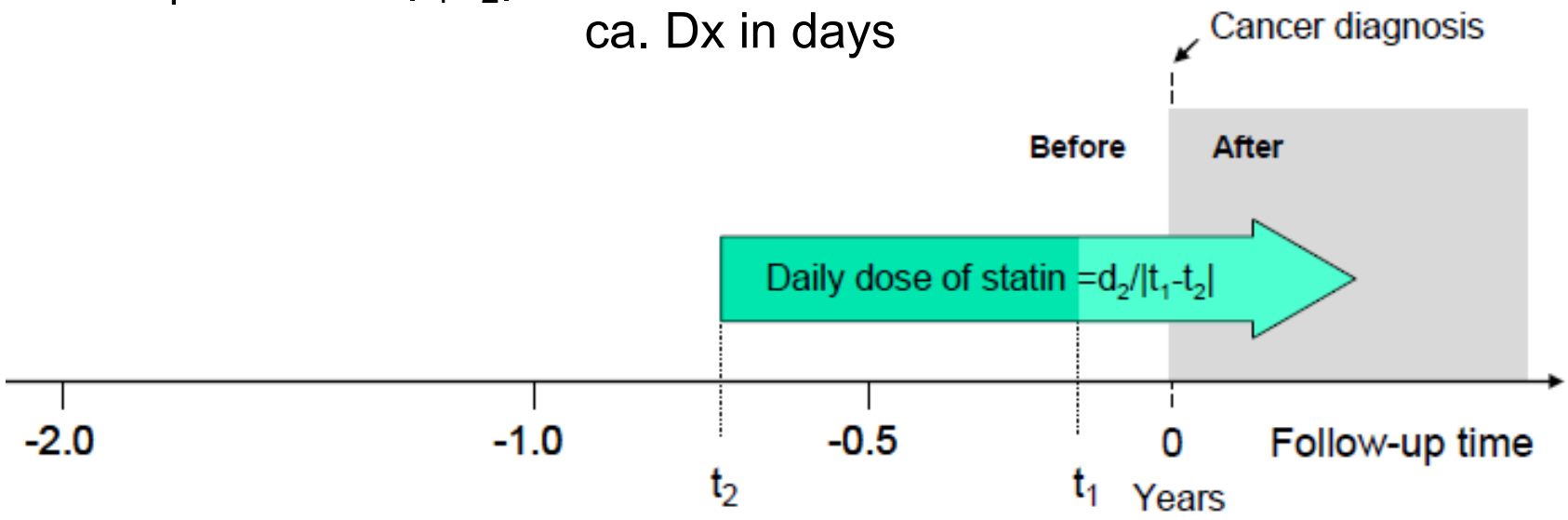
Terminology

- **Daily statin dose**: (0, 0.01-0.75, 0.76-1.50, >1.50)

$$\frac{dose_2}{|t_1 - t_2|}$$

, where $dose_2$ = penultimate Rx prior to ca. Dx in total defined daily doses (tot. mg/standard dose)

$|t_1\text{-}t_2|$ = interval between last two Rx's prior to ca. Dx in days



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Terminology

- **Regular statin user**: had Rx's filled within 6 mos. prior to ca. Dx AND within 2 yrs. Prior to ca. Dx.
- **Irregular statin user**: used statins prior to ca. Dx but do not fulfill above criteria.

Terminology

- **Nested 1:3 matched study**: each statin user is matched with 3 patients who have never used statins
  - Matched patients are similar in other parameters, eg. sex, age at Dx, yr of Dx, cancer type
  - Only statin pts with three matches were included
  - Were also adjusted using propensity-score analysis based on area code to account for unknown patterns/potential bias

