Discontinuation of statin therapy in the elderly – does a cancer diagnosis make a difference? An observational cohort study using data linkage.

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Discontinuation of statin therapy in the elderly – does a cancer diagnosis make a difference? An observational cohort study using data linkage.

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ABSTRACT

Objective: Our aim was to examine statin discontinuation rates in a cohort of elderly Australians with newly diagnosed cancer using population-based secondary health data.

Design: Observational cohort study

Setting: New South Wales, the largest jurisdiction in Australia. The Pharmaceutical Benefits and Repatriation Pharmaceutical Benefits Schemes are national programs subsidising prescription drugs to the Australian population and Australian Government Department of Veterans' Affairs clients.

Participants: Our cohort comprised of 1,731 cancer patients aged ≥65 years with evidence of statin use in the 90 days prior to diagnosis. They were matched to 3,462 non-cancer patients prescribed statins in the same period.

Main outcome measure: We compared statin discontinuation rates up to four years post-diagnosis and examined the factors associated with statin discontinuation.

Results: Discontinuation rates were comparable in the cancer and comparison cohorts at four years (27%); however, the cancer cohort discontinued statins at a significantly higher rate than the comparison cohort at three, six and 12 months of follow-up (9.7% vs. 7.4% at 12 months, respectively). More than 20% of the cancer cohort with distant disease spread at diagnosis and 35% with localized spread at diagnosis were dispensed statins within 30 days of death. Cancer patients with non-localised disease at diagnosis (p<0.001), older age (p=0.006), upper gastro-intestinal organs and liver cancer (aHR 2.95, 95%CI 1.92-4.53) and cancer of the lung, bronchus and trachea (aHR 1.99, 95%CI 1.32-3.00) were more likely to discontinue statin therapy.

Conclusion: Cancer patients would benefit from a comprehensive reassessment of all drug treatments. The original therapeutic goals of primary and secondary prevention of other diseases may be largely futile in light of a limited prognosis and add unnecessarily to therapeutic burden.

Article Summary:

Article Focus:

- There is limited clinical guidance on managing comorbid conditions after the diagnosis of life-threatening illness
- Some medications may be continued unnecessarily and may even cause harm after a cancer diagnosis
- The aim of this study is to examine the rates of statin discontinuation in a cohort of older cancer patients compared with their peers with no cancer diagnosis.

Key Messages:

- In the setting of cancer, statins may be continued unnecessarily
- A high proportion of cancer patients are dispensed statins 30 days before death
- Cancer drug treatment add to therapeutic burden so there is a strong imperative to review and reassess existing treatments in these patients

Strengths and Limitations:

- This is a large retrospective cohort study of elderly Australians using population dataset linkage
- We were unable to establish if statin therapy had been reviewed subsequent to a cancer diagnosis nor the reasons for discontinuation

INTRODUCTION

There has been much debate about the clinical and economic benefits of prescribing preventive medicines for patients with life-limiting illness.[1-3] In the area of cancer, there has been a particular focus on 'futile' drug use in the setting of advanced disease where median survival is relatively short and there is little to no evidence demonstrating the benefits of drug treatments during anticipated survival times. [2, 4-6] Consequently there have been calls from the medical community to review and reduce the therapeutic burden on patients with life-threatening disease. [4-7]

Despite the large body of evidence guiding clinicians to initiate medications for the management of comorbid conditions, there has been limited guidance on reducing or ceasing medications at the end of life. Further, there is a scarcity of studies examining the management of comorbid conditions after the diagnosis of life threatening illness. However, there is some evidence to suggest that medications used for the secondary prevention of comorbid disease are continued longer than clinically indicated.[1, 5, 8, 9]

Statins are among the most commonly prescribed medications in the developing world. Their benefit in reducing cardiovascular events and mortality after an acute coronary syndrome, as well as the reduction in risk of major cardiovascular events in people without established cardiovascular disease is well documented.[10-13] However, many questions remain about the use of these medicines with advancing age. In particular, competing risks from cancer and other comorbid conditions, drug interactions due to high levels of polypharmacy and tolerability are likely to alter the benefit/risk ratios in older patients.[14-16]

The aim of this study is to examine statin discontinuation rates in a cohort of elderly cancer patients. Specifically, we compare discontinuation rates to a matched cohort of non-cancer patients and by cancer stage at diagnosis. Finally, we assess the predictors of statin discontinuation in both cohorts.

METHODS

Setting: The Pharmaceutical Benefits and Repatriation Pharmaceutical Benefits Schemes (PBS and RPBS) are national programs subsidising prescription drugs to the Australian population and Australian Government Department of Veterans' Affairs (DVA) clients. The RPBS comprises all PBS items plus additional items available only to DVA clients. [17, 18]

Data sources and Linkage: We used the following data sets to undertake our study:

i) DVA client file (1994 - 2007): information on sex, dates of birth and death, and veteran entitlement level of DVA clients residing in New South Wales (NSW), the largest Australian state.
ii) RPBS (July 2004 to June 2009): all dispensed pharmaceutical items (RPBS item code, name and strength, date of supply, quantity supplied and entitlement at time of dispensing).
iii) NSW Central Cancer Registry (CCR) (1994-2007): mandatory notifications of invasive cancer in NSW. We used International Classification of Diseases for Oncology, Third edition (ICD-O-3)[19] codes to identify cancer types.
iv) Admitted Patient Data Collection (APDC) (July 2000 - June 2009): all public, private and repatriation hospital separations in NSW.

Data linkage was undertaken by the NSW Centre for Health Record Linkage using best practice privacy preserving protocols. The study was approved by the NSW Population and Health Services and Department of Veterans' Affairs Human Research Ethics Committees (Approval Numbers: 2008/02/060 and E008/003) and did not require consent from individuals.

