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Beta Blockers and Breast Cancer Mortality: A Population-Based Study

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ABSTRACT

Purpose
Preclinical studies have demonstrated that antagonism of β_2-adrenergic signaling inhibits several pathways necessary for breast tumor progression and metastasis. A series of population-based observational studies were conducted to examine associations between beta blocker use and breast tumor characteristics at diagnosis or breast cancer–specific mortality.

Patients and Methods
Linked national cancer registry and prescription dispensing data were used to identify women with a diagnosis of stage I to IV invasive breast cancer between January 1, 2001, and December 31, 2006. Women taking propranolol (β_1/β_2 antagonist; n = 70) or atenolol (β_1 antagonist; n = 525), in the year before breast cancer diagnosis were matched (1:2) to women not taking a beta blocker (n = 4,738). Associations between use of propranolol or atenolol and risk of local tumor invasion at diagnosis (T4 tumor), nodal or metastatic involvement at diagnosis (N2/N3/M1 tumor), and time to breast cancer–specific mortality were assessed.

Results
Propranolol users were significantly less likely to present with a T4 (odds ratio [OR], 0.24, 95% CI, 0.07 to 0.85) or N2/N3/M1 (OR, 0.20; 95% CI, 0.04 to 0.88) tumor compared with matched nonusers. The cumulative probability of breast cancer–specific mortality was significantly lower for propranolol users compared with matched nonusers (hazard ratio, 0.19; 95% CI, 0.06 to 0.60). There was no difference in T4 or N2/N3/M1 tumor incidence or breast cancer–specific mortality between atenolol users and matched nonusers.

Conclusion
The results provide evidence in humans to support preclinical observations suggesting that inhibiting the β_2-adrenergic signaling pathway can reduce breast cancer progression and mortality.

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INTRODUCTION

Epidemiologic and preclinical studies have associated several biobehavioral signaling pathways with cancer progression.[1-5] Recent studies have focused on the neuroendocrine regulation of breast tumor progression, mediated through activation of the sympathetic nervous system and release of the adrenergic neurotransmitters epinephrine and norepinephrine. These studies have shown that adrenergic signaling can regulate several pathways necessary for breast tumor progression and metastasis through direct effects on tumor cells and the tumor microenvironment.[1-5]

Preclinical models have demonstrated that epinephrine and norepinephrine induce tumor cell invasion and migration, key steps in tumor progression and the pathogenesis of metastasis.[6-15] Norepinephrine exerts chemokinetic and chemotactic effects on breast tumors, increasing the number of and influencing the direction of migrating cells.[8,9] Similar findings have been reported for several other tumor types including ovarian, colon, and prostate tumors.[9-11,14,15] β-adrenergic signaling is also involved in the regulation of immune responses to breast tumor cells,[16] the inhibition of apoptosis,[17,18] and the induction of vascular endothelial growth factor expression.[13-15,19] In vivo studies of β-adrenergic signaling in breast tumor models have demonstrated an association with increased nodal involvement and development of metastasis but no effect on primary tumor growth.[16] It has been shown that these effects are mediated through the β-adrenergic pathway, specifically the β_2

receptor, and are inhibited by β_2 receptor antagonists (eg, propranolol).[8-12,15,16,20] Similar inhibitory effects are not observed with the use of β_1 selective antagonists (eg, atenolol).[8-10,15]

On the basis of this extensive preclinical evidence, we hypothesized that the use of a beta blocker with β_2 receptor activity before breast cancer diagnosis would result in a lower risk of local tumor invasion, nodal involvement, or metastatic disease and, in addition, continued use of these medications post diagnosis would result in a decrease in breast cancer–specific mortality. A series of matched population-based observational studies were performed to determine associations between the use of propranolol, a nonselective β_1/β_2 antagonist (β_1:β_2 receptor activity, 1:2),[21] or atenolol, a selective β_1 antagonist (β_1:β_2 receptor activity, 35:1),[21] and the risk of local tumor invasion at diagnosis, nodal and metastatic involvement at diagnosis, and breast cancer–specific mortality.

PATIENTS AND METHODS

Data Sources

This study was conducted by using prescription dispensing data from Ireland's General Medical Services (GMS) scheme, linked to patient records from the National Cancer Registry Ireland (NCRI) between January 1, 2000, and December 31, 2007. The GMS provides taxpayer-funded health care, including medicines, to approximately one third of the Irish population (1.35 million people).[22] Eligibility for the scheme is primarily by means test and age, with patients older than age 70 years automatically qualifying for entry before January 2009.[23] All medicines dispensed and basic demographic information are recorded for each patient. The NCRI database is a population-based tumor registry that collects detailed patient characteristics, comprehensive tumor details, treatment data, and mortality data for each newly diagnosed cancer patient. These data are actively collected by NCRI tumor registration officers from pathology reports and patient records. Mortality data, including cause and date of death, are obtained from death certificates. Tumor registration is estimated to be in excess of 98% complete.[24] Both data sets are well characterized and have been used extensively for health care research.[25-27] Data usage agreements have been established with the GMS and NCRI, and all potentially traceable patient identifiers were removed from the data before analysis.

