Original Research

Association Between Statin Use and Endometrial Cancer Survival

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OBJECTIVE: To evaluate the association of 3 hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitor (statin) use and concordant polypharmacy with disease-specific survival from endometrial cancer.

METHODS: A retrospective cohort study was conducted of 985 endometrial cancer cases treated from January 1999 through December 2009 at a single institution. Disease-specific survival was estimated by Kaplan-Meier analyses. A Cox proportional hazards model was used to study factors associated with survival. All statistical tests were two-sided and performed using Stata.

RESULTS: At the time of analysis, 230 patients (22% of evaluable patients) died of disease and median follow-up was 3.28 years. Disease-specific survival was greater (179/220 [81%]) for women with endometrial cancer taking statin therapy at the time of diagnosis and staging compared with women not using statins (423/570 [74%]) (log rank test, P=.03). This association persisted for the subgroup of patients with nonendometrioid endometrial tumors who were statin users (59/87 [68%]) compared with nonusers (93/193 [43%]) (log rank test, P=.02). The relationship remained significant (hazard ratio 0.63, 95% confidence interval [CI] 0.40–0.99) after adjusting for age, clinical stage, radiation, and other factors. Further evaluation of polypharmacy showed an association between concurrent statin and aspirin use with an especially low disease-specific mortality (hazard ratio 0.25, 95% CI 0.09–0.70) relative to those who used neither.

CONCLUSION: Statin and aspirin use was associated with improved survival from nonendometrioid endometrial cancer.

(Obstet Gynecol 2015;126:144–50)
DOI: 10.1097/AOG.0000000000000926

The use of statins, 3 hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors, is widespread, because they are used in treating hyperlipidemia, a common condition.[1] These medications reversibly inhibit the conversion of 3 hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate and reduce cholesterol.[2] Statin use has been associated with decreased incidence and death from cancers of the breast, colon, pancreas, gastrointestinal tract, liver, endometrium, and ovary.[3–7]

Proposed mechanisms to explain the association of statin use with decreased cancer incidence and death include lowering of cholesterol and systemic antiinflammatory effects.[8,9] Lower cholesterol may reduce metabolites that affect tumor apoptosis, inhibited angiogenesis, and impaired metastasis. Murine models of breast cancer when treated with statins were found to undergo increased apoptosis as well as decreased tumor cell proliferation.[10–12] Statins also reduced the proliferation of cancer cells in murine models of colon, liver, pancreatic, ovarian, and prostate cancers.[13–16] Epidemiologic studies have shown an inverse association of statin use with the incidence of uterine and ovarian cancer.[17] Women in the Cancer in the Ovary and Uterus Study who used statins after diagnosis had an improved survival from ovarian cancer and a trend toward improved survival from endometrial cancer.

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Supported in part by the Albert Einstein Cancer Center through its National Cancer Institute Cancer Center Support Grant (P30CA013330) and National Institutes of Health K12CA 132783-03.

Presented in part at the Annual Meeting of the Society for Gynecologic Investigations, March 20–23, 2013, Orlando, Florida.

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Financial Disclosure
The authors did not report any potential conflicts of interest.

ISSN: 0029-7844/15

No prior study of statins and mortality and progression from endometrial cancer have distinguished between type 1 (endometrioid) and type 2 (nonendometrioid) tumors in the published literature in MEDLINE from 1946 until April 2015 (search terms: type 2 endometrial cancer, statins, nonendometrioid). The goal of our study was to assess the association of statin use with disease-specific survival from type 1 and type 2 endometrial cancer and the association of concordant polypharmacy to disease-specific survival.

MATERIALS AND METHODS

Institutional review board approval was obtained to review all patients treated for endometrial cancer at Montefiore Medical Center from January 1, 1999, to December 31, 2009. Statin use, age, body mass index (calculated as weight (kg)/[height (m)]^2), race, diabetes, hyperlipidemia, hypertension, metformin, aspirin, and antihypertensive medications were obtained from anesthesia records on the day of surgical staging. Patients whose anesthesia records were unavailable were excluded from the analysis. Excluded records were assumed missing at random because all anesthesia records before the electronic medical record initiation were unobtainable. Histology, stage, grade, and date of death were obtained from review of all available records. Age was reported at the date of diagnosis. Histologic subtypes were divided into type 1 (endometrioid) and type 2 (nonendometrioid). Nonendometrioid subtypes included papillary serous, clear cell, mixed, and carcinosarcomas. Sarcomas and other histologies were excluded. Stage was determined by the 1988 International Federation of Gynecology and Obstetrics criteria.[18] Cause and date of death were obtained by review of records and the National Death Index. Survival was calculated from date of diagnosis to date of death from endometrial cancer. All data were entered by trained personnel and kept in date-referenced sequential files. Histopathologic and medication records were validated by physician-level data auditors. Periodic verification of randomly chosen data points with source documents was performed to ensure data fidelity during analysis.