Cancer Cohort (n=1,731): Comprised fully-entitled clients aged ≥ 65 years, with a primary invasive cancer notification between 2005 and 2007, alive for ≥ six months post-diagnosis and with at least two statin dispensing records (ATC codes C10AA, C10BA, C10BX) in the 90 days prior to their diagnosis date (at least one within 60 days). We used the statin dispensing date immediately prior to diagnosis date as the index date for follow-up.

Comparison Cohort (n=3,462): We matched (using random selection without replacement) two clients with no evidence of a cancer notification to every cancer cohort member on year of birth (within five years), gender, a statin dispensing record within 15 days of the index date and first statin dispensing date (within 15 days) to match patients with comparable duration of statin treatment). Cohort members also were alive for at least six months after the index date.

Statistical Analyses: Differences between the characteristics of the cohorts were examined using χ^2 (Likelihood ratio) test. Our follow-up period commenced 60 days after the index date until December 31, 2009. We defined the discontinuation date as the date of last dispensing plus 30 days. We did not consider patients to have discontinued therapy if this date was within six months of the end of follow-up or in the three months before death. We calculated discontinuation rates at various time-points using Kaplan-Meier product limit estimates. Censor dates were the date of last statin dispensing before discontinuation, December 31, 2009 or death date.

We used Cox Proportional hazard regression to determine the factors associated with discontinuation following a cancer diagnosis adjusting for year of birth, spread-of-disease, cancer topography, hospitalisations prior to diagnosis, comorbidity burden and median statin daily quantity prior to diagnosis. We calculated the median daily quantity as [Tablet Strength × Quantity dispensed]/WHO Defined Daily Dose (DDD)[20])/days supplied] and comorbidity using the RxRisk Index using counts of up to 42 general drug categories (not including cancer drug categories) using pharmacy claims data within six months prior to a patient's cancer diagnosis.[21, 22] We omitted gender from this model as some cancers are gender-specific. However, gender did not show a statistically significant bivariate association with discontinuation. We also used Cox regression to examine the predictors of discontinuation in the comparison group, with age, gender, comorbidity burden, hospitalisations and median daily quantity as covariates. Statistical significance was assessed at the $p<0.05$ (two-tailed) level.

RESULTS

Cohort Characteristics: Approximately two-thirds of the cancer and comparison cohorts were aged ≥75 years on January 1 2005 and 72% were male. The most common cancer diagnoses were prostate (23%), colorectal cancer (17%) and melanoma of the skin (14%). Most cancer patients were diagnosed with localised (46%) or unknown spread (32%). The cancer cohort had fewer hospital admissions in the year prior to the index date than the comparison cohort (92% of the cancer cohort with ≤4 separations; 84% in the comparison cohort; Likelihood ratio χ^2=85.6, p<0.0001). Comorbidity burden was similar in both cohorts with 78% having four to nine comorbidities prior to the index date.

Statin Use Prior to the Index Date: More than 90% of both cohorts were prescribed atorvastatin, simvastatin or pravastatin alone. The median daily quantity prior to the index date was ≥1DDDs per day for atorvastatin, pravastatin and rovastatin. The median time between the first statin dispensing to the index date was approximately 600 days for both cohorts, with 18% of the cancer cohort and 26% of the comparison group having at least one period of ≥90 days between dispensing records; median duration of breaks in therapy were 136 days and 142 days in the cancer and comparison cohorts respectively. (Table 1)

Statin Discontinuation: Median follow-up time was 913 and 958 days for the cancer and comparison cohorts respectively (IQR 464-1297 days and 496-1289 days). We found no significant differences in the discontinuation estimates of the cancer and comparison cohorts after four years [cancer 26.5% (95%CI 24.1-29.2%); comparison 27.2% (95%CI 25.3-29.1%)]. The cancer cohort had significantly higher discontinuation rates at 3, 6 and 12 months; however, after this, rates were comparable with the comparison cohort (Figure 1). More than 31% of the cancer cohort had a statin dispensed within 30 days of their death (Figure 2) and this was the case for 21% of those with metastatic disease and 35% with localized spread at diagnosis.

Predictors of Statin Discontinuation: Older patients and those diagnosed with non-localised disease had shorter time to statin discontinuation as did patients with upper GI and liver cancer and cancer of the lung, bronchus and trachea. Patients with melanoma of the skin had

longer times to discontinuation (Table 2). Older clients in the comparison cohort also had shorter time to discontinuation than their younger counterparts (p=0.001).

DISCUSSION

This retrospective cohort study of elderly Australians highlights a need for comprehensive and ongoing review of medications after the diagnosis of life limiting illness. Our findings demonstrate that in the setting of cancer, statins may be continued unnecessarily. To complement the existing literature, which has focused on statin discontinuation in the six months prior to death, we examined rates of statin discontinuation subsequent to a cancer diagnosis and found rates of discontinuation are relatively low in the first 12 months after a diagnosis but are higher than in non-cancer patients. Beyond 12 months post-diagnosis discontinuation rates are no different to rates in the non-cancer population. We also found higher rates of discontinuation in patients diagnosed with metastatic disease. These findings may indicate some recognition on the part of doctors and or patients that medications need to be rationalized in light of a limited prognosis. Nevertheless, a large proportion of cancer patients were prescribed statins in the 30 days before death.