Source Population and Exposure Definitions

The source population consisted of all women age 40 years or older with a diagnosis of stage I to IV[28] invasive breast cancer between January 1, 2001, and December 31, 2006. Patients were excluded if they had a diagnosis of invasive breast cancer before January 1, 2001, or if their initial diagnosis of breast cancer was at death. All patients were required to have GMS eligibility in the year before breast cancer diagnosis. Systematic breast cancer screening in

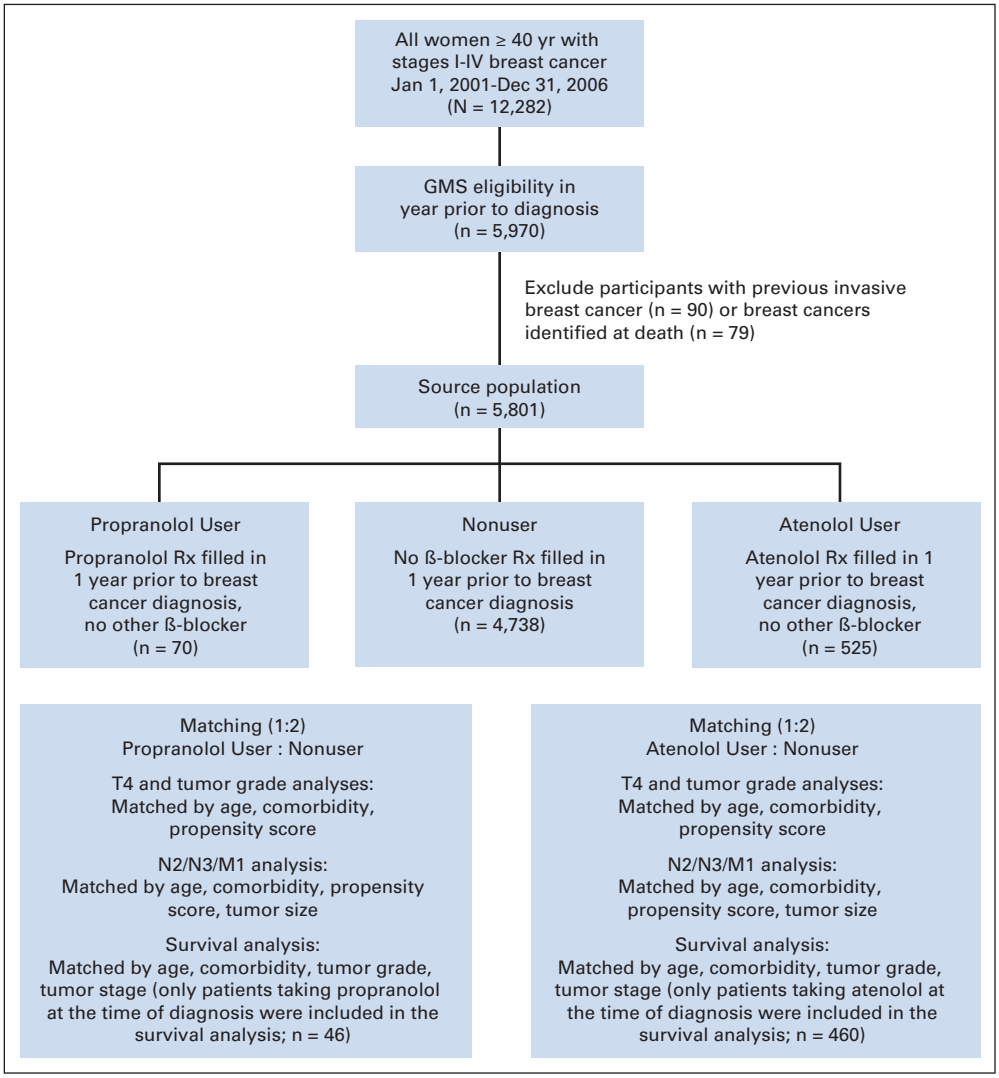

Fig 1. Study population selection and matching. GMS, General Medical Services [Ireland]; Rx, prescription.

Table 1. Characteristics of Matched Propranolol Users and Nonusers for T4 Tumor Stage, N2/N3/M1 Tumor Stage, Tumor Grade, and Survival Analyses

