Exposure to beta-blockers and survival in breast cancer patients: A cohort study using the UK General Practice Research Database.

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Lay summary

New therapeutic strategies are needed to reduce mortality in breast cancer patients. Recently, it has been proposed that cancer progression may be prevented by medicines in current use including beta-blockers (used to treat hypertension). We previously demonstrated that beta-blockers inhibit migration in breast and prostate cancer cells and in an observational study showed marked reductions in cancer-associated mortality and metastasis in breast cancer patients using beta-blockers.

Our study will be the largest yet to investigate beta-blockers and cancer progression in breast cancer patients. GPRD data allow detailed analysis of the timing of drug exposure and the effect on various outcome measures including mortality, cancer-specific mortality and cancer recurrence. Importantly, an analysis will use robust cancer data from UK cancer registries and robust death data (from the Office of National Statistics).

Objective, Specific Aims and Rationale

The primary objectives of the proposed research are to examine whether female breast cancer patients who are exposed to beta-blockers have reduced cancer-specific mortality rates, all-cause mortality rates and recurrence rates.

These objectives will be achieved by comparing the rates of cancer-specific death (all-cause mortality and cancer recurrence) in breast cancer patients who are exposed to beta-blockers with those who are not exposed to these drugs.

Background

Breast cancer is the most common cancer in UK females and one of the leading causes of cancer death (http://www.statistics.gov.uk/pdfdir/canuk0810.pdf). New strategies are needed to reduce the occurrence of metastasis in breast cancer patients because current treatments have limited effectiveness, are expensive and may cause harmful side-effects.

Beta-blockers and cancer progression

Beta-blockers are drugs used in the treatment of heart disease and hypertension[1]. There are two main types: 1) a cardioselective type targeting predominantly beta-1 adrenoreceptors, and 2) a non-cardioselective type that inhibit beta-1 and -2 adrenoceptor activity. It has been recently proposed that cancer progression may be prevented by using beta-blockers[2]. Metastasis involves the migration of cancer cells. The process is tightly regulated by exogenous signal molecules including chemokines and neurotransmitters, binding to G protein-coupled receptors (GPCRs)[3;4]. In particular, the stress-associated adrenergic hormone, norepinephrine, was shown to be a potent inducer of migratory activity in cancer cell lines derived from breast[5], prostate[5], ovary[6] and colon[7] through its action on adrenoceptors. Moreover, we found that migrational activity and metastasis development can be inhibited by propranolol, a non-selective beta-2 adrenoceptor antagonist, in human cancer cell lines[5] and in a mouse xenograft model[8], respectively. Metastatic spread involves blood and lymphatic routes[9] and may be maintained by external or tumour-paracrine norepinephrine production[10]. Beta-blockers may retard cancer progression due to their

anti-migratory and anti-angiogenic properties, causing reduced matrix metalloproteinase-9 (MMP-9) production[11] and disrupted vessel tubule formation[12]. Evidence provided by a rat model has shown propranolol leads to reduced retention of implanted lung tumour cells, slowing disease progression[13]. New pharmacological strategies targeting adrenoceptors and their downstream signalling pathways are warranted.

There have been very few attempts at translating these promising laboratory findings into a patient clinical setting to test the utility of adrenoceptors as non-conventional cancer therapy targets[14]. Observational epidemiological studies suggest that adrenoceptor antagonists may have a prophylactic role because an inverse association has been shown between beta-blocker drug use and the incidence of multiple cancer types[15]. Similarly, alpha-adrenoceptor antagonists appear to reduce the incidence of prostate cancer[16].

In late 2010, we published the first observational study investigating the association between beta-blocker therapy and breast cancer progression[2]. We investigated archived medical records of 466 consecutive female breast cancer patients attending a specialist breast clinic in Nottingham. Importantly, patients receiving beta-blockers for hypertension had a 71% reduced risk of cancer-associated mortality (HR=0.29, 95%CI= 0.12, 0.72, p=0.007) and a 57% reduction in risk of developing distant metastasis (HR=0.43, 95%CI= 0.20, 0.93, p=0.031). Since then, and in contrast, a UK study investigating various cancer sites showed no association between beta-blocker usage and all cause mortality in breast cancer patients [17]. However, this study did not investigate cancer-specific mortality or cancer recurrence, and moreover had a number of other deficiencies including a lack of consideration of the impact of beta-blocker treatment prior to cancer diagnosis and the class of beta-blocker used. Also, a more recent study from the USA [18] showed a slight reduction in the risk of cancer-specific death in individuals using beta-blockers only (HR=0.76 95%CI 0.44, 1.33) but this was based upon fewer than 200 cancer-specific deaths and 74% of these patients were given Beta-1 selective beta-blockers that we have hypothesised to be less effective at preventing tumour recurrence compared to Beta-2 specific beta-blockers [19]. Recently, we showed that Beta-2 adrenoceptor protein expression in predominantly expressed in human breast cancer whereas Beta-1 is not [19].