Our findings are consistent with previous research from North America and Australia, all of which highlight the missed opportunities to reduce the therapeutic burden of many patients after a life limiting diagnosis. [4-7] If the potential benefits of therapy are incremental and long-term then there are strong imperatives for review when cancer therapies are commenced as it is well established that the risks of adverse outcomes increases exponentially with the total number of medications (the "therapeutic burden").[23] Our study is limited in that we are unable to establish the reasons for discontinuation in our cohort. However, improved communication among physicians and patients is likely to increase the understanding about the original therapeutic goals of particular treatments. Further, more systematic guidance on ceasing medications at the end of life would reduce therapeutic burden for individual patients and have the added benefit of reducing costs placed on already stretched health care budgets.

Contributors:

Efty Stavrou (research fellow cancer epidemiology, University of New South Wales (UNSW)); Nicholas Buckley (professor of medicine, UNSW); Jake Olivier (senior biostatistician, UNSW); Sallie-Anne Pearson (senior research fellow pharmacoepidemiology, UNSW). EPS performed the statistical analyses and drafted the manuscript; JO guided the statistical analyses; NB and SAP designed the study and drafted the manuscript. All authors read and approved the final manuscript. SAP is guarantor.

Competing Interest Statement:

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The views expressed are not necessarily those of the funders.

All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing: no additional data available.

Table 1: Statin use prior to (and including) index date of cancer and comparison cohorts

Variable	Cancer Cohort N=1,731		Comparison Cohort N=3,462	
Statin type	n	%	n	%
Atorvastatin alone	685	39.6	1,304	37.8
Fluvastatin alone	13	0.8	39	1.1
Pravastatin alone	257	14.8	525	15.2
Rosuvastatin alone	1	0.0	3	0.0
Simvastatin alone	653	37.7	1,306	37.8
Two or more statins	122	7.0	285	8.2
DDD/day	Median	IQR	Median	IQR
Atorvastatin	1.00	1.0-2.00	1.00	1.00-2.00
Fluvastatin	0.67	0.33-0.67	0.67	0.33-0.67
Pravastatin Sodium	1.33	0.67-1.33	1.33	0.67-1.33
Rosuvastatin	2.00	1.00-2.00	2.00	1.00-2.31
Simvastatin	0.67	0.67-1.33	0.67	0.67-1.33
Time from first statin to index date (days)	Median	IQR	Median	IQR
	611	336-901	616	339-903
Patients with breaks of ≥90 days in therapy	n	%	n	%
	310	17.9	888	25.6
Duration of breaks in therapy (days)	Median	IQR	Median	IQR
	136	102-211	142	104-232

Table 2: Adjusted Cox-Proportional Hazard Regression analyses for association with statin discontinuation during follow-up

Variable	Cases N	Discontinued n (%)	aHR*	95% CI	p-value
Age (at 1 Jan 2005)			0.85†	0.76-0.95	0.004
≤74 years	247	35 (14.2)			
75-79 years	289	53 (18.3)			
80-84 years	832	121 (14.5)			
85+ years	363	81 (22.3)			
Prior hospital admission			1.01†	0.99-1.03	0.16
0	764	121 (15.8)			
1-4	833	148 (17.8)			
5-9	85	15 (17.6)			
10+	49	6 (12.2)			
Comorbidity burden			0.99†	0.96-1.03	0.36
0-3	261	46 (17.6)			
4-9	120	19 (15.8)			
10+	1,350	225 (16.7)			
Median DDD/day			1.14†	0.99-1.30	0.06
Degree of Spread					*<0.001*
Localised	789	106 (13.4)	1.00	1.00	Referent
Regional	275	54 (19.6)	1.73	1.28-2.35	<0.001
Distant	120	30 (25.0)	3.90	2.72-5.59	<0.001
Unknown	547	100 (18.3)	1.36	1.03-1.80	0.03
Cancer Topography					
Upper GI, Liver	69	32 (46.4)	2.95	1.92-4.53	<0.001
Lung, Bronchus, Trachea	120	38 (31.7)	1.99	1.32-3.00	0.001
Lymphoma	73	19 (26.0)	1.24	0.71-2.16	0.46
Other type	207	53 (25.1)	1.28	0.87-1.89	0.20
Colorectal	300	70 (23.3)	1.00	1.00	Referent
Bladder	65	14 (21.5)	1.19	0.66-2.13	0.56
Kidney	38	8 (21.1)	0.87	0.41-1.81	0.70
Breast	102	21 (20.6)	0.98	0.60-1.60	0.93
Head & Neck	44	9(20.4)	1.01	0.50-2.03	0.98
Leukaemia	35	7 (20.0)	1.08	0.48-2.45	0.85
Ill-defined, unspecified	42	8 (19.0)	0.51	0.24-1.09	0.08
Prostate	393	68 (17.3)	0.79	0.55-1.14	0.20
Melanoma of the skin	243	30 (12.4)	0.58	0.37-0.91	0.02

**Adjusted for all factors in the table. † aHR indicates ratio per decade, admission, comorbid illness and DDD respectively.*

Figure 1: Statin discontinuation after index date as determined with Kaplein-Meier product limit estimates

