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## **$\beta$ -Blockers and Survival among Danish Patients with Malignant Melanoma: A Population-Based Cohort Study**

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### **Abstract**

**Background**—To study whether use of  $\beta$ -blockers increases survival in patients with malignant melanoma because experimental data suggest that catecholamine hormones may be involved in stimulating the aggressiveness of malignant melanoma.

**Methods**—A total of 4,179 patients diagnosed with malignant melanoma in Denmark with a median follow-up of 4.9 years and identified in the Danish Cancer Registry participated. Data on  $\beta$ -blocker use, comorbidity, and survival were obtained from medical and administrative databases. Cox proportional hazards models were used to estimate HRs for all-cause mortality with 95% CIs with adjustment for prognostic factors.

**Results**—A total of 372 (8.9%) patients with malignant melanoma were treated with  $\beta$ -blockers within 90 days of melanoma diagnosis. The median  $\beta$ -blocker duration for exposure within 90 days of melanoma diagnosis, more than 90 days, and no prior exposure was 7.6, 1.4, and 0 years, respectively. The patients receiving  $\beta$ -blockers were older, had more comorbidities, and more cardiovascular and psychotropic drug user than the patients receiving no  $\beta$ -blockers prior to melanoma diagnosis. After adjustment for age and comorbidity index, the HR for melanoma death was 0.87 (95% CI: 0.64–1.20) and for all-cause mortality was 0.81 (95% CI: 0.67–0.97).

**Conclusion**—Increased survival time of patients with melanoma receiving  $\beta$ -blockers suggests that this class of drugs may hold promise in treatment strategy for these patients.

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#### **Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**Impact**—The observations described here suggest that catecholamines may retard melanoma progression and that  $\beta$ -blockers may have unrecognized potential as a therapeutic intervention for melanoma.

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## Introduction

Diagnosis of new melanomas is increasing annually in many countries. In 2009, a total of 68,720 new cases of melanoma were reported in the United States alone, with about 8,650 people expected to die from this disease (1, 2). As yet, there are no effective treatments of metastatic melanoma.

Increasing experimental evidence indicates that catecholamine stress hormones may affect the progression of numerous types of cancer, including melanoma (3). Recent research (4–6) has shown that the catecholamine stress hormones, norepinephrine and epinephrine, may influence the progression of ovarian cancer. Angiogenesis, a critical step in tumor progression, allows tumors to grow beyond 1 to 2 mm in diameter and involves the expression of several factors including interleukin (IL)-8 and IL-6. Catecholamine hormones modulate the expression of matrix metalloproteinases (MMP) and the angiogenic cytokine VEGF in ovarian cancer cells (7–10).

Using nasopharyngeal carcinoma as a model to study the mechanisms of norepinephrine on malignant cells, our prior research showed that treatment with norepinephrine could upregulate the production of MMP-2, MMP-9, and VEGF in the human nasopharyngeal carcinoma HONE-1 cell line (11, 12). Furthermore, norepinephrine can stimulate the invasive capability of HONE-1 cells through the expression of MMPs and upregulate the release of functional VEGF (11). We have shown that the ability of norepinephrine to upregulate MMP-2, MMP-9, and VEGF is mediated by  $\beta$ -adrenergic receptors ( $\beta$ -AR). Our experiments showed that HONE-1 cells express these receptors and that treatment with antagonists such as propranolol, to block the binding of norepinephrine to the receptors, prevented the upregulation of MMP-2, MMP-9, and VEGF. We also found that 7 of 7 nasopharyngeal carcinoma biopsy specimens obtained from tumor archives were positive for the expression of  $\beta$ 2-AR, as determined by immunohistochemistry. Our data suggested that norepinephrine, a stress hormone produced after activation of the sympathetic-adrenal-medullary axis, might play a role in nasopharyngeal carcinoma pathogenesis and prompted investigation of this axis in other types of cancer. Consistent with earlier observations, we found that exposure of C8161 human melanoma cells to norepinephrine resulted in greater secretion of VEGF, IL-8, and IL-6. Propranolol completely inhibited norepinephrine-dependent stimulation of VEGF, IL-8, and IL-6 gene expression, providing evidence for the role of  $\beta$ -ARs in norepinephrine-dependent responses in these cells (13). The data suggest that norepinephrine may be involved in stimulating the aggressiveness of malignant melanoma and that norepinephrine could be a cofactor in the progression of several different types of cancer (14). In support of this hypothesis is a study in the *Archives of Internal Medicine*, which showed that treatment with  $\beta$ -blockers may be effective for treating patients with melanoma (15). Our study supports this conclusion.