	T4 and Grade Analysis[a]		N2/N3/M1 Analysis[b]		Survival Analysis[c]	
Characteristic	Propranolol (%)[d]	Nonuser (%)	Propranolol (%)[d]	Nonuser (%)	Propranolol (%)[e]	Nonuser (%)
Mean age, years	66.9	66.9	68.0	67.7	69.0	69.1
Mean comorbidity score	11.9	11.4	11.8	10.8	11.8	10.5
Deprivation score[f]						
1	7.7	10.0	11.1	10.2	8.9	16.7
2	15.4	15.4	11.1	10.2	8.9	7.8
3	12.3	11.5	7.4	8.3	15.6	12.2
4	23.1	23.8	24.1	25.0	22.2	22.2
5	35.4	36.2	38.9	42.6	37.8	35.6
Unknown	6.2	3.1	7.4	3.7	6.7	5.6
Marital status						
Single	10.8	13.8	7.4	8.3	8.9	12.3
Married	50.8	52.3	53.7	51.9	48.9	38.9
Divorced/separated	7.7	3.1	9.3	3.7	8.9	2.2
Widowed	29.2	29.2	29.6	35.2	31.1	44.4
Unknown	1.5	1.5	0.0	0.9	2.2	2.2
Smoking status						
Current	18.5	22.3	14.8	15.7	17.8	17.8
Never	50.8	55.4	55.6	52.8	51.1	44.4
Previous	6.2	6.9	5.6	5.6	8.9	16.7
Unknown	24.6	15.4	24.1	25.9	22.2	21.1
Medication use[g]						
Aspirin	24.6	25.4	25.9	25.9	22.2	31.1
Statin	15.4	12.3	14.8	21.3	26.7	20.0
ACEi/ARB	15.4	27.7	14.8	25.0	13.3	25.6
CCB	13.8	13.1	14.8	14.8	15.6	7.8
Thiazide diuretic	10.8	18.5	14.8	25.0	8.9	20.0
Oral bisphosphonate	6.2	6.2	5.6	8.3	8.9	14.4
Metformin	3.1	6.2	3.7	2.8	4.4	5.6
Insulin	1.5	0.8	0.0	1.9	2.2	2.2
Year of incidence						
2001	20.0	19.2	16.7	14.8	17.8	17.8
2002	13.8	11.5	13.0	19.4	11.1	18.9
2003	18.5	18.5	22.2	15.7	17.8	21.1
2004	21.5	18.5	18.5	23.1	24.4	22.2
2005	20.0	15.4	22.2	18.5	20.0	10.0
2006	6.2	16.9	7.4	8.3	8.9	10.0
Estrogen receptor status[h]						
Negative	13.8	23.1	14.8	17.6	13.3	14.4
Positive	63.1	59.2	64.8	63.9	68.9	66.7
Unknown	23.1	17.7	20.4	18.5	17.8	18.9
Progesterone receptor status[h]						
Negative	20.0	25.4	18.5	21.3	17.8	23.3
Positive	44.6	43.1	46.3	50.0	48.9	43.4
Unknown	35.4	31.5	35.2	28.7	33.3	33.3
HER2 receptor status[i]						
Negative	40.0	35.4	44.4	28.7	46.7	34.4
Positive	13.8	17.7	11.2	17.6	11.1	15.6
Unknown	46.2	46.9	44.4	53.7	42.2	50.0
Tumor grade						
1	7.7	6.9	5.6	7.4	8.9	8.9
2	50.8	33.8	55.6	41.7	51.1	51.1
3	29.2	34.6	27.8	29.6	24.4	24.4
X	12.3	24.6	11.1	21.3	15.6	15.6
TNM stage						
I	20.0	19.2	14.8	14.8	17.8	17.8
II	58.5	46.2	70.4	58.3	57.8	57.8
III	6.2	19.2	3.7	8.3	8.9	8.9
IV	9.2	12.3	3.7	10.2	8.9	8.9
X	6.2	3.1	7.4	8.3	6.7	6.7

(continued on following page)

Table 1. Characteristics of Matched Propranolol Users and Nonusers for T4 Tumor Stage, N2/N3/M1 Tumor Stage, Tumor Grade, and Survival Analyses (continued)

Characteristic	T4 and Grade Analysis[a]		N2/N3/M1 Analysis[b]		Survival Analysis[c]	
	Propranolol (%)[d]	Nonuser (%)	Propranolol (%)[d]	Nonuser (%)	Propranolol (%)[e]	Nonuser (%)
Initial hormonal therapy						
Tamoxifen	—	—	—	—	53.3	53.3
Aromatase inhibitor	—	—	—	—	31.1	28.9
Chemotherapy						
Yes	—	—	—	—	31.1	36.7
No/unknown	—	—	—	—	68.9	63.3
Propranolol exposure						
1 Year prior to breast cancer diagnosis						
Duration, days						
Median	226	—	252	—	314	—
IQR	37-347		56-348		238-362	
Daily dose, mg						
Median	80	—	80	—	80	—
IQR	20-160		30-160		20-160	
Post breast cancer diagnosis						
Duration, days						
Median	—	—	—	—	703	—[j]
IQR					86-1,230	
Daily dose, mg						
Median	—	—	—	—	60	—
IQR				20-160		

NOTE. Difference in the distribution of covariates between users and nonuers were tested. No significant differences were observed between propranolol users and nonusers for any of the presented covariates.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker (dihydropyridine derivative); HER2, human epidermal growth factor receptor 2; IQR, interquartile range.

[a]Matched by age, comorbidity, and propensity score.

[b]Matched by age, tumor size, comorbidity, and propensity score.

[c]Matched by age, tumor stage, tumor grade, and comorbidity.

[d]Taking propranolol at any time in the year prior to breast cancer diagnosis.

[e]Taking propranolol at the time of breast cancer diagnosis.

[f]Lowest socioeconomic deprivation = 1; highest socioeconomic deprivation = 5.

[g]In the year prior to breast cancer diagnosis.

[h]Estrogen receptor and progesterone receptor activity was defined as positive if recorded by the National Cancer Registry Ireland (NCRI) database as unclear/possibly some receptor activity or positive/strong.

[i]HER2 receptor activity was defined as positive by immunohistochemistry (IHC) if recorded by the NCRI database as score 2+, weak/strong positive, or weak/strong complete membrane staining in > 10% of tumor cells. HER2 receptor activity was defined as positive by fluorescent in situ hybridization (FISH) if recorded by the NCRI database as weak/strong positive or some/strong amplification. If IHC and FISH results were recorded, FISH results were used.