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Study Design

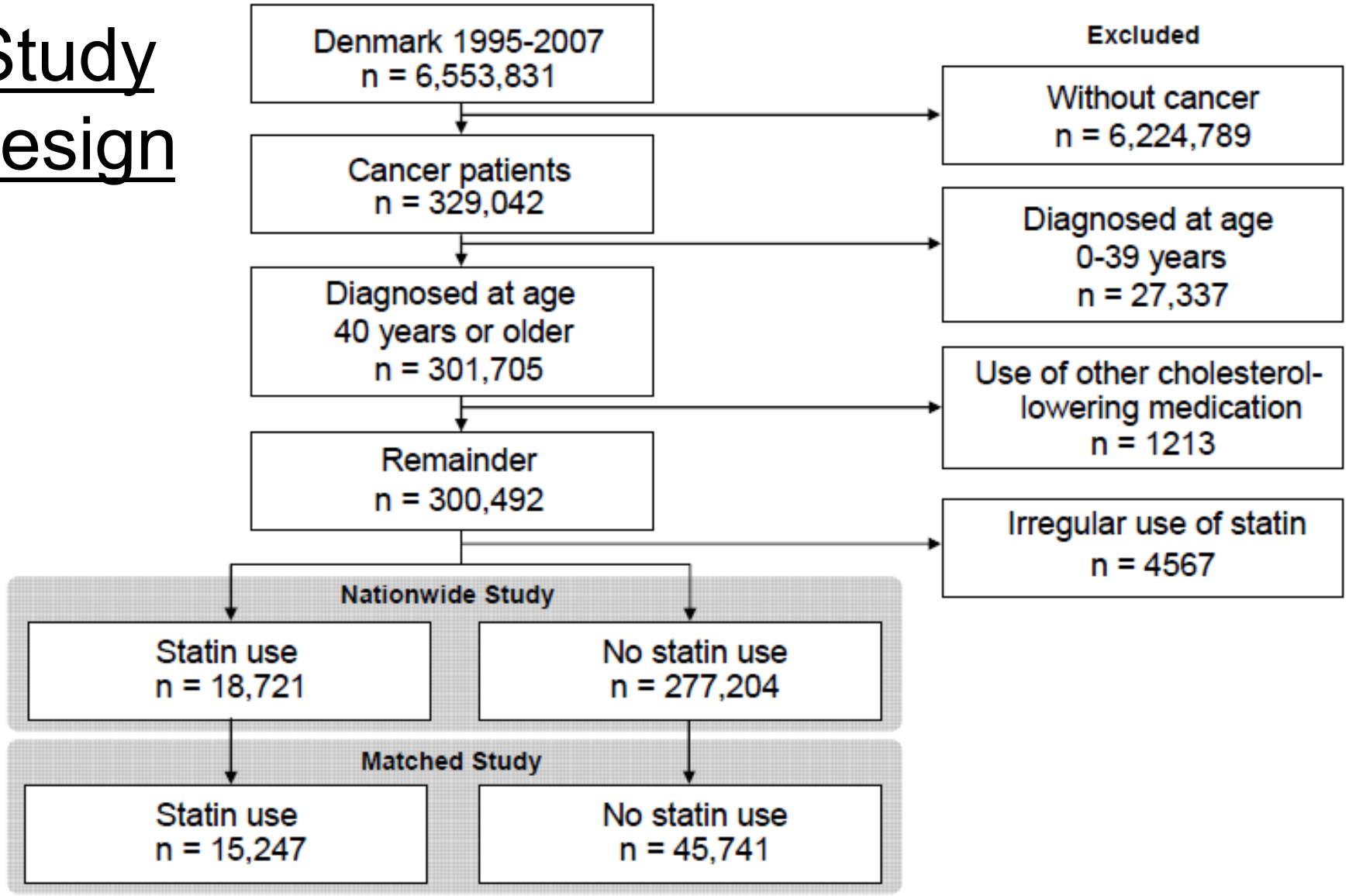


Table 1. Baseline Characteristics of the Patients, According to Statin Use, in the Nationwide and Matched Studies.*