Further investigation of the effect of beta-blockers on breast cancer progression is required to assess whether these drugs could be considered as adjunct treatments in these patients. If the proposed analyses using GPRD data demonstrate the effectiveness of beta-blockers in improving cancer prognosis then these findings would provide a strong rationale for conducting a randomised trial in cancer patients.

Study Type

The study will allow hypothesis testing. The primary hypothesis that will be tested is that breast cancer patients who are exposed to beta-blockers following diagnosis, have a reduced risk of death from breast cancer.

Study design

The proposed investigation is a retrospective cohort study including cohorts of patients with breast cancer. These population-based cohorts will be analysed using a nested case–control approach to allow for the potentially complex time-varying nature of beta-blocker usage after diagnosis of cancer. This is a common approach in the analysis of cohort data because compared with time-varying survival analysis it produces unbiased estimates with minimal loss of precision [20]. Also, its inherent time dependent nature means that it is free of biases such as immortal time bias (caused by a period of cohort follow-up during which, because of exposure definition, the

outcome under study can not occur)[21;22]. In the main analysis the cancer cohorts will be converted into nested case-control data. Cases will be members of the cancer cohorts who have died due to cancer and these will matched on age, cancer site and year of cancer diagnosis to up to 3 controls alive at the time of their death. Similar analyses will be conducted for other outcomes such as cancer recurrence and all-cause mortality.

Study population

We propose conducting three separate analyses in the breast cancer cohorts. In the first, the 'Whole GPRD analysis', we will maximise numbers by using solely information based upon GPRD diagnostic\symptom codes (Read codes) to identify cancers and outcome data. In the second, 'ONS linked analysis' we will use GPRD diagnostic\symptom codes (Read codes) to identify cancers and outcomes will be based upon Office of National Statistics data. In the third and primary analysis, the 'NCDR and ONS linked analysis', we will use data linked to the National Cancer Data Repository and Office of National Statistics to use the most robust data on cancer diagnosis and cause of death available. In all 3 analyses, individuals with previous cancer will be excluded. Sensitivity analysis will be conducted including individuals with a previous cancer, adjusting for it in the analysis, and additionally excluding ductal carcinoma in situ. Sensitivity analyses will also be conducted excluding individuals with less than 1 and 3 years of GP records prior to the cancer diagnosis, as in these individuals previous cancer may be less likely to have been ascertained.

A) Whole GPRD analysis
Breast cancer cohorts diagnosed with cancer between 1990 and 2008 will be selected from the GPRD. Primary diagnoses will be identified from GP recorded diagnostic\symptom codes (Read codes). In this analysis, from correspondence with GPRD, we anticipate around 30,000 individuals in the breast cancer cohort.

B) ONS linked analysis
A separate analysis will include only cancer patients who are linked to the ONS mortality data (providing information on date of death and cause of death). This cohort will include approximately 50% of the cancer patients in the whole GPRD analysis.

C) NCDR and ONS linked analysis
The primary analysis will include only cancer patients who are linked to the NCDR (providing information from UK cancer registries on primary cancer diagnosis, date of cancer diagnosis, date of death and cause of death and providing details on staging and cancer treatment) and using ONS mortality data (providing information on date of death and cause of death). This cohort will include approximately 35% of the cancer patients in the whole GPRD analysis.

Selection of comparison group(s) or controls

In the primary analysis, the cancer cohorts will be converted to case-control data. Cases will be members of the cancer cohorts who have died due to breast cancer and these will be matched on age and year of cancer diagnosis to 3 controls alive at the time of their death. Similar analyses will be conducted for other outcomes such as cancer recurrence and all-cause mortality.