$\beta$ -Blockers are a class of drugs used for various indications, particularly for management of cardiac arrhythmias, cardioprotection after myocardial infarction, hypertension, migraine, and tremor (16). They inhibit normal epinephrine-mediated sympathetic actions and may affect tumor progression. To clarify these issues, we undertook a large population-based cohort study focusing on whether the use of  $\beta$ -blockers increased survival in patients with malignant melanoma in Denmark.

## Methods

### Setting

We conducted this population-based cohort study in northern Denmark within a population of 1.7 million (~30% of the total Danish population). Northern Denmark consists of the former North Jutland, Aarhus, Viborg, and Ringkøbing counties (17).

The Danish National Health Service provides universal tax-supported health care, guaranteeing unrestricted access to general practitioners and hospitals, and partial reimbursement for prescribed medications, including  $\beta$ -blockers. The unique central personal registry (CPR) number assigned to each Danish citizen at birth and to residents upon immigration allows linkage among national registries (18).

### Malignant melanoma cohort

We identified all patients with an incident diagnosis of malignant melanoma from the Danish Cancer Registry (DCR), which has recorded all cancer cases in Denmark since 1943. Cancers are classified in the DCR according to the International Classification of Diseases, 10th Revision (ICD-10). Registration in the DCR is based on notification forms completed by hospital departments and practicing physicians when a cancer is diagnosed or found at autopsy or when an initial diagnosis is changed. Unreported cases are identified through computerized linkage to the Causes of Death Registry and the Danish National Registry of Patients (DNRP; refs. 19–21).

In the DCR, the extent of cancer is classified as localized, regional, metastatic to distant sites, or unknown. The entire coding process is supervised by physicians. Comprehensive validation has shown that the DCR is 95% to 98% valid and complete (20).

### Prescription data

We used the prescription database of the region to identify prospectively all prescriptions redeemed by the study population of patients with melanoma before and after their diagnosis date. Pharmacies in Denmark are equipped with electronic accounting systems, primarily used to secure reimbursement from the National Health Service (17). For each redeemed prescription, the patient's CPR number, the type and amount of drug prescribed according to the Anatomical Therapeutic Chemical classification system, and the date the drug was dispensed are transferred electronically from the pharmacy to the prescription database at Aarhus University (17). Prescription data have been available from North Jutland County since 1989, Aarhus County since 1996, and Viborg and Ringkøbing Counties since 1998. We obtained at least 1 year of prescription history for all members of the study population. We identified prescriptions for all  $\beta$ -blockers (including metoprolol, propranolol, and atenolol), statins, angiotensin-converting enzyme (ACE) inhibitors, aspirin, antidepressants, antipsychotics, and anxiolytics.

### Comorbidity

We used the DNRP, covering all Danish hospitals, to identify all prior hospitalizations of patients diagnosed with melanoma during the study period (19). The DNRP contains data on dates of hospital admission and discharge, all discharge diagnoses from nonpsychiatric hospitals since 1977, and all emergency department and outpatient clinic visits since 1995. Each discharge is associated with up to 20 discharge diagnoses assigned by physicians, including one primary diagnosis and one or more secondary diagnoses classified according to the International Classification of Diseases, 8th Revision (ICD-8), until the end of 1993 and 10th Revision (ICD-10) thereafter. This information was used to compute a Charlson Comorbidity Index (CCI) score, based on 19 major diseases, for study participants (22). We

also obtained information from the DNRP on numerous conditions that may be associated with  $\beta$ -blocker use.