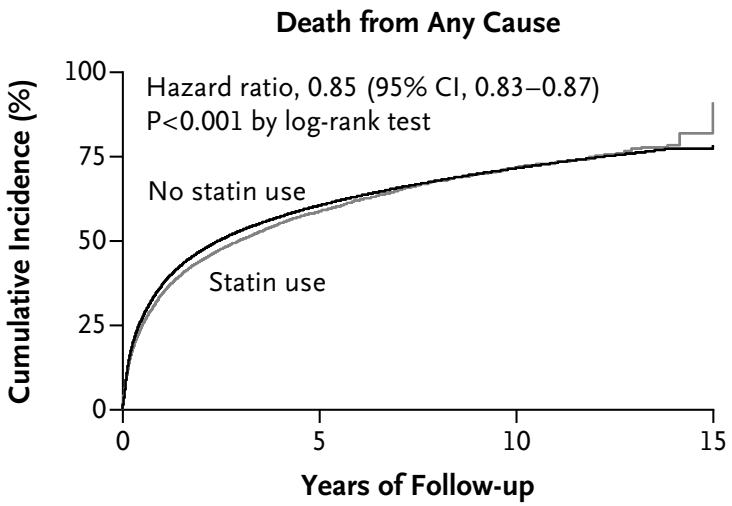
Characteristic	Nationwide Study			Nested 1:3 Matched Study		
	Statin Use (N=18,721)	No Statin Use (N=277,204)	P Value	Statin Use (N=15,247)	No Statin Use (N=45,741)	P Value
Age — yr			<0.001			1.00
Median	70	69		69	69	
Interquartile range	63–76	59–77		63–76	63–76	
Sex — no. (%)			<0.001			1.00
Female	8,077 (43)	148,881 (54)		6,726 (44)	20,178 (44)	
Male	10,644 (57)	128,323 (46)		8,521 (56)	25,563 (56)	
Tumor size — no. (%)†			<0.001			0.02
Small	6,032 (32)	36,509 (13)		4,842 (32)	13,629 (30)	
Large	6,416 (34)	38,052 (14)		4,935 (32)	15,677 (34)	
Missing data	6,273 (34)	202,643 (73)		5,470 (36)	16,435 (36)	
Cancer spread to lymphatic system — no. (%)†			<0.001			0.14
None	4,503 (24)	27,899 (10)		3,604 (24)	10,277 (22)	
Any	7,945 (42)	46,662 (17)		6,173 (40)	19,029 (42)	
Missing data	6,273 (34)	202,643 (73)		5,470 (36)	16,435 (36)	
Distant metastasis — no. (%)†			<0.001			0.26
None	6,798 (36)	42,575 (15)		5,471 (36)	16,002 (35)	
Any	5,620 (30)	31,986 (12)		4,306 (28)	13,304 (29)	
Missing data	6,303 (34)	202,643 (73)		5,470 (36)	16,435 (36)	
Chemotherapy — no. (%)‡			<0.001			1.00
None	4,557 (24)	170,665 (62)		4,224 (28)	12,511 (27)	
Any	669 (4)	25,034 (9)		623 (4)	2,062 (5)	
Missing data	13,495 (72)	81,505 (29)		10,400 (68)	31,168 (68)	

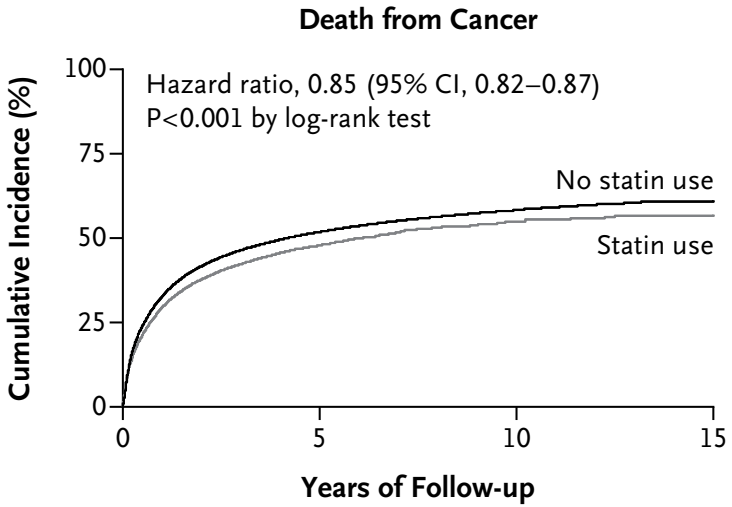
Table 1. (Continued.)