Sample size/power calculations

For the primary hypothesis, feasibility counts (provided by the GPRD) indicated that in the GPRD there are approximately 30,000 individuals diagnosed with breast cancer prior to 2010 (with 3 years of UTS follow-up). Applying England and Wales relative survival rates for women with breast cancer we would estimate approximately 5000 cancer-specific deaths[23]. Pilot data (provided by GPRD) suggest approximately 20% breast cancer patients will have received beta-blockers after diagnosis. Therefore, with 5000 cases (i.e. cancer-specific deaths) and 25000 controls, we will have over 80% power to detect as significant (at the 5% level) an odds ratio of 0.85 in patients receiving beta-blockers after diagnosis. This is equivalent to a reduction in the risk of cancer-specific death on beta-blockers of 15%. Feasibility counts provided by the GPRD indicate that the linked NCDR cohort would contain 10,000 breast cancer cases, including approximately 1700 cancer-specific deaths in individuals with breast cancer. Assuming the same beta-blocker usage in this subgroup, with 1700 cases (i.e. cancer-specific deaths) and 8500 controls we would have over 80% power to detect as significant at the 5% level an odds ratio of 0.80 in patients receiving beta-blockers. This is equivalent to a reduction in the risk of death on beta-blockers of 20%.

Additional analyses conducted on all-cause mortality, and cancer recurrence, will contain larger numbers of cases and therefore will have power to detect even smaller effects.

Exposure, outcomes and covariates

Exposure

In the primary analysis the main exposure will be beta-blocker usage determined from GP prescribing data. The main analysis will be conducted on beta-blocker prescriptions in the period following diagnosis of cancer excluding the year prior to cancer death (or censoring). Packages and tablets of prescriptions for beta-blockers will be converted to daily defined doses (DDDs). Separate analyses will be conducted by type of beta-blockers based upon cardioselectivity and ISA activity (categorisations of beta-blockers shown in Appendix 1). A secondary analysis will be conducted on beta-blocker prescriptions in the period prior to cancer diagnosis (in patients registered for at least one year at their GP practice, to ensure prescriptions are recorded). Sensitivity analysis will be conducted excluding prescriptions in the six months prior to cancer death and not making any exclusions prior to death. Sensitivity analysis will also be conducted excluding prescriptions in the first year after cancer diagnosis as these may be affected by cancer treatment.

Outcomes

The primary analysis (in the NCDR linked cohort) will be breast cancer-specific death, determined from ONS data. Secondary outcomes will also be investigated as outlined below. In the whole GPRD analysis all-cause mortality will be determined in the cancer cohorts using GP recorded death codes and cancer recurrence will be determined based upon GP recorded cancer recurrence codes as used in a previous GPRD analysis[24]. In the NCDR linked analysis, all-cause mortality and cancer recurrence will also be investigated.

Covariates

The association between beta-blocker usage and breast cancer-specific death (and all-cause mortality and cancer recurrence) will be adjusted for a number of potential confounders including the following which may be associated with beta-blocker usage and risk of breast cancer-specific death:

a) Smoking, alcohol intake and BMI, recorded by the GP (where available, as these data will be incomplete for some individuals);

b) HRT, available from prescription records;

c) Tamoxifen and aromatase inhibitors usage (for breast cancer), available from prescription records;
d) Cancer treatment including information on surgery, chemotherapy, radiotherapy and hormone therapy, available from GP records and NCDR data;
e) Stage of disease, from linkage to NCDR (although not complete, in 2008 approximately 70% of the breast cancer cases with NCDR linkage had a recorded stage (http://www.ukacr.org/content/data-quality));
f) Comorbidity based upon individual GPRD Read codes disease codes and using the Charlson co-morbidity index using GPRD Read codes, as recently described[25] ;
g) Other medication usage (including antiplatelets, anticoagulants and NSAIDs).

Additionally, potential confounding by age at diagnosis and year at diagnosis will be controlled by the matched design as described below.

Data analysis

The primary analysis will be conducted in the NCDR and ONS linked data using a time matched nested case-control analysis of the cohorts (using the STATA sttocc command to convert the cohort data to nested case control data). The cases will be members of the cancer cohorts who have died due to breast cancer. These will be individually matched on age and year of cancer diagnosis to 3 controls that are alive at the time of the death of the cases. The index date for each case will be defined as their date of death. The index for each matched control will be the date of death of their matched case. The exposure period for the main analysis will include the time from cancer diagnosis to 6 months prior to the index date in both the cases and controls. Prescriptions in the 6 month period prior to death will be removed as prescriptions in this period may reflect changes in treatment at the end of life or increased exposure to healthcare professionals. An initial analysis will be conducted comparing odds of breast cancer death in those ever using beta-blockers to those never using these drugs. Separate analysis will be conducted by duration of beta-blockers usage (in DDDs). Separate analyses will be conducted by beta-blocker type (on the basis of cardio-selectivity and ISA). Conditional logistic regression will be used to compare the risk of breast cancer death by beta-blocker usage calculating odds ratios (ORs) and 95% confidence intervals (95%CIs). A separate analysis will be conducted looking simultaneously at any potential interaction between the effect of beta-blockers and aromatase inhibitors or tamoxifen. An adjusted analysis will be conducted including the potential confounders listed earlier.

