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Statin use and all-cancer survival: prospective results from the Women's Health Initiative

Ange Wang[1], Aaron K Aragaki[2], Jean Y Tang[3], Allison W Kurian[1,4], JoAnn E Manson[5], Rowan T Chlebowski[6], Michael Simon[7], Pinkal Desai[8], Sylvia Wassertheil-Smoller[9], Simin Liu[10], Stephen Kritchevsky[11], Heather A Wakelee[1] and Marcia L Stefanick*[,12]

[1]Department of Medicine, Division of Oncology, Stanford University School of Medicine, Stanford, CA 94305, USA; [2]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA; [3]Department of Dermatology, Stanford University School of Medicine, Stanford, CA 94305, USA; [4]Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA 94035, USA; [5]Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA; [6]Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA 90502, USA; [7]Department of Oncology, Karmanos Cancer Institute at Wayne State University, Detroit, MI 48344, USA; [8]Department of Medicine, Weill Cornell Medical College, New York, NY 10065, USA; [9]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY 10461, USA; [10]Department of Medicine, Brown University School of Medicine, Providence, RI 02903, USA; [11]Wake Forest School of Medicine, Winston-Salem, NC 27157, USA and [12]Department of Medicine, Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, CA 94305, USA

Background: This study aims to investigate the association between statin use and all-cancer survival in a prospective cohort of postmenopausal women, using data from the Women's Health Initiative Observational Study (WHI-OS) and Clinical Trial (WHI-CT).

Methods: The WHI study enrolled women aged 50–79 years from 1993 to 1998 at 40 US clinical centres. Among 146 326 participants with median 14.6 follow-up years, 23 067 incident cancers and 3152 cancer deaths were observed. Multivariable-adjusted Cox proportional hazards models were used to investigate the relationship between statin use and cancer survival.

Results: Compared with never-users, current statin use was associated with significantly lower risk of cancer death (hazard ratio (HR), 0.78; 95% confidence interval (CI), 0.71–0.86, $P<0.001$) and all-cause mortality (HR, 0.80; 95% CI, 0.74–0.88). Use of other lipid-lowering medications was also associated with increased cancer survival (P-interaction (int) = 0.57). The lower risk of cancer death was not dependent on statin potency (P-int = 0.22), lipophilicity/hydrophilicity (P-int = 0.43), type (P-int = 0.34) or duration (P-int = 0.33). However, past statin users were not at lower risk of cancer death compared with never-users (HR, 1.06; 95% CI, 0.85–1.33); in addition, statin use was not associated with a reduction of overall cancer incidence despite its effect on survival (HR, 0.96; 95% CI, 0.92–1.001).

Conclusions: In a cohort of postmenopausal women, regular use of statins or other lipid-lowering medications was associated with decreased cancer death, regardless of the type, duration, or potency of statin medications used.

Cancer is the second leading cause of death among women in the United States, with over 270 000 cancer deaths in 2015 (Siegel *et al*, 2015). The use of 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor medications ('statins' or 'HMG Co-A reductase inhibitors') for cholesterol reduction has been hypothesised to interfere with cancer growth and metastasis through multiple mechanisms (Fenton *et al*, 1992; Herold *et al*, 1995; Deberardinis *et al*, 2008; Gauthaman *et al*, 2009; Mannello and Tonti, 2009). Current literature on statin use and cancer survival has been mixed (Dale *et al*, 2006; Cholesterol Treatment Trialists' (CTT)

*Correspondence: Dr ML Stefanick; E-mail: stefanick@stanford.edu

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Table 1. Participants' characteristics in the Women's Health Initiative Clinical Trial and Observational Study by statin use (current *vs* never)[a] at time of cancer diagnosis ($N = 17\,285$[b])