[j]Three women in the nonuser group received propranolol during follow-up. The mean duration of propranolol use for these women was 45 days.

the source population was commenced in Ireland on a limited basis in February 2000. The service was extended to cover all women between the ages of 50 and 64 years by the year 2009.[29] Treatment exposure was defined as follows: propranolol users were identified as all patients filling a prescription for propranolol in the year before breast cancer diagnosis and no prescription for another beta blocker during that time; atenolol users were identified as all patients filling a prescription for atenolol in the year before breast cancer diagnosis and no prescription for another beta blocker during that time; nonusers were identified as all patients without a prescription for any beta blocker in the year before breast cancer diagnosis.

Study Covariates and Outcomes

Prescription refill data from the GMS database were used to identify relevant medication use from 1 year before breast cancer diagnosis. The duration of beta blocker exposure was calculated by using the number of days' supply on each dispensed prescription. The number of distinct medication classes dispensed in the year before breast cancer diagnosis was used as a validated measure of comorbidity.[30] Medications with the same initial five characters of World Health Organization Anatomic Therapeutic Chemical (WHO-ATC)[31] classification were considered the same class for this purpose. This comorbidity score is comparable with the Charlson comorbidity score for predicting 1-year all-cause mortality (c = 0.745), and it also reasonably predicts the number of physician visits.[30] The NCRI database was used to identify demographic covariates, socioeconomic deprivation scores,[32] smoking status, tumor characteristics, treatment data (chemotherapy: yes/no), and mortality. Study outcomes were defined as T4(a-d) breast tumor at diagnosis,[28] N2 or N3 or M1 breast tumor at diagnosis,[28] grade 1 or 2 breast tumor at diagnosis, and time from breast cancer diagnosis to breast cancer–specific mortality (breast cancer as recorded cause of death on death certificate).

Matching

Propranolol and atenolol users were separately matched to two randomly selected nonusers from the same control population by using a greedy matching algorithm.[33] Matching variables were selected for each analysis outcome by using a combination of a priori and empiric considerations. Propensity scores for matching were separately estimated for propranolol exposure and atenolol exposure. Variables associated in previous studies with a delay in breast cancer presentation or participation in cancer screening and other healthy behaviors were included in the propensity score models.[34-36] These included socioeconomic deprivation scores, marital status, smoking history, and the use of long-term prophylactic medications (eg, statins or aspirin). For the analyses of T4 tumor and tumor grade at diagnosis, users were matched to nonusers by age (± 5 years), comorbidity score (± 10 prescriptions), and propensity score (± 0.000025). For the analysis of N2/N3/M1 tumor at diagnosis, users were matched to nonusers by age (± 5 years), comorbidity score

Table 2. Characteristics of Matched Atenolol Users and Nonusers for T4 Tumor Stage, N2/N3/M1 Tumor Stage, Tumor Grade, and Survival Analyses

	T4 and Grade Analysis[a]		N2/N3/M1 Analysis[b]		Survival Analysis[c]	
Characteristic	Atenolol (%)[d]	Nonuser (%)	Atenolol (%)[d]	Nonuser (%)	Atenolol (%)[e]	Nonuser (%)
Mean age, years	71.4	71.4	71.2	71.3	71.0	71.0
Mean comorbidity score	10.7	10.3	10.4	9.7	11.0	10.4
Deprivation score[f]						
1	17.6	17.9	16.0	15.8	16.6	16.6
2	14.0	13.8	12.3	12.1	13.0	12.3
3	12.1	12.1	8.9	9.5	13.5	12.1
4	15.0	15.0	14.1	14.9	16.4	16.8
5	36.0	36.0	43.5	42.9	34.1	36.7
Unknown	5.2	5.2	5.2	4.8	6.5	5.5
Marital status						
Single	14.5	16.8	13.8	16.9	14.6	14.7
Married	37.9	37.6	37.2	37.0	40.1	40.7
Divorced/separated	4.5	4.2	3.6	3.0	4.3	4.0
Widowed	38.3	38.5	40.9	39.6	36.5	38.0
Unknown	4.8	2.9	4.5	3.5	4.5	2.6
Smoking status						
Current	10.2	10.2	8.6	8.4	11.9	19.7[g]
Never	58.6	58.1	61.3	58.4	54.3	46.0[g]
Previous	7.1	6.9	6.7	5.9	10.1	11.9[g]
Unknown	24.0	24.8	23.4	27.3	23.8	22.4[g]
Medication use[h]						
Aspirin	41.0	41.0	35.7	34.6	46.4	31.7[g]
Statin	28.3	28.3	23.4	24.3	35.9	26.2[g]
ACEi/ARB	37.4	29.8[g]	34.9	22.1[g]	36.5	29.0[g]
CCB	19.3	12.4[g]	17.8	13.0	19.7	12.0[g]
Thiazide diuretic	32.1	21.8[g]	30.5	19.1[g]	32.7	22.9[g]
Oral bisphosphonate	7.4	8.9	7.1	7.4	8.1	9.5
Metformin	2.1	6.2[g]	2.6	5.4	2.7	6.2[g]
Insulin	1.1	2.8	0.0	1.9[g]	1.6	1.0
Year of incidence						
2001	10.7	14.9	11.2	13.9	10.8	15.5
2002	16.2	17.6	14.9	21.0	14.8	15.8
2003	17.1	16.7	17.8	17.5	18.2	15.4
2004	16.4	19.4	17.8	17.3	16.8	19.6
2005	19.8	16.8	21.6	16.2	19.7	17.2
2006	19.8	14.6	16.7	14.1	19.7	16.6
Estrogen receptor status[i]						
Negative	15.2	17.4	14.5	15.6	14.1	15.6
Positive	65.5	64.9	66.2	67.3	67.9	66.4
Unknown	19.3	17.7	19.3	17.1	17.9	18.0
Progesterone receptor status[i]						
Negative	23.3	24.5	23.0	24.2	22.4	22.5
Positive	45.0	41.7	46.5	41.4	48.0	42.4
Unknown	31.7	33.8	30.5	34.4	29.6	35.1
HER2 receptor status[i]						
Negative	38.8	38.6	40.5	37.9	40.4	41.1
Positive	14.1	14.9	13.4	14.3	13.0	13.0
Unknown	47.1	46.5	46.1	47.8	46.6	45.9
Tumor grade						
1	9.0	10.3	7.4	11.5	8.1	8.1
2	43.6	42.5	42.4	42.6	45.7	45.7
3	30.7	31.4	35.7	31.6	29.1	29.1
X	16.7	15.8	14.5	14.3	17.0	17.0
TNM stage						
I	21.7	23.2	16.4	17.7	20.9	20.9
II	45.7	47.1	59.9	55.9	48.4	48.4
III	12.1	13.8	8.6	13.4	11.7	11.7
IV	12.4	9.8	10.4	7.4	11.4	11.4
X	8.1	6.1	4.8	5.6	7.6	7.6

