Post-Diagnostic Statin Use, Cholesterol Levels, and Mortality Risk Among American Breast Cancer Patients: Insights from the NHANES Survey

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Background

HMG-CoA inhibitors (statins) represent a class of lipid lowering agents hypothesized to lower both breast cancer-specific mortality and breast cancer recurrence risk.[1] Although the underlying biological mechanism(s) remain elusive, emerging data suggests that manipulating cholesterol levels may induce immunogenic, antitumor responses.[2]

Utilizing lab records from 13,378 Finnish breast cancer patients collected between 1995-2013, Murto et al. find that post-diagnostic statin use reduced breast cancer-specific mortality risk by 15%, while elevated total cholesterol levels post-diagnosis increased breast cancer-specific mortality risk by 7%.[3]

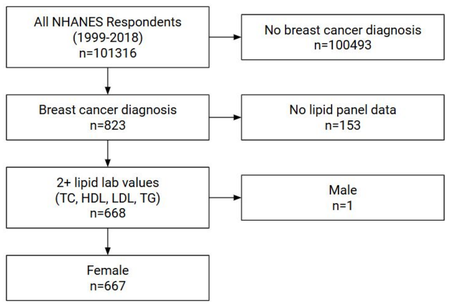
Objective

To assess whether post-diagnostic statin use led to differential **cancer-specific mortality** among a representative sample of female breast cancer patients in the United States over a 20-year span after accounting for differences in patients' lipid profiles.

Methods

Study Design: This case-control analysis was performed using biannual datasets from the National Health and Nutrition Survey (NHANES) from 1999-2018.[4] SAS® v9.4 was used to link patients' demographic, medical, prescription, and lipid lab information with public-use mortality records from 2019.[5]

Sample Selection: This analysis included data from 667 NHANES participants from 1999-2018 with at least two available lipid panel lab values (total cholesterol, HDL, LDL, or triglycerides). The full inclusion/exclusion criteria used to derive the sample are denoted in the flowchart below.



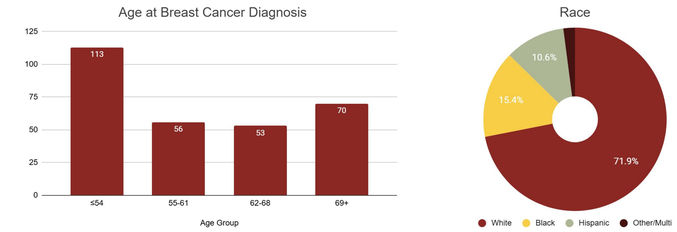
To adjust for the effects of time on mortality, we restricted our final analysis to **n=292** participants from 1999-2008.

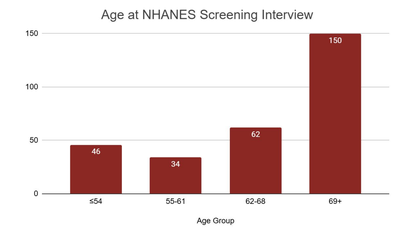
Explanatory Variables: Normal vs. elevated lipid profiles, statin use vs. nonuse (validated using corresponding pill containers)

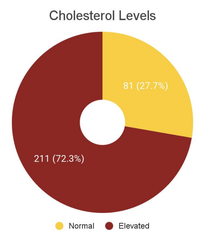
Control Variables: Age at diagnosis, age at NHANES screening interview, race, comorbidities (hypertension, diabetes, coronary heart disease)

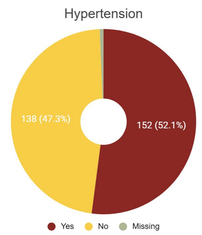
Results

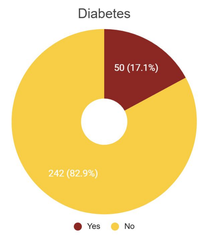
Figures 1a-h. Descriptive statistics (1999-2008, n=292)