	Current statin use ($N = 4025$)		Never used statins ($N = 13\,260$)		
	N	%	N	%	*P*-value[c]
Age at screening (years)					<0.001
50–59	1123	27.9	3973	30.0	
60–69	2089	51.9	6228	47.0	
70–79	813	20.2	3059	23.1	
Age at incident cancer					<0.001
<70	1338	33.2	6706	50.6	
70 to <80	2030	50.4	5295	39.9	
⩾80	657	16.3	1259	9.5	
Tumour stage					0.001
In situ	613	15.9	1732	13.8	
Local	1924	49.8	6203	49.4	
Regional	702	18.2	2552	20.3	
Distant	623	16.1	2079	16.5	
Race/ethnicity					0.15
White	3517	87.4	11 701	88.2	
Black	261	6.5	832	6.3	
Hispanic	86	2.1	310	2.3	
American Indian	16	0.4	38	0.3	
Asian/Pacific Islander	92	2.3	234	1.8	
Unknown	53	1.3	145	1.1	
Education					<0.001
High school/GED or less	899	22.5	2617	19.9	
School after high school	1534	38.3	4812	36.5	
College degree or higher	1570	39.2	5746	43.6	
BMI, baseline ($kg\,m^{-2}$)					<0.001
<25	1065	26.7	4745	36.1	
25 to <30	1474	37.0	4468	33.9	
30 to <35	882	22.1	2427	18.4	
⩾35	568	14.2	1522	11.6	
Smoking status					0.75
Never	1829	46.0	6115	46.7	
Past	1817	45.7	5904	45.1	
Current	326	8.2	1074	8.2	
Vitamin D intake (IU)					0.97
<200	1418	36.2	4690	36.1	
200 to <400	737	18.8	2483	19.1	
400 to <600	981	25.0	3229	24.9	
⩾600	784	20.0	2577	19.9	
Alcohol intake					<0.001
Non/past drinker	1121	28.1	3252	24.7	
<1 drink per week	1376	34.5	4367	33.2	
1–<7 drinks per week	986	24.7	3656	27.8	
⩾7 drinks per week	511	12.8	1890	14.4	
Physical activity (MET—min)					0.03
<100	824	21.7	2683	21.6	
100 to <500	1127	29.7	3420	27.5	
500 to <1200	1081	28.4	3620	29.1	
⩾1200	768	20.2	2709	21.8	
Has current health-care provider	3845	96.1	12 401	94.3	<0.001
Mammogram within last 2 years	3465	88.1	10 822	84.1	<0.001
Hysterectomy at randomisation	1526	37.9	4702	35.5	0.005
Unopposed oestrogen use status					0.64
Never used	2668	66.4	8752	66.1	
Past user	509	12.7	1752	13.2	
Current user	843	21.0	2746	20.7	
Oestrogen + progesterone use status					<0.001
Never used	2934	72.9	9166	69.2	
Past user	340	8.5	1123	8.5	
Current user	748	18.6	2964	22.4	
Age at menarche					0.31
<12	894	22.3	2900	22.0	
12–13	2262	56.4	7336	55.6	
⩾14	856	21.3	2970	22.5	

Table 1. (Continued)

	Current statin use ($N=4025$)		Never used statins ($N=13\,260$)		
	N	%	N	%	*P*-value[c]
Oral contraceptive use ever	1672	41.5	5451	41.1	0.63
CHD before cancer diagnosis	680	17.0	756	5.7	<0.001
Diabetes before cancer diagnosis	725	18.0	865	6.5	<0.001
Family history of cancer	2639	68.4	8888	69.8	0.12
Aspirin use	1136	28.2	2573	19.4	<0.001
NSAIDs	1684	41.8	4478	33.8	<0.001
DM trial					0.03
Comparison	1011	62.8	2985	59.6	
Intervention	600	37.2	2020	40.4	
CEE + MPA trial					0.007
Comparison	283	52.7	819	46.1	
Intervention	254	47.3	957	53.9	
CEE trial					0.04
Comparison	179	56.5	423	49.6	
Intervention	138	43.5	430	50.4	
CaD trial					0.15
Comparison	638	53.1	1856	50.7	
Intervention	563	46.9	1803	49.3	
Clinical trial participant	2218	55.1	6830	51.5	<0.001
	Mean	**(s.d.)**	**Mean**	**(s.d.)**	***P*-value**
Age (years)	63.6	(6.5)	63.7	(7.0)	0.37
Fruit and vegetable consumption[d]	4.0	(4.0)	4.1	(2.1)	0.004
Red meat consumption[d]	0.7	(0.5)	0.7	(0.6)	0.27
General health (0 worst–100 best)	73.6	(17.2)	75.9	(16.7)	<0.001

Abbrviations: BMI = body mass index; CaD = calcium + Vitamin D; CEE = conjugated equine estrogen; CHD = coronary heart disease; DM = dietary Modification; GED = general education development; MET = metabolic equivalent; MPA = medroxyprogesterone acetate; NSAID = nonsteroidal anti-inflammatory drugs.

[a]Statin (current *vs* never) were the exposure groups of interest for the primary analysis.