Selected patient and tumor characteristics at the time of diagnosis were summarized as continuous, ordinal, or categorical variables. Dose potencies were calculated according to published data of mean percentage reduction in low dense lipoprotein levels[19] (see Appendix 1, available online at http://links.lww.com/AOG/A659).

Statin dose potency was categorized into three levels: less than 30% reduction in low-density lipoprotein (LDL), 30–50% reduction in LDL, and greater than 50% reduction in LDL.

Disease-specific survival was estimated using the Kaplan-Meier method and the stratified log rank test was used to compare survival between strata. Univariable and multivariable Cox proportional hazard regression models were fit to determine the variables associated with disease-specific mortality. Factors related to disease-specific mortality in patients with endometrial cancer found to have $P<.10$ in univariable analysis were included in the multivariable model. Variables with evidence of colinearity were excluded from the model. All analyses were performed using Stata 12.0. All P values are two-sided.

RESULTS

Of 985 patients with endometrial cancer, 983 were considered evaluable because verification of death from disease or living was available by hospital medical record or the National Death Index. Two patients who were not verifiable were excluded from the analysis. Of the remaining, 983,220 (22.4%) had documented statin use, 629 (64%) had documentation that they were not statin users, and 198 (20%) had incomplete charts (statin use could not be verified on the day of surgery). Five hundred ninety-one (57%) had type 1 and 338 (34%) had type 2 histology. Of the type 2 cancers, 87 (26%) patients were statin users. Compared with nonstatin users, those who used statin were older (68 compared with 63 years, $P<.01$) and more likely to have hypertension (89% compared with 59%, $P<.01$) and hyperlipidemia (99.5% compared with 13%, $P<.01$). They were more likely to use aspirin (39% compared with 13%, $P<.01$), metformin (24% compared with 9%), β-blockers (43% compared with 24%, $P<.01$) and were more often treated with radiation (46% compared with 35%, $P<.01$). Complete information on specific statin type (n=221) and dose (n=180) was available for 81% of patients (Table 1).

Table 1. Statin Frequency and Dose for Patients With Endometrial Cancer

Statin	Frequency	%	Dose Range (mg)
Atorvastatin	95	43.0	10–80
Simvastatin	85	38.5	5–80
Lovastatin	13	5.9	10–80
Pravastatin	11	5.0	10–80
Rosuvastatin	8	3.6	5–40
Ezetimibe and simvastatin	8	3.6	10–10 and 10–80
Cerivastatin	1	0.5	0.4

Table 2. Patient Characteristics by Survival Status (Died of Disease vs Censoring) for Patients With Type 1 and Type 2 Endometrial Cancer