## Mortality

We accessed melanoma mortality and all-cause mortality data from the Civil Registration System, which contains complete information for the entire Danish population on migration and changes in vital status, including exact date of death, updated on daily basis (18). We also obtained information from the Causes of Death Registry, which has recorded data from all Danish death certificates issued since 1943 (21). Computerized and validated information from this registry is currently available through 2006. Whenever a Danish resident dies, the attending physician must report the cause of death; the chain of events leading to death can be specified using up to 4 diagnoses. Causes of death recorded during the study period were coded according to ICD-10 (21). In the rest of this article, we will be specific as to whether the outcome is mortality due to melanoma or all-cause mortality.

## $\beta$ -Blocker use

An intent-to-treat (ITT) method was used to access  $\beta$ -blocker use. Subjects were assigned to the  $\beta$ -blocker group if they were prescribed  $\beta$ -blockers in the 90-day period prior to melanoma diagnosis; a second group of patients were identified who were prescribed  $\beta$ -blockers more than 90 days prior to melanoma diagnosis; otherwise, subjects were assigned to the non- $\beta$ -blocker group. About the 90-day period prior to diagnosis, most Danish prescriptions cover 90 days, which ensures high specificity and sensitivity to capture  $\beta$ -blocker treatment accurately.

## Statistical methods

Mortality due to melanoma was the primary outcome of the study, and the 3 levels of ITT  $\beta$ -blocker use constituted the primary prognostic factor. Follow-up began on the date of melanoma diagnosis and ended on the date of death. Observations were censored on the last follow-up date or date of emigration from Denmark. Cox proportional hazards models were used to generate HRs associated with ITT  $\beta$ -blocker use.

The goal of the study was to identify the role of  $\beta$ -blockers on survival. Two separate analyses were carried out—one with mortality due to melanoma and the other with all-cause mortality as the outcome of interest. Despite the fact that this is a large, population-based study, the actual number of deaths due to melanoma is quite small within subgroups of melanoma staging. In an attempt to build up the number of patients in smaller subgroups, we have pooled patients in stage I and II melanoma and have similarly pooled those in stages III and IV. To identify the role of  $\beta$ -blocker usage on survival, we used a risk factor modeling approach to determine which covariates to add to the model. Only covariates that acted either as a confounder or as an effect modifier were included. A confounder was identified when its addition changed the HR associated with the risk factor ( $\beta$ -blocker usage) by more than 10% in either direction, without considering statistical significance. A covariate that had a statistically significant interaction ( $P < 0.05$ ) with  $\beta$ -blocker use was considered to be an effect modifier. A covariate that is an effect modifier cannot be a confounder. The following covariates were evaluated: age, gender, CCI score, Danish county of residence, and use of aspirin, statins, or ACE inhibitors. The method of fractional polynomials was used to determine whether the continuous variables were linear in the log-hazard function. All analyses were conducted using Stata 10.1 (Stata Corporation).