[b]At the time of incident cancer, 23 067 participants were at risk for death and included in the primary analyses. Of these, 4025 participants were currently taking statins; 13 260 participants never used statins; 397 participants had reported using statins at baseline or follow-up, but were not currently taking statins; and 5385 participants had medication inventories that were out of date, so their follow-up was censored. Exposure groups were modelled as a time-dependent exposure, so a participants' group status may change during follow-up (e.g., participants with an out-of-date inventory were allowed to re-enter the model when a current medications inventory was collected).

[c]On the basis of χ^2-test of association for categorical variables and *t*-test for continuous variables.

[d]Medium servings per day.

Collaborators *et al*, 2012; Murtola *et al*, 2014; Cardwell *et al*, 2015; Desai *et al*, 2015; Wu *et al*, 2015; Zhong *et al*, 2015), although a retrospective nationwide Danish study found a statistically significant 15% reduction in all-cancer mortality among patients who used statins before cancer diagnosis (Nielsen *et al*, 2012).

Given the widespread and rapidly growing statin use in the United States (Stone *et al*, 2014), we aimed to investigate the relationship between statin use and all-cancer survival in the Women's Health Initiative (WHI). To our best knowledge, this is the first prospective study to investigate statins and all-cancer survival.

MATERIALS AND METHODS

Design, setting, and participants. The WHI is a large, multicentre study designed to study major causes of morbidity and mortality in postmenopausal women. The WHI includes a clinical trial (CT) and an observational study (OS) cohort, with details described previously (Hays *et al*, 2003). Women meeting eligibility criteria (age 50–79, postmenopausal, minimum life expectancy 3 years) were recruited at 40 US clinical centres between 1 September 1993 and 31 December 1998. Primary analyses focused on current statin users among the $N=23\,067$ women who experienced an incident cancer during follow-up (Supplementary Figure 1).

Exposures, confounders, and classification of cases. WHI implementation details have been previously published (Anderson *et al*, 2003). The medication inventory was repeated at years 1, 3, 6, and 9 for the CT, and year 3 for the OS during the initial study period, which ended on 31 March 2005. The overall follow-up period for the study was through 20 September 2013. Cancers were initially verified at the local clinical centre, and then confirmed by centrally trained physician adjudicators (Curb *et al*, 2003).

Statistical analysis. Multivariable-adjusted Cox regression techniques were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) by modelling two-ordered events: time from enrolment to incident cancer (secondary end point) and time from incident cancer to cancer death (primary end point). Statin use was modelled as a time-dependent categorical variable (Therneau and Grambsch, 2000), with the following levels: (0) never use, (1) current use (at the time of the latest medication inventory), (2) past use, and (3) out-of-date medication inventory (Gong *et al*, 2016). The primary analysis compared

current (1) *vs* never used statins (0), to investigate the effect of regular statin use.

The Cox proportional hazard analyses were adjusted for potential confounders and included baseline covariates age, race/ethnicity, education, smoking, body mass index, physical activity, family history of cancer, current health-care provider, oral contraception use, prior unopposed oestrogen use, prior oestrogen plus progestin use, solar irradiance (latitude), prior CHD history, prior diabetes history, randomisation into the CaD trial, and age at menarche. Participants who did not die of cancer were censored at death due to other causes, last contact, or out-of-date medication collection.

All analyses were conducted using SAS software, version 9.3 (SAS Institute, Cary, NC, USA) and R software version 2.15 (R Foundation for Statistical, Vienna, Austria).

RESULTS

In our analysis, 146 326 participants contributed 1 805 759 person-years, median (interquartile range, IQR) = 14.6 (8.1–16.2) years of follow-up. A cumulative 24 404 women were diagnosed with an incident cancer (Supplementary Figure 1). Of this group, 23 067 women had additional follow-up, median (IQR) of 4.8 (1.8–9.4) years, with 7411 all-cause mortalities: 5837 cancer deaths following a diagnosis of incident cancer (78.8%), 613 cardiovascular deaths (8.3%), and 961 other causes (12.9%). After censoring the follow-up of women with out-of-date medication inventories, 3152 cancer deaths were included in the primary analysis of current *vs* never statin users (709 current statin users and 2443 non-users). Table 1, and Supplementary Tables 1 and 2 display baseline characteristics.