	Type 1 and 2 Cancers		Type 1 Cancers		Type 2 Cancers	
Variable	Censored (Alive or Died of Other causes)	Died of Disease	Censored (Alive or Died of Other Causes)	Died of Disease	Censored (Alive or Died of Other Causes)	Died of Disease
Frequency	753 (76.6)	230 (23.4)	548 (92.7)	43 (7.3)	180 (53.3)	158 (46.7)
Follow-up (y)	4.49 (2.32–7.20)	1.19 (0.60–2.39)	4.78 (2.47–7.35)	1.89 (0.79–3.35)	3.55 (1.90–6.64)	1.10 (0.61–2.05)
Age (y)	62.7±11.2	67.7±10.7	61.5±11.6	66.7±12.2	67.4±8.5	69.7±9.1
BMI (kg/m^2)	33.1±8.5	29.6±7.1	34.1±8.8	30.8±6.0	30.6±7.2	29.2±7.2
Stage						
1	599 (79.5)	65 (28.3)	467 (85.2)	17 (39.4)	117 (65.0)	37 (23.4)
2	57 (7.6)	23 (10.0)	37 (6.8)	7 (16.3)	19 (10.6)	15 (9.5)
3	67 (8.9)	50 (21.7)	30 (5.5)	6 (14.0)	30 (16.7)	39 (24.7)
4	19 (2.5)	76 (33.0)	5 (0.9)	7 (16.3)	12 (6.6)	59 (37.3)
Unstaged (biopsy only)	11 (1.5)	16 (7.0)	9 (1.6)	6 (14.0)	2 (1.1)	8 (5.1)
Grade						
1	377 (50.1)	19 (8.3)	365 (66.6)	14 (32.6)	2 (1.1)	1 (0.6)
2	125 (16.6)	17 (7.4)	121 (22.1)	15 (34.8)	1 (0.6)	1 (0.6)
3	248 (32.9)	193 (83.9)	61 (11.1)	14 (32.6)	175 (97.2)	155 (98.2)
No grade	3 (0.4)	1 (0.4)	1 (0.2)	0 (0.0)	2 (1.1)	1 (0.6)
Hypertension						
No	297 (39.4)	84 (36.5)	226 (41.2)	17 (39.5)	55 (30.6)	55 (34.8)
Yes	455 (60.4)	146 (63.5)	322 (58.8)	26 (60.5)	125 (69.4)	103 (65.2)
Diabetes						
No	552 (73.3)	180 (78.3)	404 (73.7)	34 (79.1)	125 (69.4)	123 (77.8)
Yes	201 (26.7)	50 (21.7)	144 (26.3)	9 (20.9)	55 (30.6)	35 (22.2)
Hyperlipidemia						
No	483 (64.1)	174 (75.7)	362 (66.1)	32 (74.4)	102 (56.7)	120 (75.9)
Yes	270 (35.9)	56 (24.3)	186 (33.9)	11 (25.6)	78 (43.3)	38 (24.1)
Statin use						
No	423 (56.2)	147 (63.9)	314 (57.3)	31 (72.1)	93 (51.7)	100 (63.3)
Yes	179 (23.8)	41 (17.8)	118 (21.5)	7 (16.3)	59 (32.8)	28 (17.7)
Missing	151 (20.0)	42 (18.3)	116 (21.2)	5 (11.6)	28 (15.5)	30 (19.0)
Aspirin use						
No	476 (63.2)	153 (66.5)	353 (64.4)	30 (69.8)	108 (60.0)	104 (65.8)
Yes	122 (16.2)	34 (14.8)	77 (14.1)	8 (18.6)	42 (23.3)	23 (14.6)
Missing	155 (20.6)	43 (18.7)	118 (21.5)	5 (11.6)	30 (16.7)	31 (19.6)
Metformin						
No	653 (86.7)	212 (92.2)	477 (87.0)	39 (90.7)	153 (85.0)	146 (92.4)
Yes	98 (13.0)	18 (7.8)	70 (12.8)	4 (9.3)	26 (14.4)	12 (7.6)
Missing	2 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.6)	0 (0.0)
β-blocker						
No	434 (57.6)	118 (51.3)	317 (57.9)	20 (46.5)	104 (57.8)	83 (52.5)
Yes	167 (22.2)	63 (27.4)	115 (21.0)	17 (39.5)	48 (26.7)	40 (25.3)
Missing	152 (20.2)	49 (21.3)	116 (21.1)	6 (14.0)	28 (15.5)	35 (22.2)
Radiation						
None	490 (65.1)	120 (52.2)	419 (76.5)	20 (46.5)	58 (32.2)	85 (53.8)
Any	263 (34.9)	110 (47.8)	129 (23.5)	23 (53.5)	122 (67.8)	73 (46.2)
Chemotherapy						
None	582 (77.3)	85 (37.0)	512 (93.4)	25 (58.1)	55 (30.6)	45 (28.5)
Any	171 (22.7)	145 (63.0)	36 (6.6)	18 (41.9)	125 (69.4)	113 (71.5)

BMI, body mass index.
Data are n (%), median (interquartile range), or mean±standard deviation.