Characteristic	Nationwide Study			Nested 1:3 Matched Study		
	Statin Use (N = 18,721)	No Statin Use (N = 277,204)	P Value	Statin Use (N = 15,247)	No Statin Use (N = 45,741)	P Value
Radiotherapy — no. (%)‡			<0.001			1.00
None	4,486 (24)	169,023 (61)		4,164 (27)	12,587 (28)	
Any	740 (4)	26,676 (10)		683 (4)	1,986 (4)	
Missing data	13,495 (72)	81,505 (29)		10,400 (68)	31,168 (68)	
Cardiovascular disease before cancer — no. (%)			<0.001			<0.001
No	5,677 (30)	219,388 (79)		4,724 (31)	33,232 (73)	
Yes	13,044 (70)	57,816 (21)		10,523 (69)	12,509 (27)	
Diabetes mellitus before cancer — no. (%)			<0.001			<0.001
No	15,314 (82)	268,202 (97)		12,529 (82)	43,854 (96)	
Yes	3,407 (18)	9,002 (3)		2,718 (18)	1,887 (4)	
Size of residential area — no. (%)§			<0.001			0.11
<12,000 residents	7,508 (40)	108,684 (39)		6,118 (40)	18,724 (41)	
12,000–100,000 residents	5,027 (27)	72,361 (26)		4,070 (27)	12,105 (26)	
>100,000 residents	6,186 (33)	96,159 (35)		5,059 (33)	14,895 (33)	
Highest level of education — no. (%)			<0.001			0.003
Primary and high school	8,990 (48)	110,591 (40)		7,332 (48)	21,376 (47)	
Vocational training	6,249 (33)	73,956 (27)		5,077 (33)	14,762 (32)	
College degree	2,589 (14)	39,262 (14)		2,117 (14)	7,290 (16)	
Missing data	893 (5)	53,395 (19)		721 (5)	2,313 (5)	

Statin use and mortality

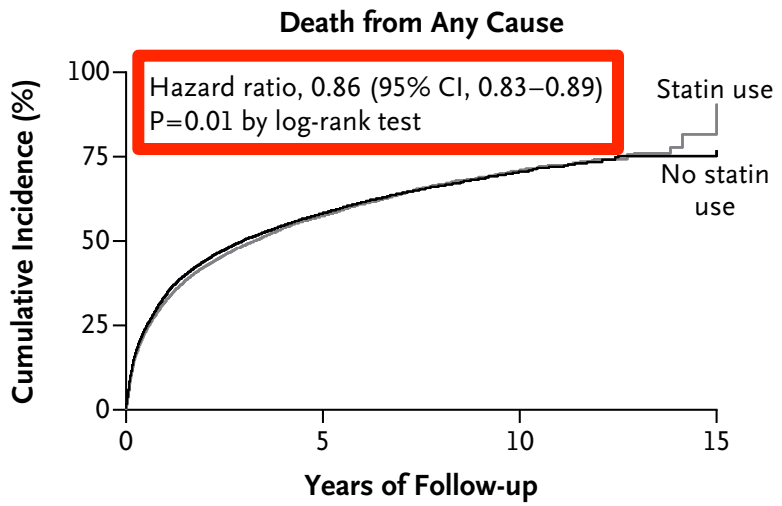
A Nationwide Study

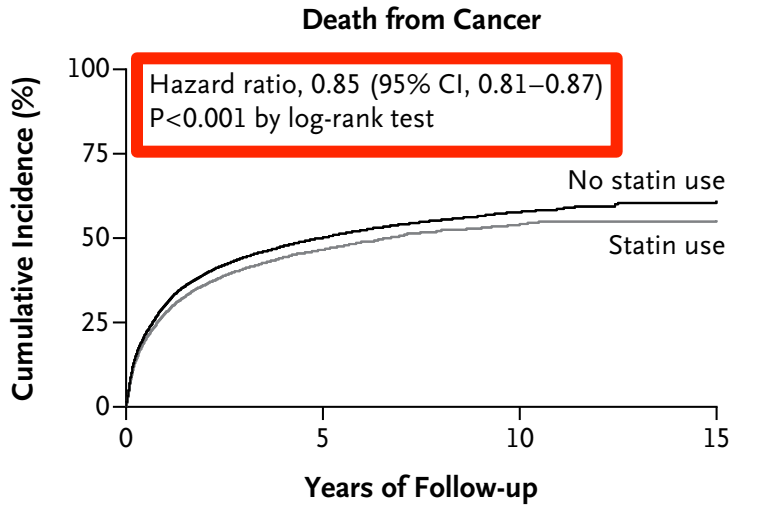




No. of Patients at Risk				
Statin use	18,721	3,005	365	0
No statin use	227,204	82,137	27,954	378

