Beta-adrenergic blocking drugs in breast cancer: a perspective review

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Abstract: The purpose of this review is to present the preclinical, epidemiological and clinical data relevant to the association between β -blockers and breast cancer progression. Preclinical studies have shown that β -adrenergic receptor (β -AR) signalling can inhibit multiple cellular processes involved in breast cancer progression and metastasis, including extracellular matrix invasion, expression of inflammatory and chemotactic cytokines, angiogenesis and tumour immune responses. This has led to the hypothesis that the commonly prescribed class of β -AR antagonist drugs (β -blockers) may favourably impact cancer progression. A number of recent pharmacoepidemiological studies have examined the association between β -blocker exposure and breast cancer progression. The results from these studies have suggested a potential role for targeting the β -AR pathway in breast cancer patients. Larger observational studies are, however, required to confirm these results. Questions regarding the type of β -blocker, predictive biomarkers or tumour characteristics, appropriate treatment paradigms and, most importantly, efficacy must also be answered in randomized clinical studies before β -blockers can be considered a therapeutic option for patients with breast cancer.

Keywords: adrenergic beta-agonists, adrenergic beta-antagonists, adrenergic receptors, breast neoplasms, neoplasms, propranolol

Introduction

The importance of host factors in cancer aetiology and outcome has been highlighted recently [Goodwin *et al.* 2010]. Epidemiological and clinical studies have associated psychosocial factors such as chronic stress and depression with cancer progression and, to a lesser extent, cancer onset [Spiegel *et al.* 2007; Chida *et al.* 2008]. These effects are mediated in part through activation of the autonomic nervous system and the hypothalamic–pituitary–adrenal axis, causing the release of catecholamines, glucocorticoids and other stress hormones from the adrenal gland, brain and sympathetic nerve terminals [Entschladen *et al.* 2004; Antoni *et al.* 2006; Thaker *et al.* 2007; Armaiz-Pena *et al.* 2009; Lutgendorf *et al.* 2010]. In this review we focus on the sympathetic nervous system component of the physiological stress response, which results in release of epinephrine and norepinephrine. Both of these neurotransmitters have been shown in preclinical studies to impact several pathways necessary for tumour progression and

metastasis through direct tumour effects and indirect effects on the tumour microenvironment [Entschladen *et al.* 2004; Antoni *et al.* 2006; Thaker *et al.* 2007; Armaiz-Pena *et al.* 2009; Goodwin *et al.* 2010; Lutgendorf *et al.* 2010]. Specifically, these studies have demonstrated that the protumour and prometastatic effects of epinephrine and norepinephrine are mediated primarily through the β -adrenergic receptor (β -AR) signalling pathway. This has led a number of authors to hypothesize that the commonly prescribed class of β -AR antagonist drugs (β -blockers) may favourably impact cancer progression [Entschladen *et al.* 2004; Antoni *et al.* 2006; Thaker *et al.* 2007; Armaiz-Pena *et al.* 2009; Lutgendorf *et al.* 2010]. The purpose of this review is to present the epidemiological and clinical data relevant to the association between β -blockers and breast cancer progression within the context of current preclinical evidence [Pérez-Sayáns *et al.* 2010]. The effects of β -blockers on breast cancer incidence will not be discussed.

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Preclinical studies

β-Adrenergic receptor expression in breast cancer

β-Adrenergic receptors are G_s-protein-coupled receptors that activate adenylate cyclase to elevate intracellular 3',5'-cyclic adenosine monophosphate (cAMP) and activate protein kinase A. There are three β-AR subtypes, β₁-AR, β₂-AR and β₃-AR, each with specific physiological actions. The expression of β-ARs has been characterized in several breast cancer cell lines [Vandewalle *et al.* 1990; Badino *et al.* 1996; Slotkin *et al.* 2000; Sloan *et al.* 2010; Madden *et al.* 2011; Park *et al.* 2011; Shi *et al.* 2011] as well as in collections of human breast cancer tissue samples [Draoui *et al.* 1991; Powe *et al.* 2011; Shi *et al.* 2011] and in mammary tumours from rodents induced by administration of dimethylbenz(a)anthracene [Marchetti *et al.* 1991] (see Table 1). Studies have shown that these β-ARs are predominantly of the β₂-adrenergic receptor (β₂-AR) subtype [Draoui *et al.* 1991; Badino *et al.* 1996; Slotkin *et al.* 2000] and are functionally active, with pharmacological ligation resulting in significant cAMP production [Vandewalle *et al.* 1990; Badino *et al.* 1996; Slotkin *et al.* 2000; Sloan *et al.* 2010; Madden *et al.* 2011].