## Results

The study population consisted of 4,179 patients diagnosed with melanoma. Median follow-up time was 4.9 years with a maximum of 20.7 years. Table 1 presents patient characteristics by ITT  $\beta$ -blocker use. Six hundred sixty (15.8%) of the 4,179 subjects with melanoma were prescribed  $\beta$ -blockers before their diagnosis. Three hundred seventy-two (8.9%) subjects were assigned to the ITT  $\beta$ -blocker exposure 90 days prior to diagnosis group and used  $\beta$ -blockers for 8.0 years (mean). Two hundred eighty-eight (6.9%) subjects had  $\beta$ -blocker exposure more than 90 days prior to diagnosis group and used  $\beta$ -blockers for 2.7 years (mean). [We note that 314 (8.9%) of the 3,519 patients who received no  $\beta$ -blockers prior to diagnosis were subsequently prescribed  $\beta$ -blockers following melanoma diagnosis. Mean time of use of  $\beta$ -blockers in this subgroup of 314 patients was 2.5 years.] Both  $\beta$ -blocker group patients were older and took more cardiovascular and psychotropic drugs than the group with no prior  $\beta$ -blocker exposure. The 90-day prior exposure group had higher mortality, whereas the more than 90-day prior exposure group had a lower mortality than the no-exposure group. In addition, a larger number of patients in the more than 90-day prior exposure group, compared with the other 2 groups, had missing or unspecified stage information. The wide variety of comorbidities considered in the study generally occurred with low frequency in all 3 groups. However, history of osteomyelitis, autoimmune disease, and pneumonia was significantly more common in both  $\beta$ -blocker groups. The distribution of CCI scores was collapsed to 0, 1, and 2 or more within each of the  $\beta$ -blocker subgroups. Only 56% of patients in the 90-day  $\beta$ -blocker exposure group and 51% in the more than 90-day exposure had no comorbidities compared with 81% in the group with no prior  $\beta$ -blocker exposure. This suggests that patients who were prescribed  $\beta$ -blockers prior to diagnosis had more underlying chronic conditions (and may have been in poorer health) than those not prescribed this medication prior to diagnosis. All-cause mortality rates classified by  $\beta$ -blocker use and melanoma stage are presented in Table 1. As expected, mortality rates increased with more severe disease. The results indicate that for each stage of melanoma, mortality rates were higher in the  $\beta$ -blocker groups than those in the group not prescribed this medication, although statistical significance was reached only in the group with stage I and II disease. In results not presented here, we observed that 5-year survival rate among patients who ultimately died of melanoma decreased with increasing severity of disease (89%, 69%, and 13% for stages II, III, and IV, respectively).

HRs generated from Cox proportional hazards models are presented in Table 2. Because patients receiving  $\beta$ -blockers were older and sicker than those not receiving  $\beta$ -blockers, only the adjusted Cox models are shown. These models control for age and comorbidity index score, as these were the only covariates that confounded the relationship between  $\beta$ -blocker use and the hazard of death. For both death due to melanoma and death due to all-cause mortality, the odds of death was generally lower for patients receiving  $\beta$ -blockers than for those receiving no  $\beta$ -blockers prior to diagnosis. For example, the odds of melanoma mortality among patients diagnosed in any stage of melanoma are 13% lower for those receiving  $\beta$ -blockers within 90 days prior to diagnosis than for those never receiving  $\beta$ -blockers. The OR for this subgroup does not attain statistical significance but is of similar order of magnitude observed in a similar analysis using all-cause mortality. In that case, significance was attained due, primarily, to the much larger number of patients who actually died. With the exception of patients with stage III or IV disease receiving  $\beta$ -blockers within 90 days, all other subgroups, for both death due to melanoma and death due to any cause, showed HRs below 1.

## Discussion

Our population-based cohort study shows the association of  $\beta$ -blocker use with reduced risk of death in patients diagnosed with malignant melanoma, the most deadly form of skin cancer.