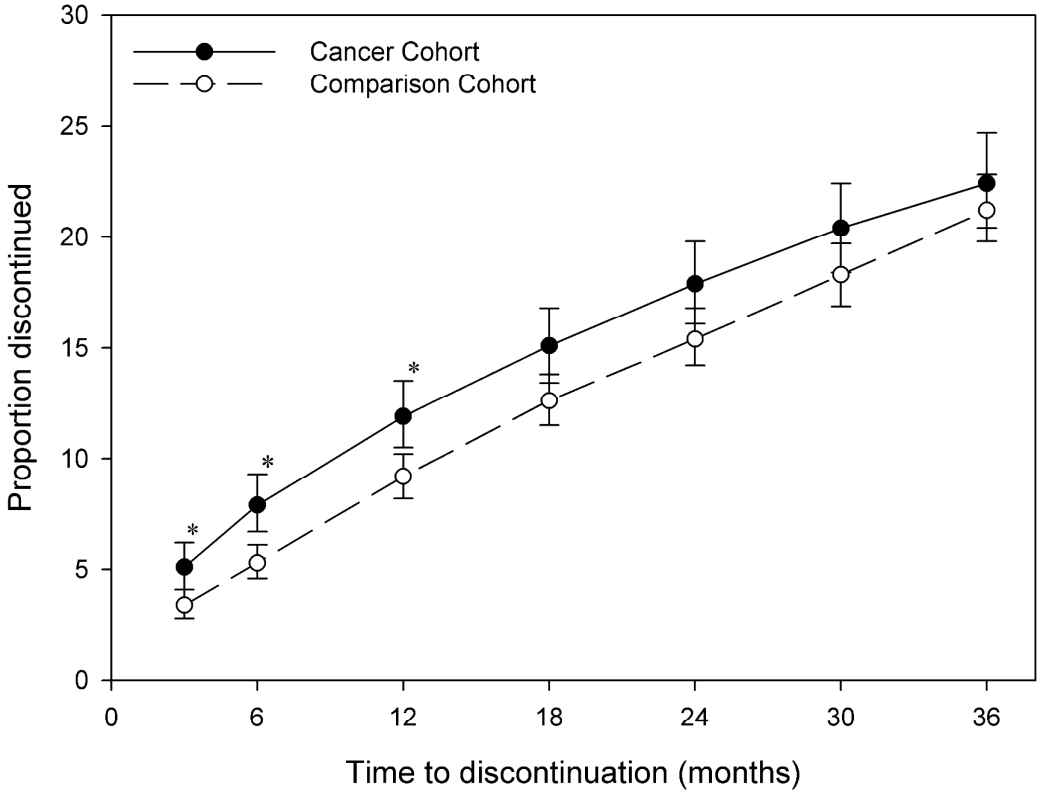
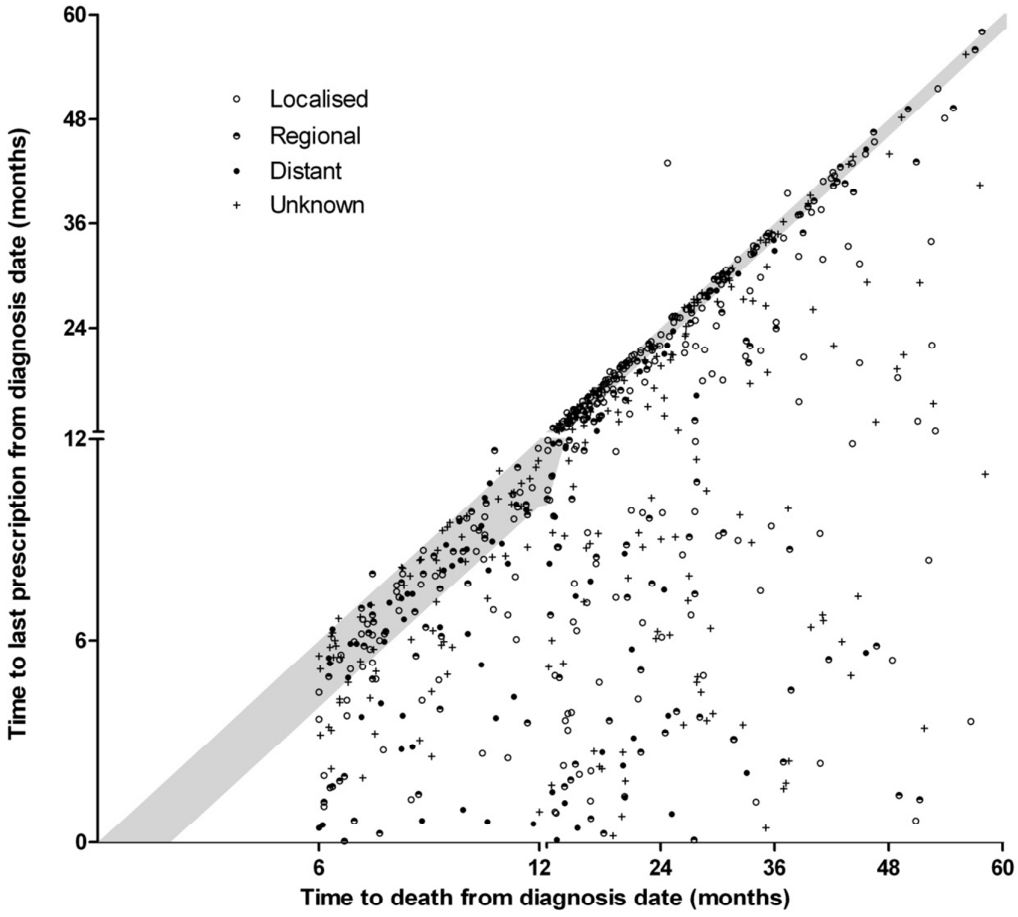


Figure 2: Scatter plot of time to last statin prescription against time to death from diagnosis date.

Shaded area indicates the period within 30days of death.