B Matched Study



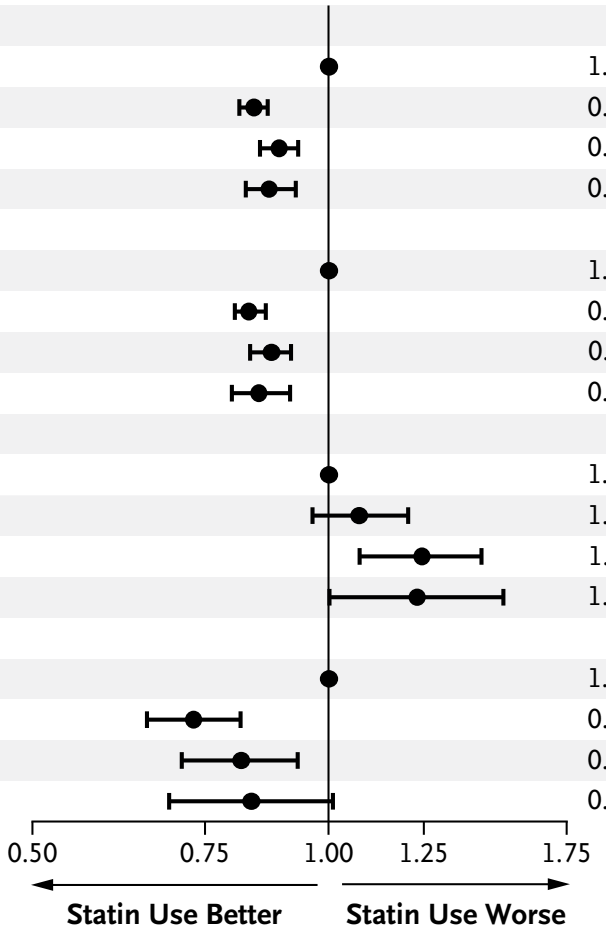


No. of Patients at Risk				
Statin use	15,247	2,779	349	0
No statin use	45,741	8,060	976	4

Statin dose and all-cause mortality

B **Matched Study**

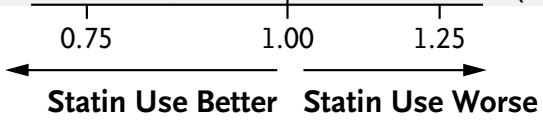
Cause of Death and Statin Dose	No. of Patients	No. of Deaths	Hazard Ratio (95% CI)	P Value
Any cause				
0.00	45,741	26,271	1.00	
0.01–0.75	8,162	4,741	0.83 (0.81–0.87)	<0.001
0.76–1.50	4,927	2,721	0.88 (0.85–0.93)	<0.001
>1.50	2,158	1,176	0.87 (0.81–0.93)	<0.001
Cancer				
0.00	45,741	22,584	1.00	
0.01–0.75	8,162	3,844	0.82 (0.80–0.86)	<0.001
0.76–1.50	4,927	2,203	0.87 (0.82–0.91)	<0.001
>1.50	2,158	946	0.85 (0.80–0.91)	<0.001
Cardiovascular cause				
0.00	45,741	1,373	1.00	
0.01–0.75	8,162	468	1.08 (0.95–1.21)	0.19
0.76–1.50	4,927	258	1.24 (1.08–1.42)	0.002
>1.50	2,158	108	1.23 (1.00–1.50)	0.05
Other cause				
0.00	45,741	2,314	1.00	
0.01–0.75	8,162	429	0.73 (0.66–0.81)	<0.001
0.76–1.50	4,927	260	0.81 (0.70–0.93)	0.002
>1.50	2,158	122	0.82 (0.68–1.00)	0.06