In the other cohorts similar analyses will be conducted for tumour recurrence and all-cause mortality. In the cancer recurrence analysis cases will include individuals who have cancer recurrence. These will be individually matched on age (in 5 year intervals) and year of cancer diagnosis to 3 controls who are alive and free of cancer at the time of the cancer recurrence in the case and who are also members of the same cancer cohort. An outline of the planned primary and secondary analyses is shown in Appendix 2. All statistical analyses will be conducted in STATA version 11.

Sensitivity analyses will be conducted analysing the entire cohorts, prior to conversion to case-control data, and applying survival analysis to investigate beta-blocker exposure as a time varying covariate (after 6 months, 1 years and 2 years DDDs)[21]. Also, for the investigation of cancer-specific mortality, analysing the entire cohorts will allow adjustments for the competing risk of deaths from other causes, using competing-risks regression based on Fine and Gray's proportional subhazards model[26]. A propensity score adjusted analysis will also be conducted in

this cohort. Secondary analyses will also be conducted by stage (early and late) and by age group (under 55 years and over 55 years at diagnosis).

Limitations of the study design, data sources and analytic methods

As with all pharmaco-epidemiology studies, there is the possibility of confounding by indication (in which the indication for the drug rather than the drug itself is causing effects on the outcome). If a reduced cancer-specific mortality in individuals receiving beta-blockers is observed it seems unlikely that confounding by indication could be an explanation (as individuals taking beta-blockers with, most likely, hypertension would be expected to have higher mortality rates). However, a sensitivity analysis will be conducted comparing breast cancer-specific mortality in users of beta-blockers with users of other antihypertensive medications, who are likely to have more similar indications.

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Appendix 1: Beta-blocker categorisations

Drug	Selectivity	Dose	Active agent	Cardio-selective*	ISA†
Antipressan	Beta-1	25, 100mg	Atenolol	2	0
Atenix	Beta-1	25mg	Atenolol	2	0
Atenolol	Beta-1	25, 50, 80, 100mg		2	0
Atenolol with amiloride and hydrochlorothiazide capsules	Beta-1			2	0
Atenolol with nifedipine	Beta-1		Atenolol with a diuretic	2	0
Berkolol	Beta-1/2	10, 40mg	Propranolol	1	0
Beta-adalat	Beta-1	20, 50mg	Atenolol with Ca2+ channel blocker	2	0
Beta-cardone	Beta-1/2	40, 80mg	Sotolol	1	0
Betaloc SA Durule	Beta-1		Metoprolol	2	0
Bisoprolol	Beta-1	1.25, 2.5, 3.75, 5, 7.5, 10mg		2	0
Blocadren	Beta-1/2	10mg	Timolol	1	0
Cardicor	Beta-1	1.25, 2.5mg	Bisoprolol	2	0
Carvedilol	Beta-1	3.125, 6.25, 12.5, 25mg	Alpha-1 activity too	2	0
Corgard	Beta-1/2	40, 80mg	Nadolol - long acting	1	0
Co-tenidone	Beta-1	?	Atenolol and chlortalidone	2	0
Emcor	Beta-1	5, 10mg	Bisoprolol	2	0
Eucardic	Beta-1/2	12.5, 25mg	Carvedilol, alpha activity	1	0
Inderetic	Beta-1/2		Propranolol with benzofluzide	1	0
Inderex	Beta-1/2		Propranolol with benzofluzide	1	0
Lopresoretic	Beta-1		Metoprolol	2	0
Lopressor	Beta-1	50, 100, 200mg	Metaprolol	2	0
Metoprolol	Beta-1	50, 100mg		2	0
Moducren	Beta-1/2		Timolol with amiloride, hydrochlorothiazide	1	0
Monocor	Beta-1	10mg	Bisoprolol	2	0
Monocor	Beta-1		Bisoprolol	2	0
Nadolol	Beta-1/2	40mg	Long acting	1	0
Nebivolol	Beta-1	5mg		2	0
Prestim	Beta-1/2		Timolol & bendroflumethiazide		0