(continued on following page)

Table 2. Characteristics of Matched Atenolol Users and Nonusers for T4 Tumor Stage, N2/N3/M1 Tumor Stage, Tumor Grade, and Survival Analyses (continued)

Characteristic	T4 and Grade Analysis[a]		N2/N3/M1 Analysis[b]		Survival Analysis[c]	
	Atenolol (%)[d]	Nonuser (%)	Atenolol (%)[d]	Nonuser (%)	Atenolol (%)[e]	Nonuser (%)
Hormonal therapy						
Tamoxifen	—	—	—	—	36.8	41.7
Aromatase inhibitor	—	—	—	—	43.3	36.2
Chemotherapy						
Yes	—	—	—	—	34.8	31.2
No/unknown	—	—	—	—	65.2	68.8
Atenolol exposure						
1 Year prior to breast cancer diagnosis						
Duration, days						
Median	330	—	324	—	344	—
IQR	178-364	185-363	257-365			
Daily dose, mg						
Median	50	—	50	—	50	—
IQR	50-100	50-100	50-100			
Post breast cancer diagnosis						
Duration, days						
Median	—	—	—	—	720	—[k]
IQR					353-1,158	
Daily dose, mg						
Median	—	—	—	—	50	—
IQR					50-100	

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker (dihydropyridine derivative); HER2, human epidermal growth factor receptor 2; IQR, interquartile range.
[a]Matched by age, comorbidity, and propensity score.
[b]Matched by age, tumor size, comorbidity, and propensity score.
[c]Matched by age, tumor grade, tumor stage, and comorbidity.
[d]Taking atenolol at any time in the year prior to breast cancer diagnosis.
[e]Taking atenolol at the time of breast cancer diagnosis.
[f]Lowest socioeconomic deprivation = 1; highest socioeconomic deprivation = 5.
[g]$P < .05$, χ^2 test.
[h]In the year prior to breast cancer diagnosis.
[i]Estrogen receptor and progesterone receptor activity was defined as positive if recorded by the National Cancer Registry Ireland (NCRI) database as unclear/possibly some receptor activity or positive/strong.
[j]HER2 receptor activity was defined as positive by immunohistochemistry (IHC) if recorded by the NCRI database as score 2+, weak/strong positive, or weak/strong complete membrane staining in > 10% of tumor cells. HER2 receptor activity was defined as positive by fluorescent in situ hybridization (FISH) if recorded by the NCRI database as weak/strong positive or some/strong amplification. If IHC and FISH results were recorded, FISH results were used.
[k]Forty-six women in the nonuser group received atenolol during follow-up. The mean duration of atenolol use for these women was 385 days.

(± 10 prescriptions), propensity score (± 0.00015). and tumor size (± 0). For the analysis of time to breast cancer–specific mortality, women taking propranolol or atenolol at the time of breast cancer diagnosis were matched to nonusers by age (± 5 years), comorbidity score (± 10 prescriptions), tumor grade (± 0), and tumor stage (± 0).

Statistical Analysis

Propensity scores for matching were estimated by using logistic regression (SAS, PROC LOGISTIC; SAS Institute, Cary, NC), with the outcome being exposure to the respective beta blocker. Conditional logistic regression (SAS, PROC LOGISTIC) was used to estimate odds ratios (ORs) and 95% CIs for a T4 tumor at diagnosis, an N2/N3/M1 tumor at diagnosis, and a grade 1 to 2 tumor at diagnosis. The cumulative probability of breast cancer–specific‘ mortality was estimated from Kaplan-Meier plots (SAS, PROC LIFETEST). Multivariable Cox proportional hazards models adjusted for age, stage, grade, and comorbidity were used to estimate hazard ratios (HRs) with 95% CIs for breast cancer–specific mortality (SAS, PROC PHREG). Survival analyses were conducted on an as-matched basis. Observations were censored at the time of breast cancer–specific mortality, non–breast cancer–specific mortality, or end of follow-up (December 31, 2007, or 5 years). All patients were followed for between 1 and 5 years from breast cancer diagnosis. Statistical analyses were performed with SAS version 9.2 (TS2M0 x64 VSPRO).