Several issues should be considered when interpreting the data. The main strengths of our study are its large size, the well-defined population, and the uniformly organized health care system with complete population coverage and follow-up. We were able to link population-based registries with complete data on drug use, cancer diagnosis, outpatient visits, and hospitalizations. The universal provision of health care considerably reduces the likelihood that our findings are a result of substantial confounding by social characteristics of  $\beta$ -blocker users. The diagnoses used in the CCI have a high level of validity (23). However, because our study is nonrandomized, we cannot exclude uncontrolled confounding. Because data concerning lifestyle factors were not available, it was impossible to control for these factors. Melanoma was either histologically or cytologically confirmed in 80.6%, not confirmed in 1%, and missing in 18.4% of the patients. It is possible that this missing information could result in bias. As sampled, the  $\beta$ -blocker and non- $\beta$ -blocker groups differed strikingly with respect to age and CCI score. These variables act as confounders of the association between  $\beta$ -blocker use and mortality. After controlling for both age and CCI score, HRs suggest that  $\beta$ -blocker use has a strong protective association with mortality and this same association holds for the subgroup when the cause of death is melanoma. The use of observational data presents challenges of drug efficacy. We have used the approach of determining whether a patient was prescribed  $\beta$ -blockers during the 90-day interval prior to diagnosis. This was done for 2 major reasons: (i) simulate as best as possible an ITT analysis from an observational study and (ii) eliminate, to the extent possible, immortal time bias.

Our study extends prior studies that have attempted to determine whether a link exists between  $\beta$ -blocker use and cancer risk. These prior studies yielded inconsistent results, due in part to small sample sizes and potential sources of bias (24–28). A further analytic complication of prior prospective or retrospective studies was that too few cancer cases were typically observed to allow for detailed analysis of individual cancer subtypes. This limitation was highlighted in an ambitious 10-year prospective study by Algazi and colleagues (29) that analyzed cancer risk in 836 patients, 326 of whom were  $\beta$ -blocker users.

A recent published study from our laboratory showed that blocking  $\beta$ -ARs on human melanoma cell lines led to complete inhibition of *VEGF*, *IL-8*, and *IL-6* gene expression following norepinephrine stimulation (13). The role of these proangiogenic factors in driving tumor progression and immunosuppression, which promotes metastasis, has long been recognized. Our *in vitro* data using melanoma (13) and other cancer cell lines (11,30,31) suggest that  $\beta$ -blockers exert an antitumor effect via direct action on malignant cells. The mechanisms by which  $\beta$ -blockers could improve overall survival of patients with melanoma are not completely understood and it is possible that a percentage of melanoma tumors might not respond at all. Furthermore, although our prior data indicate the  $\beta$ -blockers can act directly upon the tumors, these data do not exclude that  $\beta$ -blockers may exert a portion of their antitumor action via effects on host stromal tissue or through an immunomodulatory effect. Our data did not reveal any impact of  $\beta$ -blocker use on melanoma incidence in this Danish population. The improved overall survival of patients with melanoma receiving  $\beta$ -blockers following their diagnosis does suggest that these compounds might prevent metastatic progression of disease.

The observations described here support the hypothesis that catecholamines can affect melanoma progression and that  $\beta$ -blockers may have unrecognized potential as a therapeutic

intervention for melanoma and possibly other forms of cancer. Although data from this study strongly support a link between  $\beta$ -blocker use and increased overall survival of patients with melanoma, we acknowledge that it may be difficult to assess the exact dosage of  $\beta$ -blocker received by patients. Also, although the study is very large, it represents a somewhat geographically isolated group of people. Thus, it would be of interest to conduct similar studies in other cohorts to confirm our findings. Despite these potential limitations, the DNRP allowed for a uniquely accurate assessment of melanoma incidence, use of pharmacologic agents, comorbidity, and overall survival.