At the time of analysis, 280 patients (28%) had died of whom 230 (22%) patients had died of endometrial cancer, 48 (5%) patients had died without evidence of disease, and the cause of death for two patients was undetermined. In the subset of patients with confirmed statin use data (n=790), 18.6% (n=41) of statin users had died of disease and 81.4% (n=180) were censored. In the statin nonusers, 25.8% (n=147)

had died of disease and 74.2% (n=423) were censored. Median follow-up time for the entire cohort was 3.28 years (range 0.03–13.9 years). Median survival in statin users that died of disease was 1.14 years (interquartile range 0.42–2.49 years) and in nonusers was 1.21 years (interquartile range 0.60–2.28 years), respectively. Median follow-up in statin users who were censored was 3.4 years (interquartile range 2.08–5.41 years) and in nonusers was 3.6 years (interquartile range 2.10–6.07 years), respectively. Patient baseline characteristics by survival status are presented in tabular form in Table 2. Disease-specific survival was greater (179/220 [81%]) for women with endometrial cancer taking statin therapy at the time of diagnosis and staging compared with women not using statins (423/570 [74%]) (log rank test, *P*=.03) (Fig. 1). The association of improved disease-specific survival for the subgroup of patients with type 2 endometrial tumors who were statin users (59/87 [68%]) compared with nonusers (93/193 [43%]) persisted (log rank test, *P*=.02) but not for the subgroup of patients with type 1 tumors (Figs. 2 and 3). On further stratification by statin and aspirin use, there was an of improved disease-specific survival in those patients with type 2 histology (stratified log rank *P*=.03; Fig. 4) for users of both statins and aspirin. In type 2 cancers statin potency was associated with disease-specific survival (*P*=.04) and test of trend between categories was noted (*P*=.05; Fig. 5).

Type 2 cancers were further studied using Cox models. In univariate models factors associated with disease-specific mortality included age, stage, radiation, aspirin, metformin, hyperlipidemia, and statin use (Table 3). As a result of the suggested colinearity

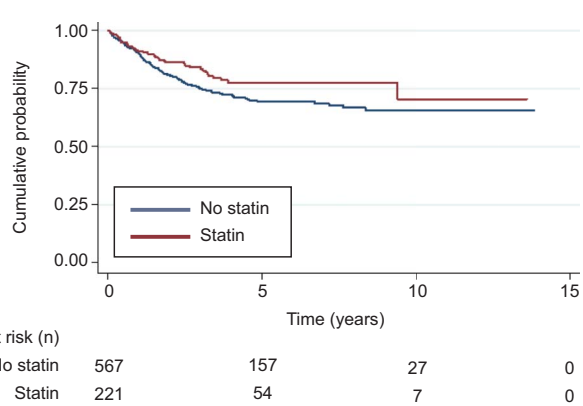

Fig. 1. Kaplan-Meier survival analysis comparing patients with endometrial cancer who were statin users compared with nonusers (*P*=.03).

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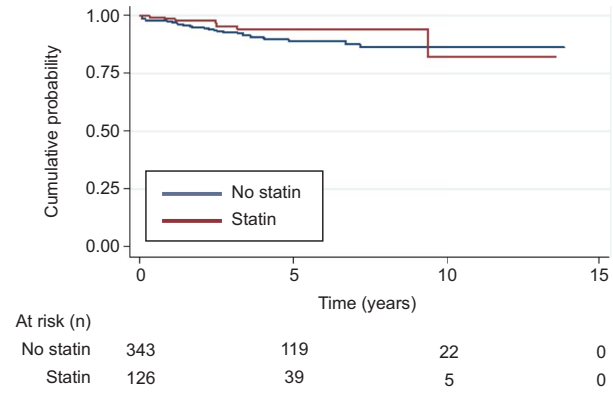

Fig. 2. Kaplan-Meier survival analysis comparing patients with endometrial cancer who were statin users and nonusers as stratified by endometrioid (type 1) histologic subtype.

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of hyperlipidemia with the statin use variable (variance inflation factor = 3.2), it was not maintained in the final model. Statin use remained statistically significant in multivariable modeling (hazard ratio [HR] 0.63, 95% confidence interval [CI] 0.40–0.99, *P*=.045) after adjusting for age, stage, radiation, and aspirin use. Concurrent use of statin and aspirin had an inverse association with disease-specific mortality (HR 0.25, 95% CI 0.09–0.70) relative to those who used neither and additionally relative to those who used a statin only (HR 0.29, 95% CI 0.14–0.61) or aspirin only (HR 0.25, 95% CI 0.11–0.53). Adjustment for metformin had no discernable effect on these associations nor was an interaction by metformin use observed.