RESULTS

A source population of 5,801 women was identified from the linked GMS/NCRI database (Fig 1). This GMS-eligible source population differed as expected from the full NCRI population, with a higher mean age (67.4 *v* 61.6 years) and a greater proportion of women with the highest level of socioeconomic deprivation (34.7% *v* 27.6%). Three exposure groups were identified from this source population. Propranolol users consisted of 70 women taking propranolol and no other beta blocker in the year before breast cancer diagnosis. Atenolol users consisted of 525 women taking atenolol and no other beta blocker in the year before breast cancer diagnosis. Nonusers consisted of 4,738 women not taking a beta blocker in the year before breast cancer diagnosis. Table 1 and Table 2 outline the characteristics of the matched propranolol and atenolol groups with respect to selected variables.

The median duration of propranolol exposure in the year before diagnosis was 232 days. The median daily dose of propranolol during this time was 80 mg. Propranolol users were significantly less likely to

Table 3. Results From Conditional Logistic Regression Analyses of T4 Tumor Stage, N2/N3/M1 Tumor Stage, and Tumor Grade at Diagnosis for Propranolol Users and Atenolol Users Versus Matched Nonusers

Variable	Propranolol				Atenolol			
	User (%)	Nonuser (%)	OR	95% CI	User (%)	Nonuser (%)	OR	95% CI
Model 1								
T stage at diagnosis								
T1	27.7	29.2	0.93	0.49 to 1.78	29.8	32.2	0.89	0.68 to 1.16
T2	50.8	42.3	1.37	0.77 to 2.43	40.5	41.8	0.95	0.74 to 1.21
T3	9.2	9.2	1.00	0.34 to 2.93	5.9	7.6	0.76	0.46 to 1.24
T4	4.6	16.2	0.24	0.07 to 0.85	13.6	10.8	1.31	0.91 to 1.88
TX	7.7	3.1	3.68	0.68 to 19.86	10.2	7.6	1.41	0.93 to 2.14
Model 2								
N/M stage at diagnosis								
N0	48.2	39.8	1.43	0.72 to 2.83	37.9	40.2	0.90	0.65 to 1.24
N1	40.7	31.5	1.51	0.76 to 2.99	35.3	33.1	1.12	0.81 to 1.55
N2 or N3 or M1	3.7	16.7	0.20	0.04 to 0.88	14.1	13.0	1.10	0.72 to 1.70
NX and MX	7.4	12.0	0.48	0.01 to 1.91	12.7	13.7	0.88	0.53 to 1.45
Model 3								
Tumor grade at diagnosis								
1 or 2	58.5	40.8	2.33	1.19 to 4.56	52.6	52.7	1.00	0.79 to 1.26
3	29.2	34.6	0.77	0.40 to 1.49	30.7	31.4	0.94	0.73 to 1.22
X	12.3	24.6	0.38	0.15 to 0.96	16.7	15.9	1.07	0.77 to 1.48

Abbreviation: OR, odds ratio.

present with a T4 tumor at diagnosis compared with nonusers matched by age, comorbidity, and propensity score (Table 3; OR, 0.24; 95% CI, 0.07 to 0.85). During the same period, no significant difference in the incidence of T4 tumors between atenolol users and nonusers was observed (Table 3; OR, 1.31; 95% CI, 0.91 to 1.88). Propranolol users were also significantly less likely to present with N2/N3 nodal involvement or metastatic disease compared with nonusers matched by age, comorbidity, propensity score, and tumor

Table 4. Results From Cox Proportional Hazards Models of 5-Year Breast Cancer–Specific Mortality for Propranolol Users and Atenolol Users Versus Matched Nonusers (breast cancer stages I to IV)

Variable	Propranolol Analysis				Atenolol Analysis			
	User %	Nonuser %	HR	95% CI	User %	Nonuser %	HR	95% CI
Breast cancer–specific mortality	8.9		22.2			20.9		19.1
Non–breast cancer–specific mortality	6.7		4.4			7.6		8.5
Median follow-up, years	3.5	3.6			2.7	3.0		
Person years	151	295			1,284	2,645		
Incidence rate*	26.5		67.9			72.4		64.3
Five-year cumulative probability of breast cancer–specific mortality	9.4		26.8			26.8		26.0
Multivariate Cox proportional hazards model								
Exposure								
User			0.19	0.06 to 0.60			1.08	0.84 to 1.40
Nonuser			1.00	—			1.00	—
Age			0.99	0.94 to 1.04			1.03	1.02 to 1.05
TNM stage								
I			1.00	—			1.00	—
II			3.75	0.40 to 34.92			2.88	1.53 to 5.41
III			9.83	1.09 to 88.91			6.79	3.47 to 13.30
IV			124.5	10.12 to 1,532.5			27.15	14.47 to 50.93
X			19.39	0.76 to 492.65			7.06	3.47 to 14.37
Grade								
1			—	—			0.59	0.29 to 1.22
2			1.00	—			1.00	—
3			6.38	1.71 to 23.74			1.45	1.09 to 2.94
X			10.63	2.92 to 38.65			1.28	0.92 to 1.77
Comorbidity score			1.16	1.05 to 1.28			1.03	1.00 to 1.05