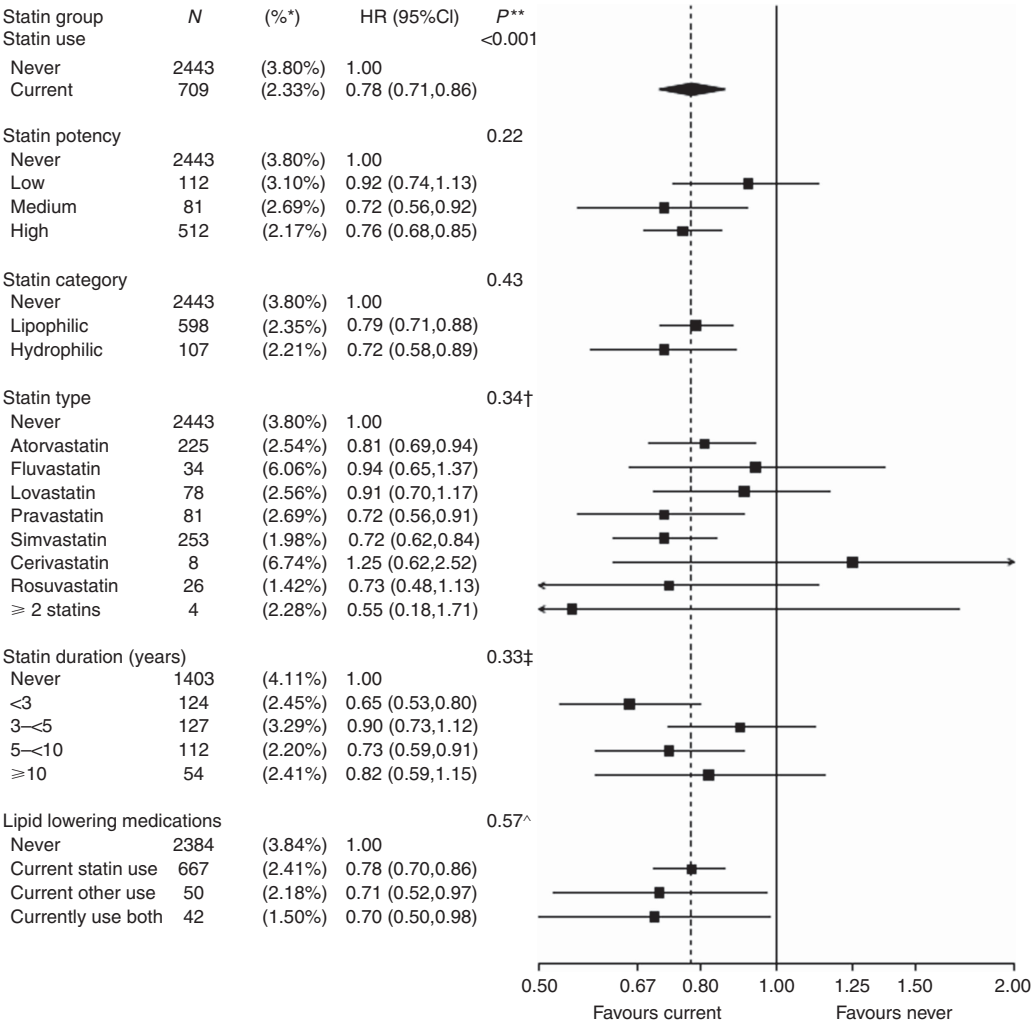

Figure 1. Number of cancer deaths (annualised %) and multivariable-adjusted HR (95% CI) for statin use (current *vs* never). Annualised percentages by exposure group (time dependent) were computed by dividing the total number of cancer deaths, by the corresponding cumulative person-time since cancer diagnosis, for each exposure group. Cox regression models were adjusted for age at baseline, race/ethnicity, education, smoking, body mass index (BMI), physical activity, family history of cancer, current health-care provider, oral contraception use, prior unopposed oestrogen use, prior oestrogen plus progestin use, solar irradiance (latitude), prior CHD history, prior diabetes history, randomisation into the CaD trial, age at menarche, and stratified by age group, study groups (randomisation arms of the HT trials, DM trial, and OS enrolment) and enrolment in WHI extensions (I/II). *Annualised percentage. **Significance test of the main effect or test of heterogeneity between non-referent exposure groups. †Test of heterogeneity between atorvastatin, simvastatin, lovastatin, and pravastatin. ‡Analysis of statin duration included only CT participants; at the time of cancer diagnosis, among current statin users ($n = 2218$), 893 (40.3%) used statins <3 years, 539 (24.3%) 3 to <5 years, 593 (26.7%) 5 to <10 years, and 193 (8.7%) 10+ years. Test of heterogeneity based on a 1 degree-of-freedom test for trend. ^Test of heterogeneity between statin use and other use.