## Acknowledgments

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Table 1

Melanoma patient demographics and clinical outcomes by ITT  $\beta$ -blocker use

Characteristic	No prior exposure	Exposure 90 d prior to diagnosis	Exposure >90 d prior to diagnosis	<i>pa</i>
Count (%)	2,916 (85.1)	275 (8.0)	237 (6.9)	
Age at diagnosis, mean, y	52.9	66.0	62.7	0.001
Male, %	41.7	46.9	42.2	0.247
Deceased, <i>n</i> (%)	359 (12.3)	46 (16.7)	11 (4.6)	<0.001
Stage, %				
I	13.1	17.2	15.2	<0.001
II	53.2	48.7	23.6	
III	4.7	4.0	2.5	
IV	2.3	3.6	1.3	
Unspecified	9.4	14.9	7.6	
Missing	17.3	11.6	49.8	
Use of aspirin (%)				
No prior exposure	93.5	58.9	59.1	<0.001
Exposure 90 d prior	3.9	34.6	14.8	
Exposure >90 d prior	2.6	6.5	26.1	
Statins, %				
No prior exposure	96.3	77.5	74.3	<0.001
Exposure 90 d prior	2.7	20.0	9.7	
Exposure >90 d prior	1.0	2.5	16.0	
ACE Inhibitors, %				
No prior exposure	92.4	62.9	54.9	<0.001
Exposure 90 d prior	5.5	31.3	21.0	
Exposure >90 d prior	2.1	5.8	24.1	
Antidepressants, %				
No prior exposure	89.9	84.4	75.1	<0.001
Exposure 90 d prior	5.5	9.8	11.4	
Exposure >90 d prior	4.6	5.8	13.5	
Antipsychotics, %				
No prior exposure	96.1	93.1	90.3	<0.001
Exposure 90 d prior	1.6	3.3	2.5	
Exposure >90 d prior	2.3	3.6	7.2	
History of				
Osteomyelitis, %	3.7	5.8	2.5	0.118
Autoimmune disease, %	4.2	7.6	7.6	0.003
Pneumonia, %	2.1	4.0	7.6	<0.001
Charlson score [comorbidity index], %				
0	85.6	60.7	54.9	
1	7.0	18.9	20.7	<0.001
2+	7.4	20.4	24.5	

Characteristic	No prior exposure	Exposure 90 d prior to diagnosis	Exposure >90 d prior to diagnosis	<i>P</i> <sup>a</sup>
Mortality by melanoma stage [ <i>n</i> ], <i>b</i> %				
I [464]	1.1	4.3	2.8	0.112
II [1,740]	13.6	20.2	5.4	0.019
III [155]	30.4	45.5	50.0	0.354
IV [82]	86.9	90.0	66.7	0.445

<sup>a</sup>*P* values based on 2-sided Pearson's  $\chi^2$  test except for age for which the *P* value is based on the 2-sided *t* test.

<sup>b</sup>*P* values based on Fisher's exact test due to small cell sizes.

All-cause mortality HR of prior melanoma diagnosis  $\beta$ -blocker use obtained from an ITT analysis using Cox proportional hazards models

**Table 2**

Models <sup>a</sup>	Melanoma as a cause of death (N = 3,428)			All-cause mortality (N = 4,179)				
	Number of deaths <sup>b</sup>	$\beta$ -Blocker HR <sup>b</sup>	95% CI	P	Number of deaths <sup>b</sup>	$\beta$ -Blocker HR <sup>a</sup>	95% CI	P
All subjects	416				1,167			
Exposure 90 d prior to diagnosis	46	0.87	0.64–1.20	0.408	143	0.81	0.67–0.97	0.020
Exposure >90 d prior to diagnosis	11	0.36	0.20–0.66	0.001	62	0.78	0.60–1.00	0.052
Stage I and II melanoma								
Exposure 90 d prior to diagnosis	29	0.93	0.62–1.40	0.734	92	0.83	0.67–1.05	0.120
Exposure >90 d prior to diagnosis	4	0.31	0.12–0.85	0.022	23	0.69	0.46–1.06	0.088
Stage III and IV melanoma								
Exposure 90 d prior to diagnosis	14	1.26	0.71–2.23	0.421	24	1.20	0.78–1.86	0.405
Exposure >90 d prior to diagnosis	5	0.87	0.34–2.23	0.765	10	0.93	0.48–1.80	0.843

<sup>a</sup> $\beta$ -Blocker HR is adjusted for age and comorbidity index score, and the referent group is no  $\beta$ -blocker exposure prior to melanoma diagnosis.

<sup>b</sup>Counts in stages I to IV do not total to the all subjects count because of missing or unspecified stage data.