Abbreviation: HR, hazard ratio.
*Incidence rates expressed as events per 1,000 person years.

size (Table 3; OR, 0.20; 95% CI, 0.04 to 0.88). No effect was observed for women taking atenolol (Table 3; OR, 1.10; 95% CI, 0.72 to 1.70). Stratifying T4 and N2/N3/M1 tumor rates by propranolol exposure showed that there were no T4 tumors (0 of 33 *v* 3 of 32) and one N2/N3/M1 tumor (1 of 27 *v* 1 of 27) in women taking propranolol for longer than the median duration of use. Propranolol users were significantly more likely to present with grade 1 or 2 tumors at diagnosis (Table 3; OR, 2.33; 95% CI, 1.19 to 4.56). There was, however, a higher proportion of missing tumor grade data for nonusers in this analysis. Stratification of grade by tumor stage provides a likely explanation for this, because the proportion of missing grade data increased with tumor stage, and nonuse of propranolol was associated with higher tumor stage (Tables 1 and 3; T4 analysis). Sensitivity analyses were undertaken to determine the effect of including tumor grade as a matching variable in the T4 and N2/N3/M1 analyses. These did not have a notable effect on the observed associations.

There were four (8.9%) breast cancer–specific deaths among propranolol users for an incidence rate of 26.5 per 1,000 woman years and 20 (22.2%) deaths among nonusers matched by age, tumor grade, tumor stage, and comorbidity for an incidence rate of 67.9 per 1,000 woman years (Table 4). The median follow-up was 3.5 years for propranolol users and 3.6 years for matched nonusers. The median duration of propranolol exposure post breast cancer diagnosis was 1.92 years. The median daily dose of propranolol during this time was 60 mg. At 5 years post breast cancer diagnosis, the risk of breast cancer–specific mortality was 81% lower for propranolol users than for nonusers (Fig 2A; Table 4; HR, 0.19; 95% CI, 0.06 to 0.60). Rates of non–breast cancer–specific mortality were similar between propranolol users and nonusers. There was no difference in the cumulative probability of breast cancer–specific mortality between atenolol users and matched nonusers, 26.8% *v* 26.0% (Fig 2B; Table 4; HR, 1.08; 95% CI, 0.84 to 1.40). These analyses were repeated, excluding patients with stage IV breast tumors. Propranolol users continued to have a significantly lower risk of breast cancer–specific mortality, compared with matched nonusers (HR, 0.20; 95% CI, 0.04 to 0.94). There was no difference in breast cancer–specific mortality between atenolol users and matched nonusers (HR, 1.16; 95% CI, 0.84 to 1.61). Where differences in the distribution of covariates, such as medication use, existed between user and nonuser groups, we performed sensitivity analyses to determine the influence of these on the observed results. None of these had a notable effect on the results.

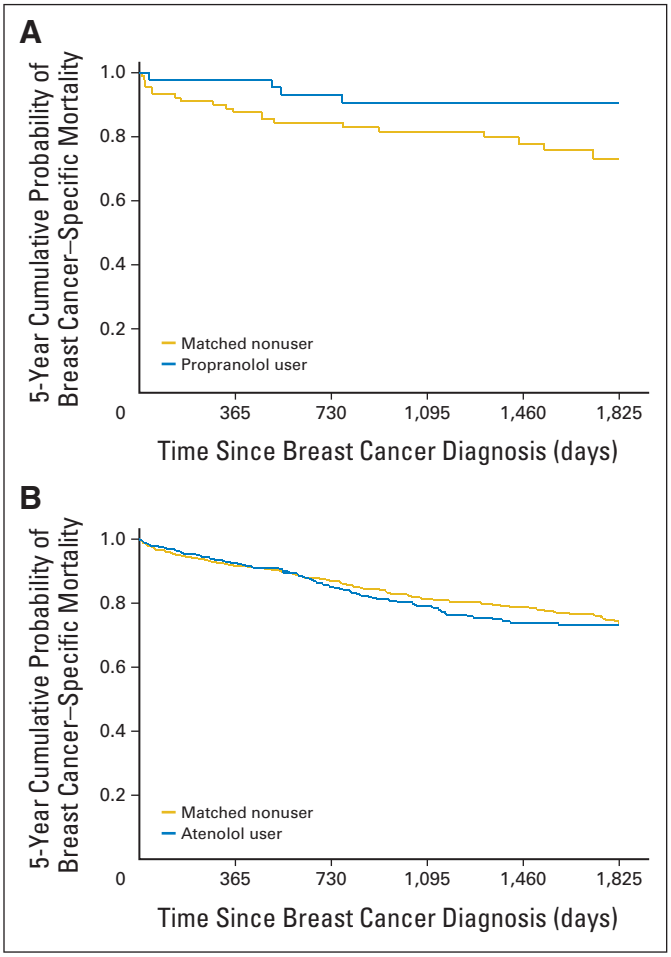

Fig 2. Five-year cumulative probability (unadjusted) of breast cancer–specific mortality in propranolol users (A) or atenolol users (B) versus matched nonusers.