Current statin use was associated with lower risk of cancer death compared with never-use (HR, 0.78; 95% CI, 0.71–0.86; $P<0.001$; Figure 1), and lower risk of all-cause mortality (HR, 0.80; 95% CI, 0.74–0.88). The lower risk of cancer death associated with statin use did not depend on statin potency (P-interaction (int) = 0.22), category (P-int = 0.43), type (P-int = 0.34), or duration (P-int = 0.33). Other lipid-lowering medications, used alone, were associated with a similar reduction in cancer deaths compared with monotherapy statin use (P-int = 0.57). Prior statin users were not at lower risk of cancer death compared with never-users (HR, 1.06; 95% CI, 0.85–1.33).

Statin use was associated with a significantly lower risk of multiple, but not all cancer types (P-int = 0.001; Figure 2). With the exception of current NSAID use (which attenuated the effect of statins), current statin use was not modified by any other subgroups (Supplementary Figure 2).

In a secondary analysis on cancer incidence, beginning at enrolment, statin use was not associated with a reduction of incident cancer (HR, 0.96; 95% CI, 0.92–1.001; $P = 0.056$).

DISCUSSION

In this prospective cohort study, we found that current statin use in postmenopausal women with cancer was associated with lower risk of cancer death. Use of other lipid-lowering medications was also associated with a lower risk of cancer death; this finding suggests that a reduction in circulating cholesterol levels may mediate increased cancer survival. However, a dose–response relationship was not found, suggesting that results should be interpreted cautiously. Multiple molecular mechanisms have been linked to statins and cancer, including the mevalonate pathway (Fenton *et al*, 1992; Herold *et al*, 1995; Deberardinis *et al*, 2008; Boudreau *et al*, 2010), G-proteins (Wong *et al*, 2002; Demierre *et al*, 2005), isoprenoid-mediated suppression (Wong *et al*, 2002), the RAF-mitogen-activated protein kinase 1 pathway (Wu *et al*, 2004), and anti-angiogenic properties of statins (Weis *et al*, 2002).

Comparison with other studies. Our study results are similar to findings from a retrospective nationwide Danish study, which found a statistically significant 15% reduction in all-cancer mortality among patients who used statins before cancer diagnosis (Nielsen *et al*, 2012). Our analysis is additionally strengthened by its prospective format, ethnically heterogeneous population, and covariate data. In addition, other studies of specific cancers in women (including breast and uterine) have suggested the protective effects of statins on cancer mortality and survival (Murtola *et al*, 2014; Cardwell *et al*, 2015; Nevadunsky *et al*, 2015). Also, some prospective cohort studies of cardiovascular disease have found associations between lower cholesterol levels and lower risk of death from several cancers (Cambien *et al*, 1980; Kagan *et al*, 1981; Keys *et al*, 1985).

However, several smaller studies and RCTs have found no significant associations. A meta-analysis of 27 RCTs in the Cholesterol Treatment Trialists' (CTT) Collaborators (2015) database did not find an association with cancer mortality or incidence; however, the study used the time from randomisation rather than the time from incident cancer. A meta-analysis of 26 RCTs also found no effect of statin use on cancer incidence or survival (Dale *et al*, 2006). These conflicting results suggest the need for additional prospective studies and larger RCTs, particularly with cancer survival as the primary outcome.