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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p.2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p.2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	p.3
Objectives	3	State specific objectives, including any prespecified hypotheses	p.3
Methods			
Study design	4	Present key elements of study design early in the paper	p.4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	pp.4,5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	pp.4,5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	pp 4,5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p.5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	pp.4,5
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	p. 4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p.5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	p.5
		(*b*) Describe any methods used to examine subgroups and interactions	p.5
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	p.4,6,9
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	p.6,9
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	p6
Outcome data	15*	Report numbers of outcome events or summary measures over time	pp.6,9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	pp.6, 9 Table 2

		which confounders were adjusted for and why they were included	Fig 1, 2
		(*b*) Report category boundaries when continuous variables were categorized	p6, Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	p.6
Discussion			
Key results	18	Summarise key results with reference to study objectives	pp.7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p.12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	pp.7
Generalisability	21	Discuss the generalisability (external validity) of the study results	p.7
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	p.1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Secondary Subject Heading:	Oncology, Cardiovascular medicine, Pharmacology and therapeutics
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ABSTRACT

Objective: Our aim was to examine statin discontinuation rates in a cohort of elderly Australians with newly diagnosed cancer using population-based secondary health data.

Design: Observational cohort study

Setting: New South Wales, the largest jurisdiction in Australia. The Pharmaceutical Benefits and Repatriation Pharmaceutical Benefits Schemes are national programs subsidising prescription drugs to the Australian population and Australian Government Department of Veterans' Affairs clients.

Participants: Our cohort comprised of 1,731 cancer patients aged ≥65 years with evidence of statin use in the 90 days prior to diagnosis. They were matched to 3,462 non-cancer patients prescribed statins in the same period.

Main outcome measure: We compared statin discontinuation rates up to four years post-diagnosis and examined the factors associated with statin discontinuation.

Results: Discontinuation rates were comparable in the cancer and comparison cohorts at four years (27%); however, the cancer cohort discontinued statins at a significantly higher rate than the comparison cohort at three, six and 12 months of follow-up (9.7% vs. 7.4% at 12 months, respectively). More than 20% of the cancer cohort with distant disease spread at diagnosis and 35% with localized spread at diagnosis were dispensed statins within 30 days of death. Cancer patients with non-localised disease at diagnosis (p<0.001), older age (p=0.006), upper gastro-intestinal organs and liver cancer (aHR 2.95, 95%CI 1.92-4.53) and cancer of the lung, bronchus and trachea (aHR 1.99, 95%CI 1.32-3.00) were more likely to discontinue statin therapy.

Conclusion: Cancer patients would benefit from a comprehensive reassessment of all drug treatments. The original therapeutic goals of primary and secondary prevention of other diseases may be largely futile in light of a limited prognosis and add unnecessarily to therapeutic burden.

Article Summary:

Article Focus:

- There is limited clinical guidance on managing comorbid conditions after the diagnosis of life-threatening illness
- Some medications may be continued unnecessarily and may even cause harm after a cancer diagnosis
- The aim of this study is to examine the rates of statin discontinuation in a cohort of older cancer patients compared with their peers with no cancer diagnosis.

Key Messages:

- In the setting of cancer, statins may be continued unnecessarily
- A high proportion of cancer patients are dispensed statins 30 days before death
- Cancer drug treatment add to therapeutic burden so there is a strong imperative to review and reassess existing treatments in these patients

Strengths and Limitations:

- This is a large retrospective cohort study of elderly Australians using population dataset linkage
- We were unable to establish if statin therapy had been reviewed subsequent to a cancer diagnosis nor the reasons for discontinuation

INTRODUCTION

There has been much debate about the clinical and economic benefits of prescribing preventive medicines for patients with life-limiting illness.[1-3] In the area of cancer, there has been a particular focus on 'futile' drug use in the setting of advanced disease where median survival is relatively short and there is little to no evidence demonstrating the benefits of drug treatments during anticipated survival times. [2, 4-6] Consequently there have been calls from the medical community to review and reduce the therapeutic burden on patients with life-threatening disease. [4-7]

Despite the large body of evidence guiding clinicians to initiate medications for the management of comorbid conditions, there has been limited guidance on reducing or ceasing medications at the end of life. Further, there is a scarcity of studies examining the management of comorbid conditions after the diagnosis of life threatening illness. However, there is some evidence to suggest that medications used for the secondary prevention of comorbid disease are continued longer than clinically indicated.[1, 5, 8, 9]

Statins are among the most commonly prescribed medications in the developing world. Their benefit in reducing cardiovascular events and mortality after an acute coronary syndrome, as well as the reduction in risk of major cardiovascular events in people without established cardiovascular disease is well documented.[10-13] However, many questions remain about the use of these medicines with advancing age. In particular, competing risks from cancer and other comorbid conditions, drug interactions due to high levels of polypharmacy and tolerability are likely to alter the benefit/risk ratios in older patients.[14-16]

The aim of this study is to examine statin discontinuation rates in a cohort of elderly cancer patients. Specifically, we compare discontinuation rates to a matched cohort of non-cancer patients and by cancer stage at diagnosis. Finally, we assess the predictors of statin discontinuation in both cohorts.

METHODS

Setting: The Pharmaceutical Benefits and Repatriation Pharmaceutical Benefits Schemes (PBS and RPBS) are national programs subsidising prescription drugs to the Australian population and Australian Government Department of Veterans' Affairs (DVA) clients. The RPBS comprises all PBS items plus additional items available only to DVA clients. [17, 18]

Data sources and Linkage: We used the following data sets to undertake our study:

i) DVA client file (1994 - 2007): information on sex, dates of birth and death, and veteran entitlement level of DVA clients residing in New South Wales (NSW), the largest Australian state.
ii) RPBS (July 2004 to June 2009): all dispensed pharmaceutical items (RPBS item code, name and strength, date of supply, quantity supplied and entitlement at time of dispensing).
iii) NSW Central Cancer Registry (CCR) (1994-2007): mandatory notifications of invasive cancer in NSW. We used International Classification of Diseases for Oncology, Third edition (ICD-O-3)[19] codes to identify cancer types.
iv) Admitted Patient Data Collection (APDC) (July 2000 - June 2009): all public, private and repatriation hospital separations in NSW.