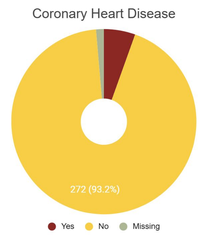


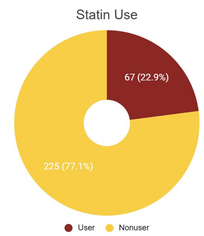












Chi-squared tests were performed on each explanatory and control variable, as well as all-cause and cancer-specific mortality, to determine whether their distributions were consistent across biannual NHANES cycles from 1999-2008. At the 99% confidence level race was the only variable that differed significantly across cycles, likely due to efforts to oversample Hispanic-Americans starting the 2007-08 cycle.[6] The visibly large discrepancy between the distributions of age at diagnosis and age at screening interview are similarly explained by NHANES's efforts to oversample adults age 80 and older (a trend we verified by generating comparable age distributions for n=187 colon cancer patients recruited into NHANES between 1999-2008).[6]

Tables 1-2. Statin use, lipid levels vs. cancer-specific mortality

	Cancer-specific death	No cancer-specific death	Total
Statin user	10 (14.9%)	57 (85.1%)	67
Statin nonuser	42 (18.7%)	183 (81.3%)	225
Total	52	240	292

OR: 0.76 (0.36, 1.62); p=0.48

	Cancer-specific death	No cancer-specific death	Total
Elevated lipid profile	39 (18.5%)	172 (81.5%)	211
Normal lipid profile	13 (16.0%)	68 (84.0%)	81
Total	52	240	292

OR: 1.19 (0.60, 2.36); p=0.63

Post-diagnostic statin use was associated with a 24% reduction in cancer-specific mortality risk. By contrast, elevated lipid profiles post-diagnosis were associated with a 19% increase in cancer-specific mortality. While neither result was significant at the 95% confidence level, both findings are consistent with those of Murto et al.

Tables 3-4. Statin use, lipid levels vs. cancer-specific mortality in patients with diabetes (1999-2010, n=63)

	Cancer-specific death	No cancer-specific death	Total
Statin user	1 (4.2%)	23 (95.8%)	24
Statin nonuser	11 (28.2%)	28 (81.3%)	39
Total	12	51	63

OR: 0.11 (0.01, 0.92); p=0.04

	Cancer-specific death	No cancer-specific death	Total
Elevated lipid profile	10 (20.8%)	38 (79.2%)	48
Normal lipid profile	2 (13.3%)	13 (86.7%)	15
Total	12	51	63

OR: 1.71 (0.33, 8.85); p=0.52

Post-diagnostic statin use was associated with significantly reduced cancer-specific mortality risk within this subgroup of 63 NHANES participants with comorbid diabetes. By contrast, elevated lipid profiles were not associated with significantly elevated cancer-specific mortality within this subgroup. These findings are consistent with those of Hosio et al., who report that statin use was consistently associated with reduced breast cancer-specific mortality in 3,165 Finnish breast cancer patients with type 2 diabetes observed between 1998-2013 using national cancer registry data similar to Murto et al.[3,7] Notably, Hosio et al. report no significant associations between antidiabetic medication use and reduced breast cancer-specific mortality within these patients.[7]

Conclusions

As diabetes-associated insulin resistance plays a known role in breast cancer tumorigenesis,[8] our findings suggest that statins may possess certain other antitumorigenic properties beyond the cholesterol reduction pathway.

Providers treating breast cancer patients with comorbid diabetes should be urged to initiate these patients on statin therapy (if not already prescribed) for potential life-preserving benefits beyond cholesterol reduction.

Definitions

Elevated lipid profile - A lipid profile with at least one of the following lab values:

- Total cholesterol (TC) > 193.05 mg/dL
- HDL < 46.32 mg/dL
- LDL > 115.84 mg/dL
- Triglycerides (TG) > 150.44 mg/dL

Statin use - Use of one or more of the following medications: amlodipine/atorvastatin, atorvastatin, ezetimibe/simvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, or simvastatin

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