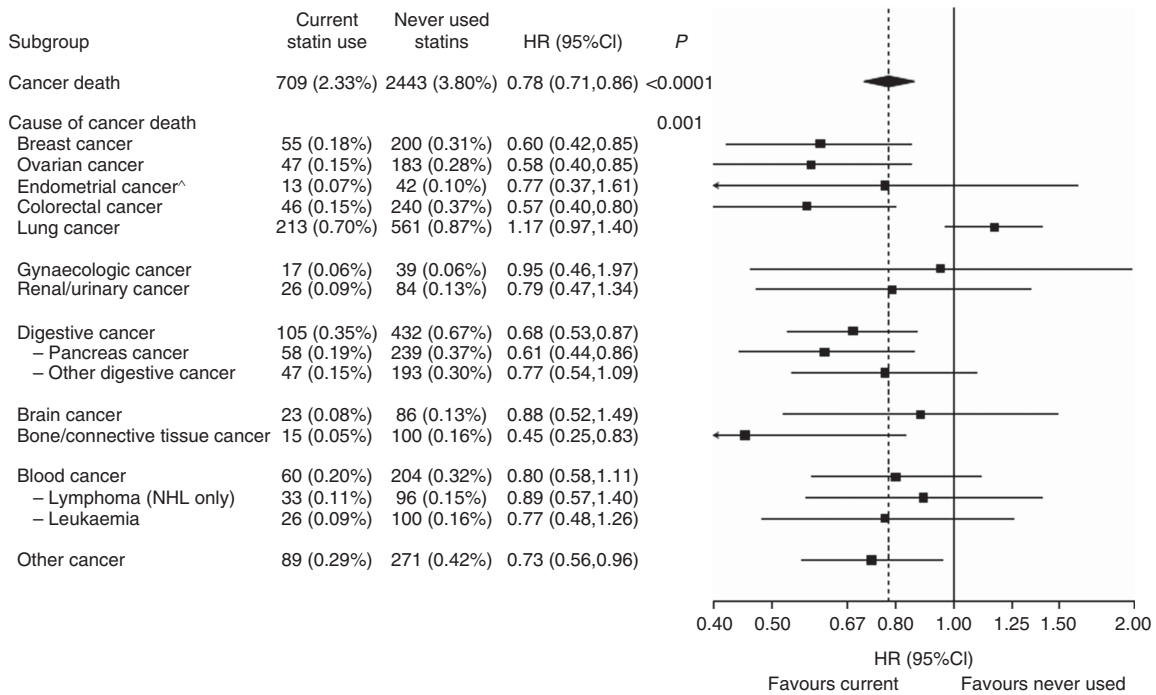

Figure 2. Number of cancer deaths (annualised %) and multivariable-adjusted HR (95% CI) for statin use (current *vs* never) by cause of cancer death. Summary statistics are from a Cox regression model, using cause-specific baseline hazard functions, with the covariate adjustments described above. *Corresponds to a significance test of the main effect, or an 11-df test of heterogeneity for cause of cancer death. To avoid double counting, test of heterogeneity is between the main causes of death listed and does not include subtypes (i.e., cancer of the pancreas or other digestive organs, non-Hodgkins lymphoma, and leukaemia). ^Only participants without a baseline hysterectomy were used to compute the number of cases and annualised rates. There was one endometrial cancer case among the group of no statin use that reported having had a hysterectomy.

Cancer incidence has been studied more extensively than cancer survival in relation to statin use, but results on the subject have been mixed (Bjerre and LeLorier, 2001; Bonovas *et al*, 2005; Browning and Martin, 2007; Kuoppala *et al*, 2008; Haukka *et al*, 2010; Jagtap *et al*, 2012; Simon *et al*, 2012; Desai *et al*, 2013; Singh and Singh, 2013; Tan *et al*, 2013). Similarly, biomarker-based studies of statins as candidate breast cancer chemoprevention agents have shown mixed results (Higgins *et al*, 2012; Bjarnadottir *et al*, 2013; Vinayak *et al*, 2013).

Strengths and limitations. The strengths of this study include its prospective nature, large size and geographic distribution, adjudication of cancer cases, and detailed information on confounders and exposures. Limitations of the study include the fact that medication use was not continuously updated, observational format, and majority Caucasian participants. The study may not be generalisable to populations other than postmenopausal women with similar age at cancer diagnosis. Residual confounding or reverse causation bias may be present.

Healthy user bias due to socioeconomic factors may also present in this analysis; however, this should be reduced as WHI data allow for rich covariate adjustment. In addition, the effect of statin use on cancer survival remained significant even with sensitivity analyses including tumour stage, physical functioning, and mammogram use.

CONCLUSIONS

In conclusion, in a prospective cohort of postmenopausal women, current use of statins and other cholesterol-lowering medications was associated with increased all-cancer survival, as well as increased survival of multiple cancer types. These findings, along with the previous Danish cohort study, suggest that statin use and/or lower cholesterol levels may have a protective effect on cancer death. Further research is needed in an RCT format to better control for healthy user bias and to study cancer as a primary outcome.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTORS

AW, JT, HW, AK, and MS participated in study conception and design. AA performed the data analysis. AW, AA, JT, HW, AK, and MS participated in initial data interpretation. AW and AA wrote the initial draft of the manuscript. All authors contributed to additional data interpretation and revisions and approval of the manuscript.

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