Data linkage was undertaken by the NSW Centre for Health Record Linkage using best practice privacy preserving protocols. The study was approved by the NSW Population and Health Services and Department of Veterans' Affairs Human Research Ethics Committees (Approval Numbers: 2008/02/060 and E008/003) and did not require consent from individuals.

Cancer Cohort (n=1,731): Comprised fully-entitled clients aged ≥ 65 years, with a primary invasive cancer notification between 2005 and 2007, alive for ≥ six months post-diagnosis and with at least two statin dispensing records (ATC codes C10AA, C10BA, C10BX) in the 90 days prior to their diagnosis date (at least one within 60 days). We used the statin dispensing date immediately prior to diagnosis date as the index date for follow-up.

Comparison Cohort (n=3,462): We matched (using random selection without replacement) two clients with no evidence of a cancer notification to every cancer cohort member on year of birth (within five years), gender, a statin dispensing record within 15 days of the index date and first statin dispensing date (within 15 days) to match patients with comparable duration of statin treatment). Cohort members also were alive for at least six months after the index date.

Statistical Analyses: Differences between the characteristics of the cohorts were examined using χ^2 (Likelihood ratio) test. Our follow-up period commenced 60 days after the index date until December 31, 2009. We defined the discontinuation date as the date of last dispensing plus 30 days. We did not consider patients to have discontinued therapy if this date was within six months of the end of follow-up or in the three months before death. We calculated discontinuation rates at various time-points using Kaplan-Meier product limit estimates. Censor dates were the date of last statin dispensing before discontinuation, December 31, 2009 or death date.

We used Cox Proportional hazard regression to determine the factors associated with discontinuation following a cancer diagnosis adjusting for year of birth, spread-of-disease, cancer topography, hospitalisations prior to diagnosis, comorbidity burden and median statin daily quantity prior to diagnosis. We calculated the median daily quantity as [Tablet Strength × Quantity dispensed]/WHO Defined Daily Dose (DDD)[20])/days supplied] and comorbidity using the RxRisk Index using counts of up to 42 general drug categories (not including cancer drug categories) using pharmacy claims data within six months prior to a patient's cancer diagnosis.[21, 22] We omitted gender from this model as some cancers are gender-specific. However, gender did not show a statistically significant bivariate association with discontinuation. We also used Cox regression to examine the predictors of discontinuation in the comparison group, with age, gender, comorbidity burden, hospitalisations and median daily quantity as covariates. Statistical significance was assessed at the $p<0.05$ (two-tailed) level.

RESULTS

Cohort Characteristics: Approximately two-thirds of the cancer and comparison cohorts were aged ≥75 years on January 1 2005 and 72% were male. The most common cancer diagnoses were prostate (23%), colorectal cancer (17%) and melanoma of the skin (14%). Most cancer patients were diagnosed with localised (46%) or unknown spread (32%). The cancer cohort had fewer hospital admissions in the year prior to the index date than the comparison cohort (92% of the cancer cohort with ≤4 separations; 84% in the comparison cohort; Likelihood ratio χ^2=85.6, p<0.0001). Comorbidity burden was similar in both cohorts with 78% having four to nine comorbidities prior to the index date.

Statin Use Prior to the Index Date: More than 90% of both cohorts were prescribed atorvastatin, simvastatin or pravastatin alone. The median daily quantity prior to the index date was ≥1DDDs per day for atorvastatin, pravastatin and rovastatin. The median time between the first statin dispensing to the index date was approximately 600 days for both cohorts, with 18% of the cancer cohort and 26% of the comparison group having at least one period of ≥90 days between dispensing records; median duration of breaks in therapy were 136 days and 142 days in the cancer and comparison cohorts respectively. (Table 1)

Statin Discontinuation: Median follow-up time was 913 and 958 days for the cancer and comparison cohorts respectively (IQR 464-1297 days and 496-1289 days). We found no significant differences in the discontinuation estimates of the cancer and comparison cohorts after four years [cancer 26.5% (95%CI 24.1-29.2%); comparison 27.2% (95%CI 25.3-29.1%)]. The cancer cohort had significantly higher discontinuation rates at 3, 6 and 12 months; however, after this, rates were comparable with the comparison cohort (Figure 1). More than 31% of the cancer cohort had a statin dispensed within 30 days of their death (Figure 2) and this was the case for 21% of those with metastatic disease and 35% with localized spread at diagnosis.

Predictors of Statin Discontinuation: Older patients and those diagnosed with non-localised disease had shorter time to statin discontinuation as did patients with upper GI and liver cancer and cancer of the lung, bronchus and trachea. Patients with melanoma of the skin had

longer times to discontinuation (Table 2). Older clients in the comparison cohort also had shorter time to discontinuation than their younger counterparts (p=0.001).

DISCUSSION

This retrospective cohort study of elderly Australians highlights a need for comprehensive and ongoing review of medications after the diagnosis of life limiting illness. Our findings demonstrate that in the setting of cancer, statins may be continued unnecessarily. To complement the existing literature, which has focused on statin discontinuation in the six months prior to death, we examined rates of statin discontinuation subsequent to a cancer diagnosis and found rates of discontinuation are relatively low in the first 12 months after a diagnosis but are higher than in non-cancer patients. Beyond 12 months post-diagnosis discontinuation rates are no different to rates in the non-cancer population. We also found higher rates of discontinuation in patients diagnosed with metastatic disease. These findings may indicate some recognition on the part of doctors and or patients that medications need to be rationalized in light of a limited prognosis. Nevertheless, a large proportion of cancer patients were prescribed statins in the 30 days before death.