Although β₂-AR is expressed by both oestrogen receptor (ER)-positive and ER-negative breast cancer cell lines, the highest levels of expression have been observed in cell lines that are ER-negative, progesterone receptor (PR)-negative and human epidermal growth factor receptor 2 (HER-2)-negative (triple-negative breast cancer [TNBC]) [Vandewalle *et al.* 1990; Madden *et al.* 2011]. This has led to suggestions that the β₂-AR signalling may be of greatest significance in the pathogenesis and progression of TNBC [Melhem-Bertrandt *et al.* 2011]. Results from studies in human breast cancer tissue samples have not been as consistent as those of studies in cell lines [Draoui *et al.* 1991; Powe *et al.* 2011; Shi *et al.* 2011]. In a study by Draoui and colleagues, the authors reported only a weak correlation between β-AR and PR expression and no correlation with the ER [Draoui *et al.* 1991]. However, in a recent study of breast tumour samples from 690 women [Powe *et al.* 2011], β₂-AR expression was strongly correlated with ER and PR expression, 80% and 65% of tumours with high β₂-AR expression co-expressing ER and PR respectively. There was no correlation between β₂-AR and HER-2 expression in this study, although a correlation has been noted in another study of both clinical samples and breast cancer

cell lines [Shi *et al.* 2011]. β-Blocker use by patients included in these breast tumour sample studies was not reported.

The prognostic significance of β₂-AR expression is also unclear. In the study by Powe and colleagues, patients with high levels of β₂-AR expression had a nonsignificant increase in survival when compared with patients with low-level expression [Powe *et al.* 2011]. The authors suggest that this may be due to the observed association between β₂-AR expression and small ER-positive tumours of low clinical stage and low proliferation. In unadjusted Kaplan–Meier analyses they also observed among ER-positive tumours a decrease in survival for tumours that co-expressed β₂-AR, which may reflect interactions between the ER and β₂-AR. However, further analyses are necessary before drawing such conclusions. A recently published abstract has also suggested that β-AR expression was not correlated with an observed association between β-blocker exposure and improved outcomes in women with breast cancer [Powe *et al.* 2010a]. It is, however, possible that the effects of β-AR signalling in breast cancer may be independent of β-AR expression by breast tumour cells. β₂-AR signalling may impact breast cancer progression through its effects on tumour immune responses and the regulation of the tumour microenvironment.

Blocking β-adrenergic receptor signalling in breast cancer

Preclinical studies have shown that antagonism of β-AR signalling by a β-blocker can inhibit multiple cellular processes involved in breast cancer progression, including tumour cell proliferation, metastasis development, apoptosis, extracellular matrix invasion, matrix metalloprotease activation, expression of inflammatory and chemotactic cytokines, angiogenesis and tumour immune responses (see Table 2).

Tumour growth

There is evidence to suggest that β-AR signalling plays a role in the regulation of tumour growth in a number of cancers; however, the evidence relating to breast tumour growth is conflicting. β-AR stimulation has been shown to both inhibit [Slotkin *et al.* 2000; Carie and Sebt, 2007] and promote breast tumour growth [Re *et al.* 1992; Cakir *et al.* 2002; Thaker *et al.* 2006; Shi *et al.* 2011], and more recent studies report that β-AR

Table 1. Overview of studies examining β -adrenergic receptor expression in breast cancer cell lines and tumour samples.