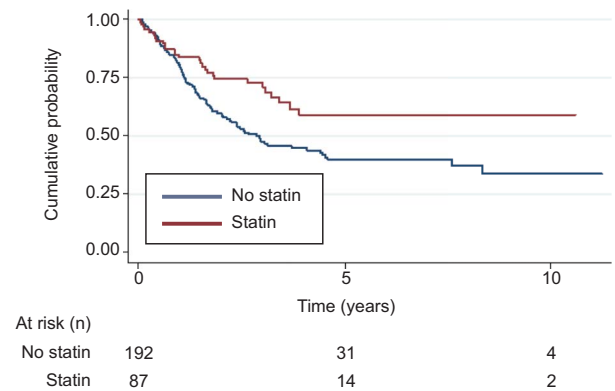

Fig. 3. Kaplan-Meier survival analysis comparing patients with endometrial cancer who were statin users and nonusers as stratified by nonendometrioid (type 2) histologic subtype (*P*=.02).

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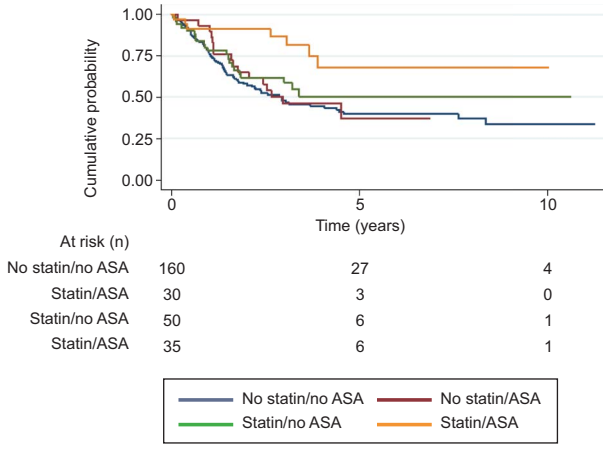

Fig. 4. Kaplan-Meier survival analysis comparing patients with endometrial cancer who were users of statins only, aspirin only, neither statin nor aspirin, and statin and aspirin (ASA) of nonendometrioid type 2 histologic subtype (P=.03).

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DISCUSSION

In this retrospective single-institution cohort, statin use was associated with an improved disease-specific survival for women with endometrial cancer. This association persisted for women with type 2 but not type 1 cancers after stratification for histologic subtype. There was also a synergistic relationship between stain and aspirin use. These data suggest that further study of statin and aspirin use in women with type 2 endometrial cancers should be considered.

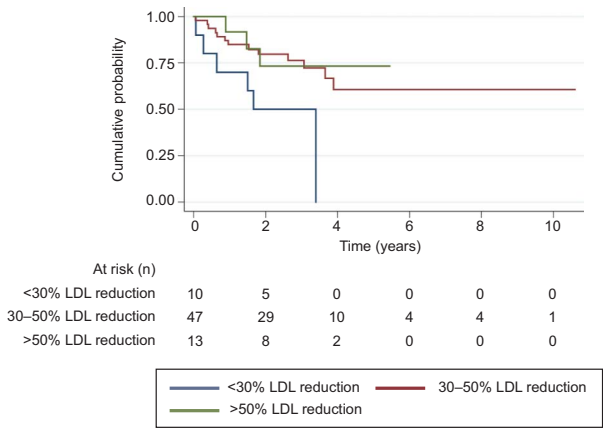

Fig. 5. Kaplan-Meir survival analysis of patients with nonendometrioid (type 2) histologic subtype as stratified by statin dose potency (P=.04, test of trend P=.05). LDL, low-density lipoprotein.

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Our data are in agreement with the published associations of decreased mortality from cancers for statin users compared with nonusers by a retrospective-based study by Neilsen et al.[20] In that population-based study of Danish patients who had a diagnosis of cancer, the multivariable adjusted HR was 0.85 (95% CI 0.82–0.87) for statin users. Elmore et al[21] reported on improved overall survival for women with epithelial ovarian cancer who were statin users compared with nonusers (P=.04). Additionally, in a study of both endometrial and ovarian cancers, Lavie et al[17] found improved survival for ovarian (log rank P=.02, HR 0.45, 95% CI 0.23–0.87) and a trend toward improved survival for endometrial cancers for patients taking statin therapy.