Our findings are consistent with previous research from North America and Australia, all of which highlight the missed opportunities to reduce the therapeutic burden of many patients after a life limiting diagnosis. [4-7] If the potential benefits of therapy are incremental and long-term then there are strong imperatives for review when cancer therapies are commenced as it is well established that the risks of adverse outcomes increases exponentially with the total number of medications (the "therapeutic burden").[23] Our study is limited in that we are unable to establish the reasons for discontinuation in our cohort. However, improved communication among physicians and patients is likely to increase the understanding about the original therapeutic goals of particular treatments. Further, more systematic guidance on ceasing medications at the end of life would reduce therapeutic burden for individual patients and have the added benefit of reducing costs placed on already stretched health care budgets.

Contributors:

Efty Stavrou (research fellow cancer epidemiology, University of New South Wales (UNSW)); Nicholas Buckley (professor of medicine, UNSW); Jake Olivier (senior biostatistician, UNSW); Sallie-Anne Pearson (senior research fellow pharmacoepidemiology, UNSW). EPS performed the statistical analyses and drafted the manuscript; JO guided the statistical analyses; NB and SAP designed the study and drafted the manuscript. All authors read and approved the final manuscript. SAP is guarantor.

Competing Interest Statement:

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing: no additional data available.

Table 1: Statin use prior to (and including) index date of cancer and comparison cohorts

Variable	Cancer Cohort N=1,731		Comparison Cohort N=3,462	
Statin type	n	%	n	%
Atorvastatin alone	685	39.6	1,304	37.8
Fluvastatin alone	13	0.8	39	1.1
Pravastatin alone	257	14.8	525	15.2
Rosuvastatin alone	1	0.0	3	0.0
Simvastatin alone	653	37.7	1,306	37.8
Two or more statins	122	7.0	285	8.2
DDD/day	Median	IQR	Median	IQR
Atorvastatin	1.00	1.0-2.00	1.00	1.00-2.00
Fluvastatin	0.67	0.33-0.67	0.67	0.33-0.67
Pravastatin Sodium	1.33	0.67-1.33	1.33	0.67-1.33
Rosuvastatin	2.00	1.00-2.00	2.00	1.00-2.31
Simvastatin	0.67	0.67-1.33	0.67	0.67-1.33
Time from first statin to index date (days)	Median	IQR	Median	IQR
	611	336-901	616	339-903
Patients with breaks of ≥90 days in therapy	n	%	n	%
	310	17.9	888	25.6
Duration of breaks in therapy (days)	Median	IQR	Median	IQR
	136	102-211	142	104-232

Table 2: Adjusted Cox-Proportional Hazard Regression analyses for association with statin discontinuation during follow-up

Variable	Cases N	Discontinued n (%)	aHR*	95% CI	p-value
Age (at 1 Jan 2005)			0.85†	0.76-0.95	0.004
≤74 years	247	35 (14.2)			
75-79 years	289	53 (18.3)			
80-84 years	832	121 (14.5)			
85+ years	363	81 (22.3)			
Prior hospital admission			1.01†	0.99-1.03	0.16
0	764	121 (15.8)			
1-4	833	148 (17.8)			
5-9	85	15 (17.6)			
10+	49	6 (12.2)			
Comorbidity burden			0.99†	0.96-1.03	0.36
0-3	261	46 (17.6)			
4-9	120	19 (15.8)			
10+	1,350	225 (16.7)			
Median DDD/day			1.14†	0.99-1.30	0.06
Degree of Spread					*<0.001*
Localised	789	106 (13.4)	1.00	1.00	Referent
Regional	275	54 (19.6)	1.73	1.28-2.35	<0.001
Distant	120	30 (25.0)	3.90	2.72-5.59	<0.001
Unknown	547	100 (18.3)	1.36	1.03-1.80	0.03
Cancer Topography					
Upper GI, Liver	69	32 (46.4)	2.95	1.92-4.53	<0.001
Lung, Bronchus, Trachea	120	38 (31.7)	1.99	1.32-3.00	0.001
Lymphoma	73	19 (26.0)	1.24	0.71-2.16	0.46
Other type	207	53 (25.1)	1.28	0.87-1.89	0.20
Colorectal	300	70 (23.3)	1.00	1.00	Referent
Bladder	65	14 (21.5)	1.19	0.66-2.13	0.56
Kidney	38	8 (21.1)	0.87	0.41-1.81	0.70
Breast	102	21 (20.6)	0.98	0.60-1.60	0.93
Head & Neck	44	9(20.4)	1.01	0.50-2.03	0.98
Leukaemia	35	7 (20.0)	1.08	0.48-2.45	0.85
Ill-defined, unspecified	42	8 (19.0)	0.51	0.24-1.09	0.08
Prostate	393	68 (17.3)	0.79	0.55-1.14	0.20
Melanoma of the skin	243	30 (12.4)	0.58	0.37-0.91	0.02

**Adjusted for all factors in the table. † aHR indicates ratio per decade, admission, comorbid illness and DDD respectively.*

Figure 1: Statin discontinuation after index date as determined with Kaplein-Meier product limit estimates