Study	Breast cell type	ER*	PR*	HER-2*	β -AR	β_1 -AR	β_2 -AR	Comments/functional significance
Marchetti <i>et al.</i> [1991]	Induced rodent mammary tumours	–	–	–	Yes	–	–	Influence of oestrogen levels on β -AR concentration assessed. Ovariectomy reduced β -AR expression and subsequent treatment with oestrogen caused a significant increase in β -AR levels.
Vandewalle <i>et al.</i> [1990]	MCF-7 T47-D MDA-MB-231 BT-20 VHB-1	Yes Yes No No Yes	Yes – No No –	No – No No –	Low Low High Low Low	– – – – –	– – – – –	β -AR agonists stimulated cAMP production in a dose-dependent manner. Response was greatest in the triple-negative MDA-MB-231 cell line. The pathophysiological significance of this was not studied.
Badino <i>et al.</i> [1996]	CG-5	Yes	–	–	Yes	Yes	Yes	The ratio of β_2 -AR to β_1 -AR expression was 3:1. β -AR agonists stimulated cAMP production in a dose-dependent manner. The pathophysiological significance of this was not studied.
Slotkin <i>et al.</i> [2000]	MDA-MB-231	No	No	No	High	No	High	β -AR agonists reduced DNA synthesis and cell replication.
Sloan <i>et al.</i> [2010]	66cl4	No	No	No	Low	–	Low	β -AR agonists stimulated cAMP production. The pathophysiological significance of this was unclear as the effects of β -AR signalling on the development of tumour metastases were shown to be mediated through induction of tumour macrophage infiltration.
Madden <i>et al.</i> [2011]	MCF-7 MDA-MB-361 MDA-MB-231 MDA-MB-231BR	Yes Yes No No	Yes – No No	No Yes No No	Low Low High High	– – – –	Low Low High High	β -AR agonists stimulated cAMP production in proportion to β -AR expression levels. β -AR stimulation induced VEGF expression in the MDA-MB-231BR cell line but not others.
Shi <i>et al.</i> [2011]	MCF-7 BT-474 MDA-MB-435 MCF-7(HER-2) Human breast tumour samples	Yes No No Yes –	Yes Yes No Yes –	No Yes Yes Yes –	Low High High High Yes	– – – – –	Low Low High High Yes	β -AR expression was strongly correlated with HER-2 expression in cell lines and clinical samples. β -AR expression was upregulated in MCF-7(HER-2) cells overexpressing HER-2. Suggestion that β_2 -AR and HER-2 expression comprises a positive feedback loop in human breast cancer cells.
Draoui <i>et al.</i> [1991]	Human breast tumour samples	–	–	–	Yes	No	Yes	β -AR normally coupled with G-protein. A slight correlation was shown between β -AR and PR, and no correlation between β -AR and ER.
Powe <i>et al.</i> [2011]	Human breast tumour samples	–	–	–	Yes	–	Yes	β -AR expression was negative in 2%, weak in 42% and strong in 55% of samples. β -AR expression was significantly associated with tumours of small size, low histological grade, early clinical stage, and ER and PR expression. High expression was associated with a nonsignificant increase in survival.

ER, oestrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2; β -AR, β -adrenergic receptor; β_2 -AR, β_2 -adrenergic receptor; VEGF, vascular endothelial growth factor; cAMP, cyclic adenosine monophosphate.

Table 2. Overview of preclinical studies examining the effects of β -adrenergic receptor signalling in breast cancer.

Study	Breast cell type	Model	Tumour characteristic	β -AR agonist effect	β -AR antagonist effect (β -blockers)
Re <i>et al.</i> [1992]	CG-5	<i>In vitro</i>	Tumour growth	β -AR signalling (pharmacological agonists) stimulated tumour growth.	–
Slotkin <i>et al.</i> [2000]	MDA-MB-231	<i>In vitro</i>	Tumour growth	β_2 -AR signalling (pharmacological agonists) inhibited tumour growth through a cAMP activated pathway.	Inhibited by the β_1/β_2 -AR nonselective antagonist propranolol. Propranolol itself had no effect on tumour growth.
Drell <i>et al.</i> [2003]	MDA-MB-468	<i>In vitro</i>	Migration and invasion	β -AR signalling (pharmacological agonists) stimulated tumour cell migration.	Promigratory effects of β -AR signalling were completely inhibited by the β_2 -AR-selective antagonist ICI-118,551 and partially inhibited by the β_1 -AR-selective antagonist atenolol.
Lang <i>et al.</i> [2004]	MDA-MB-468	<i>In vitro</i>	Migration and invasion	β_2 -AR signalling (pharmacological agonists) stimulated tumour cell migration.	Promigratory effects of β_2 -AR signalling were inhibited by the β_1/β_2 -AR-nonselective antagonist propranolol.
Melamed <i>et al.</i> [2005]	MADB106	<i>In vivo</i>	Metastasis Immune response	β -AR signalling (surgical stress induced) inhibited natural killer cell cytotoxicity against tumour cells and increased metastasis.	Reduced natural killer cell activity and increased metastasis inhibited by the β_1/β_2 -AR-nonselective antagonist nadolol. Effect of nadolol was greater in combination with the COX1/COX2 inhibitor indomethacin.
Thaker <i>et al.</i> [2006]	MDA-MB-231	<i>In vivo</i>	Tumour growth Angiogenesis Metastasis	β_2 -AR signalling (pharmacological agonists and stress-induced) stimulated tumour growth, tumour angiogenesis and metastatic spread.	–
Carie and Sebtì [2007]	MDA-MB-231	<i>In vitro</i> <i>In vivo</i>	Tumour growth Cell death	β_2 -AR signalling (pharmacological agonists) inhibited tumour growth <i>in vitro</i> and induced <i>in vivo</i> tumour regression through cAMP activation, and subsequent inhibition of the RAF-1/MEK-1/ERK-1,2 pathway.	Inhibited by β_2 -AR-selective antagonist ICI-118,551.
Benish <i>et al.</i> [2008]	MADB106	<i>In vivo</i>	Metastasis Immune response	β -AR signalling (surgical stress induced) inhibited natural killer cell cytotoxicity against tumour cells and increased metastasis.	Reduced natural killer cell activity and increased metastasis inhibited by the β_1/β_2 -AR-nonselective antagonist propranolol. Effect of propranolol was greater in combination with the COX2 inhibitor etodolac.