DISCUSSION

The results of this study suggest that the use of propranolol, a nonselective β_1/β_2-adrenergic receptor antagonist, is associated with less advanced disease at diagnosis and lower breast cancer–specific mortality. Women taking propranolol in the year before breast cancer diagnosis were significantly less likely to present with a T4 tumor, node-positive (N2/N3), or metastatic disease when compared with those not taking a beta blocker. Furthermore, a longer duration of propranolol use was associated with fewer T4 tumors suggesting the possibility of a dose-response relationship. Propranolol use was also associated with low or intermediate tumor grade at diagnosis. The most notable result from this study was the finding that propranolol users had a significantly lower risk of breast cancer–specific mortality when compared with nonusers matched for age, comorbidity, tumor stage, and grade. There was no association observed between any of the study outcomes and use of the β_1 selective antagonist atenolol. This is also consistent with data from preclinical studies[8-10,13,15,17] and suggests that the effects of propranolol observed in this study are the result of β_2- adrenergic receptor antagonism.

Evidence from preclinical studies has demonstrated that β_2-adrenergic signaling plays a role in several pathways necessary for breast tumor progression and metastasis. These include the promotion of tumor cell invasion and migration,[8-10] the regulation of immune responses to tumor cells,[16] the inhibition of apoptosis,[17,18] and the induction of vascular endothelial growth factor expression.[13] It has been shown that these effects are mediated through several downstream signaling pathways.[5] Preclinical evidence has also shown that the upregulation of β-adrenergic signaling does not exert a significant effect on primary breast tumor growth.[16] This is supported by results from the analysis of T4 tumor incidence (Table 3), which suggest that propranolol use is not associated with an overall reduction in tumor size. Studies comparing β_1 and β_2 receptor antagonists have demonstrated that the effects of β-adrenergic signaling on tumor progression and metastasis are inhibited by β_2 antagonists but not β_1 antagonists.[9,17] Similar results have been observed in studies that used short

interfering RNA to selectively inhibit the expression of β_1 or β_2 adrenergic receptors by tumor cells.[13,17] Several factors predictive of in vitro or in vivo responses to the inhibition of β_2 adrenergic signaling have been identified. These include the expression of β_2 adrenergic receptors by breast tumor cells and the level of sympathetic nervous system activation.[16]

Although the effects of β-adrenergic signaling and its inhibition on breast tumor progression and metastasis have been well established in preclinical models, little clinical data exist to confirm these observations. Several observational studies of beta blocker use and breast cancer have been published.[37-40] However, most of these studies have focused on the association between beta blocker use and cancer incidence. They have also studied beta blockers as a single homogenous pharmacologic group, without accounting for differences in β_1 and β_2 receptor activity. None of these studies have demonstrated an association between beta blocker use and breast tumor incidence.[38-40] This is consistent with evidence from epidemiologic and preclinical studies, which have shown little association between the upregulation of adrenergic signaling and tumorigenesis.[2] In a recently published observational study, it was shown that the use of beta blockers by hypertensive women with breast cancer was associated with a significant reduction in the formation of distant metastases and a 71% reduced risk of breast cancer–related mortality.[37] However, no distinction was made in this study between the use of beta blockers with selective β_1 (n = 32) or β_2 (n = 11) receptor activity. Two studies examining the perioperative use of propranolol in patients with breast[41] and colon[42] cancer are ongoing and their findings, if promising, will provide support for further investigation of agents targeting β-adrenergic signaling pathways.

This study has several strengths. It is the first, to the best of our knowledge, to examine the association between the use of beta blockers with varying β_1/β_2-adrenergic receptor activity and breast cancer–specific mortality. It is based on prospectively collected data from a large nationally representative linked cancer and prescribing database. Detailed information on patient demographics, patient outcomes, tumor characteristics and, importantly, the dose, duration, and timing of beta blocker exposure was available from this database. There were also several limitations to this study. The inclusion of prevalent propranolol users, in addition to new initiators, may have introduced confounding due to healthy adherer effects.[34] However, the effects of this are likely to have been reduced by matching based on propensity scores that reflect participation in healthy behaviors. These inclusion criteria were also used to define atenolol users for whom no association between exposure and outcome was observed. Propranolol and atenolol are primarily prescribed for similar cardiovascular indications, such as hypertension, although because of its broader receptor activity and ability to cross the blood-brain barrier, propranolol is also indicated for the control of tremor, migraine prophylaxis, and treatment of cluster or tension headache. These additional indications are minor and are unlikely to have been associated with substantial confounding. Finally, although a large source population (n = 5,801) was available for this study, the size of the propranolol user group limits the ability to fully explore dose-response relationships and the effects of propranolol exposure on subgroups of patients. We cannot exclude the possibility that the results were due to chance. Further studies in larger cohorts are required to confirm our findings.

In conclusion, the results presented here provide evidence in humans that confirm in vivo and in vitro observations that antagonism of the β_2-adrenergic receptor alters its signaling and subsequent tumor-related sequelae in a favorable manner. These results support the role of β-adrenergic signaling pathways in the regulation of breast tumor progression and suggest that interventions targeting these pathways may complement existing breast cancer therapies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Manuscript writing: All authors
Final approval of manuscript: All authors

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