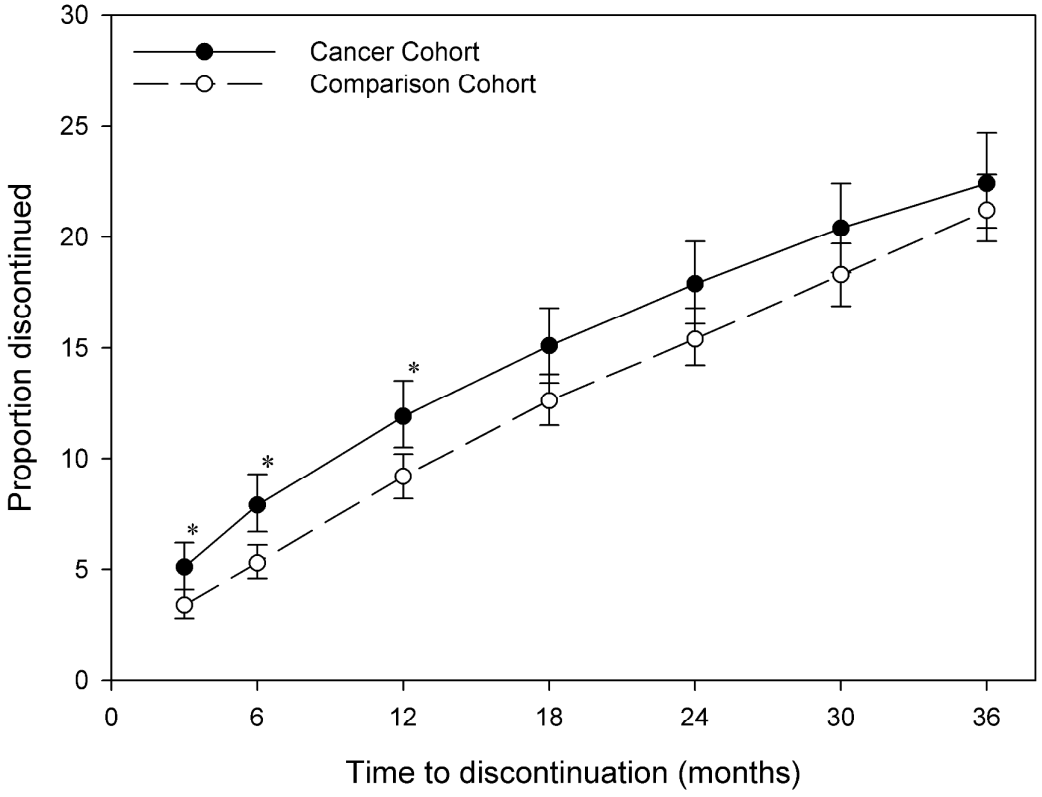
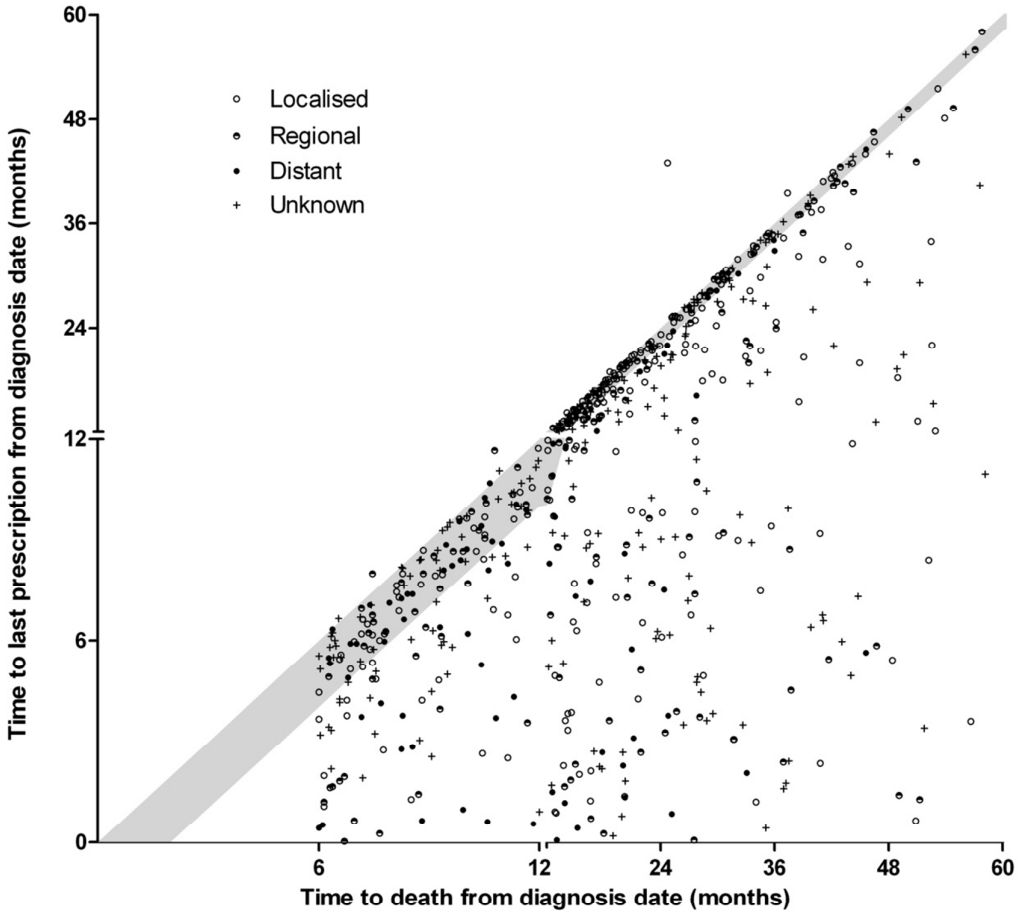


Figure 2: Scatter plot of time to last statin prescription against time to death from diagnosis date.

Shaded area indicates the period within 30days of death.



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