The mechanism for the association of statin use with improved survival has not been fully explained. However, Schointuch et al[22] have reported antiproliferative and antimetastatic effects in vitro of endometrial cancer cell lines treated with statins as a result of modulation of the mitogen-activated protein kinase and AKT/mammalian target of rapamycin pathways. Effect of statin and aspirin use on development of deep vein thrombosis, as a contributor to mortality, has failed to show a decreased risk of thromboembolic events, so it is unlikely that the survival benefit is related to prevention of thrombosis.[23] Li et al[24] have reported that decreased LDL was associated with survival in advanced-stage epithelial ovarian cancers of predominately papillary serous histologic types. These data suggest biological plausibility for a mechanism related to lipid metabolism as an explanation of the effect of statin therapy on mortality from cancer.

There is an important distinction in our data from previous evaluations of the effect of statin on cancer mortality in that none of the previous studies evaluated the effect of histologic type of cancer.[17,20] Differences in the effect of statins on histologic type may reflect biomolecular pathways that are influenced by statin and aspirin use. Additionally, in the work by Lavie et al, the survival advantage was only appreciated when patients used statins after diagnosis in their cohort. By the exclusion of patients using statin before diagnosis, those data may have been subject to time lag bias. The cohort of Lavie et al also included both ovarian and uterine cancers and did not attempt distinction of histologic subtypes or polypharmacy. Similarly, in a meta-analysis of the effect of statin use on risk of gynecologic cancers, there was no association of decreased incidence of endometrial cancers found for statin users.[25] However, in this meta-analysis, there was no distinction made between histopathologic subtypes of endometrial cancers. Studies confined to

Table 3. Univariable and Multivariable Cox Proportional Hazards Regression Models for Type 2 Endometrial Cancers

	Cox Regression Models for Type 2 (Nonendometrioid) Cancers (n=282)					
	Univariate			Multivariate		
Variable	HR	95% CI	*P*	HR	95% CI	*P*
Age (y)	1.02	1.00–1.04	.02	1.03	1.00–1.05	.02
BMI (kg/m^2)	0.98	0.96–1.00	.11			
Stage			<.01*			<.01*
1	1.00 (ref)			1.00 (ref)		
2	1.95	1.07–3.55	.03	2.02	1.04–3.93	.04
3	3.93	2.50–6.20	<.01	4.55	2.73–7.58	<.01
4	8.86	5.76–13.63	<.01	7.60	4.56–12.67	<.01
Unstaged	7.18	3.33–15.48	<.01	5.60	2.35–13.34	<.01
Grade			.62*			
1	1.00 (ref)					
2	1.90	0.17–21.02	.60			
3	1.88	0.47–6.58	.38			
No grade						
Hypertension						
No	1.00 (ref)					
Yes	0.86	0.62–1.20	.38			
Diabetes						
No	1.00 (ref)					
Yes	0.73	0.50–1.06	.10			
Hyperlipidemia						
No	1.00 (ref)					
Yes	0.49	0.34–0.71	<.01			
Statin use						
No	1.00 (ref)			1.00 (ref)		
Yes	0.56	0.37–0.85	<.01	0.63	0.40–0.99	.048
Aspirin use						
No	1.00 (ref)			1.00 (ref)		
Yes	0.62	0.40–0.98	.04	0.60	0.36–0.99	.046
Metformin						
No	1.00 (ref)			1.00 (ref)		
Yes	0.53	0.28–0.98	.04	1.02	0.54–1.94	.95
β-blocker						
No	1.00 (ref)					
Yes	1.06	0.73–1.55	.75			
Radiation						
None	1.00 (ref)			1.00 (ref)		
Any	0.41	0.30–0.56	<.01	0.58	0.40–0.84	<.01
Chemotherapy						
None	1.00 (ref)					
Any	1.09	0.77–1.54	.62			

HR, hazard ratio; CI, confidence interval; ref, reference; BMI, body mass index.
* Overall Wald.

Asian populations only showed a significant association (relative risk −0.46, 95% CI 0.28–0.74); however, the authors did not report on the histopathology of these confined cases.

Limitations of this study included retrospective data collection as well as information related to timing, dose, and adherence to disease occurrence, recurrence, and survival. The finding of an association of improved survival with statin use may reflect improved health awareness in statin and aspirin users as opposed to a biological effect on cancer cells.

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