Statin dose and cancer-related mortality

B **Cancer-Related Mortality in Matched Study**

Subgroup	No. of Patients	No. of Deaths	Hazard Ratio (95% CI)	P Value
Regular statin use	60,988	29,577	0.85 (0.81–0.87)	<0.001
Sex				
Female	25,904	12,203	0.87 (0.83–0.92)	<0.001
Male	34,084	17,374	0.82 (0.80–0.86)	<0.001
Age at diagnosis				
40–69 yr	29,188	12,871	0.86 (0.81–0.89)	<0.001
>69 yr	31,800	16,706	0.83 (0.80–0.87)	<0.001
Chemotherapy				
No	16,735	9,280	0.79 (0.75–0.83)	<0.001
Yes	2,685	1,990	0.99 (0.87–1.12)	0.91
Radiotherapy				
No	16,751	9,633	0.81 (0.77–0.86)	<0.001
Yes	2,669	1,637	0.82 (0.73–0.93)	<0.001
Tumor size				
Small	18,471	4,825	0.81 (0.75–0.87)	<0.001
Large	20,612	12,447	0.87 (0.83–0.92)	<0.001
Metastasis				
No	12,118	2,383	0.86 (0.77–0.94)	0.003
Yes	26,965	14,889	0.86 (0.81–0.88)	<0.001
Cardiovascular disease before cancer				
No	37,956	17,977	0.81 (0.77–0.86)	<0.001
Yes	23,032	11,600	0.87 (0.83–0.89)	<0.001
Diabetes mellitus before cancer				
No	56,383	27,208	0.85 (0.81–0.87)	<0.001
Yes	4,605	2,369	0.81 (0.75–0.88)	<0.001
Calendar period				
1995–2002	9,956	3,932	0.80 (0.73–0.86)	<0.001
2003–2007	51,032	23,515	0.86 (0.82–0.88)	<0.001
Any statin use	75,988	36,966	0.86 (0.83–0.87)	<0.001



Results: Summary

- Statin use and all-cause mortality: hazard ratio 0.86 (95%CI 0.83-0.89)
- Statin use and cancer-related mortality: hazard ratio 0.85 (95%CI 0.81-0.87)
- No dose-response relationship; reduction in incidence of mortality seen at any dose

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Discussion

- Support: statistical & clinical significance
  - Large sample size, f/u, good study design
- Fits with current literature?
  - Mevalonate pathway inhibition → blocks mutated p53, ↓ MMPs, ↓ angiogenesis, cell cycle arrest, increased radiosensitisation
  - Verified in advanced prostate ca., ↓ recurrence in prostate or breast ca.
  - In CVD, statin does not influence ca. incidence

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Discussion: Limitations

- Selection bias?
- Omitted variable bias?
- Healthy user bias?
- Lead-time bias?
- Incomplete data?

Discussion: Limitations

- Selection bias
  - Followed entire Danish population
  - 97% white of Danish descent
- Omitted variable bias
  - Smoking: statin users due to CVD more likely to be counseled re: cessation → reduced mortality?

Discussion: Limitations

- Healthy user bias
  - May request more screening, comply w/ meds eg. OHAs, NSAIDs → influences mortality?
- Lead-time bias
  - Statin user - more f/u?, Ca. detected earlier?
- Incomplete data
  - Re: CTX, RTX, surgery, TNM staging
  - Authors mitigate but don't eliminate these biases

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Discussion: Future Directions

- Authors advocate clinical trials.
- Potential issues:
  - Ideal agent? Statin v. others, which statin?
  - Which dose to use? Verify effect at all doses?
  - Ideal follow-up? Recency bias? Latency effect?
  - Population as a confounder? Smoking?
  - Is there varying genetic susceptibility among pts?
  - Is it applicable to all neoplastic processes?

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Based on this article's findings, would you commence a patient with newly diagnosed cancer who is otherwise healthy on a statin?

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Teaching Points

- A good study addressing an important public health question.
- A case can be made for several potential limitations.
- Steps should be taken to verify findings before clinical trials ensue.

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Thank you!

A special thank-you to Prof. Ronan Conroy.

Questions?

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