Propanix	Beta-1/2	10mg	Propranolol	1	0
Propranolol	Beta-1/2	10, 40, 80, 160mg, modified release	Inderal	1	0
Secadrex	Beta-1		Nebivolol	2	0
Sectral	Beta-1/2	400mg	Timolol	1	0
Sotalol	Beta-1/2	40, 160, 200mg		1	0
Sotazide	Beta-1/2		Sotolol	1	0
Tenif	Beta-1	20, 50mg	Atenolol with Ca2+ channel blocker	2	0
Tenoret	Beta-1	12.5, 50mg	Atenolol and chlortalidone	2	0
Tenoretic	Beta-1	25, 100mg	Atenolol and chlortalidone	2	0
Tenormin	Beta-1	50, 100mg	Atenolol	2	0
Timolol	Beta-1/2	10mg		1	0
Timolol with bendroflume	Beta-1/2			1	0
Totamol	Beta-1	50, 100mg	Atenolol	2	0
Acebutolol	Beta-1	5mg		2	3
Atenixco	Beta-1		Acebutalol	2	3
Celectol	Beta-1	400mg	Weak alpha-2 antagonist, weak beta-2 agonist	2	3
Celiprolol	Beta-1	200, 400mg	Weak alpha-2 antagonist, weak beta-2 agonist	2	3
Labetalol	Beta-1/2			1	3
Nebilet	Beta-1/2	5mg	Pindolol	1	3
Oxprenolol	Beta-1/2	20mg		1	3
Oxprenolol	Beta-1/2			1	3
Pindolol with clopamide	Beta-1/2			1	3
Sectral	Beta-1	100mg	Acebutalol	2	3
Trandate	Beta-1/2	100, 200mg	Labetalol	1	3
Trandate	Beta-1/2	50, 400mg	Labetalol	1	3
Trasicor	Beta-1/2	20, 80mg	Slow release oxyprenolol	1	3
Trasidex	Beta-1/2		Oxprenolol	1	3
Visken	Beta-1/2	5, 15mg	Pindolol	1	3
Betaloc	Beta-1	50mg	Metoprolol	2	3
Trasicor	Beta-1/2	40, 80mg	Oxprenolol	1	3

* 1 denotes cardio-non-selective (Beta-1 and -2 activity), 2 denotes cardio-selective (Beta-1 activity).
† 3 denotes ISA activity, 0 denotes no ISA activity.

Appendix 2: Analysis plan

Primary analysis

Dataset: *NCDR and ONS linked analysis*

Exclusions:	Individuals with previous cancers
Outcomes:	Breast cancer-specific death
Exposures:	Beta-blocker usage (in DDDs) Cardio-selective beta-blocker (see appendix) usage (in DDDs) Non-cardioselective beta-blocker (see appendix) usage (in DDDs) ISA beta-blocker (see appendix) usage (in DDDs) Non-ISA beta-blocker (see appendix) usage (in DDDs)
Exposure period:	Excluding usage in year prior to cancer death (or censoring date)
Confounders:	Smoking, alcohol and BMI HRT Tamoxifen and aromatase inhibitors usage Cancer treatment Cancer stage Comorbidity Other medication usage (including antiplatelets, anticoagulants and NSAIDs, particularly Cox-2 inhibitors)

Secondary analyses

(1) Dataset: *NCDR and ONS linked analysis*

Exclusions, Exposures, Exposure period, Confounders: same as primary analysis
Outcomes: Breast cancer-specific death or cancer recurrence (based on GPRD code)

(2) Dataset: *NCDR and ONS linked analysis*
Exclusions, Exposures, Exposure period, Confounders: same as primary analysis
Outcomes: All-cause mortality

(3) Dataset: *ONS linked analysis*

Exclusions, Exposures, Exposure period: same as primary analysis
Confounders: Smoking, alcohol and BMI
HRT
Tamoxifen and aromatase inhibitor usage
Comorbidity
Other medication usage (including antiplatelets, anticoagulants and NSAIDs, particularly Cox-2 inhibitors)
Outcomes: Breast cancer-specific death

(4) Dataset: *ONS linked analysis*

Exclusions, Exposures, Exposure period, Confounders: same as 3
Outcomes: Breast cancer-specific death or cancer recurrence (based on GPRD code)

(5) Dataset: *ONS linked analysis*

Exclusions, Exposures, Exposure period, Confounders: same as 3
Outcomes: All-cause mortality

(6) Dataset: *Whole GPRD analysis*

Exclusions, Exposures, Exposure period, Confounders: same as 3
Outcomes: All-cause mortality

(7) Dataset: *Whole GPRD analysis*

Exclusions, Exposures, Exposure period, Confounders: same as 3
Outcomes: Cancer recurrence (based on GPRD code)

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