Table 2. (Continued).

Study	Breast cell type	Model	Tumour characteristic	β_2 -AR agonist effect	β_2 -AR antagonist effect (β -blockers)
Avraham <i>et al.</i> [2010]	MADB106	<i>In vivo</i>	Metastasis Immune response	β_2 -AR signalling (surgical stress induced) inhibited natural killer cell cytotoxicity against tumour cells and increased metastasis.	Reduced natural killer cell activity and increased metastasis inhibited by the β_1/β_2 -AR-nonselective antagonist nadolol in combination with the COX1/COX2 inhibitor indomethacin and immune stimulant poly I-C.
Sloan <i>et al.</i> [2010]	66cl4	<i>In vivo</i>	Metastasis Angiogenesis Immune response	β_2 -AR signalling (pharmacological agonists and stress-induced) induced 30-fold increase in metastasis to distant tissues. Effects mediated by tumour macrophage infiltration and production of the pro-angiogenic and prometastatic factors VEGF and MMP-9.	Tumour metastasis, macrophage infiltration and angiogenesis were Inhibited by the β_1/β_2 -AR-nonselective antagonist propranolol. Propranolol had no effect on primary tumour growth.
Shi <i>et al.</i> [2011]	MCF-7	<i>In vitro</i>	Tumour growth Angiogenesis Metastasis	β_2 -AR signalling (pharmacological agonists) stimulated the expression of HER-2 and induced tumour growth in a dose-dependent manner. β_2 -AR signalling also upregulated production of the pro-angiogenic and prometastatic factors VEGF and IL-8.	Expression of HER-2 was inhibited by the β_2 -AR-selective antagonist ICI-118.551.
Madden <i>et al.</i> [2011]	MCF-7 MDA-MB-361 MDA-MB-231 MDA-MB-231BR	<i>In vitro</i>	Angiogenesis	β_2 -AR signalling (pharmacological agonists) stimulated production of pro-angiogenic factors VEGF (MDA-MB-231BR) and IL-6 (MDA-MB-231BR and MDA-MB-231)	Production of the pro-angiogenic factors VEGF and IL-6 inhibited by the β_2 -AR-selective antagonist ICI-118.551.
Park <i>et al.</i> [2011]	MDA-MB-231		Angiogenesis	β_2 -AR signalling (pharmacological agonists) stimulated production of the pro-angiogenic factor VEGF via a HIF-1 α -dependent pathway.	Upregulation of VEGF and HIF-1 α expression were inhibited by the β_1/β_2 -AR-nonselective antagonist propranolol.
β -AR, β -adrenergic receptor; β_2 -AR, β_2 -adrenergic receptor; VEGF, vascular endothelial growth factor; IL, interleukin; COX, cyclooxygenase; HIF, hypoxia-inducible factor ; Poly I-C, Polynosinic:polycytidylic acid.					

signalling has negligible effect on *in vitro* or *in vivo* breast tumour growth [Sloan *et al.* 2010; Madden *et al.* 2011]. The reasons for such heterogeneity are not entirely clear. Results from ovarian cancer models have demonstrated that the effect of β -AR signalling on tumour growth is associated with β_2 -AR expression by tumour cells [Thaker *et al.* 2006]. This does not appear to be the case for breast cancer, for which studies using cell lines with high β_2 -AR expression have produced opposing results [Slotkin *et al.* 2000; Thaker *et al.* 2006; Carie and Sebti, 2007; Madden *et al.* 2011]. In one of these studies, the effect β -AR stimulation on tumour growth varied across β -AR agonist type. This has led to the suggestion that differences between β -AR agonists may contribute to functional heterogeneity in breast cancer cell responses to β -AR stimulation [Madden *et al.* 2011]. It is also possible that the direct effects of β -AR signalling on the tumour microenvironment may explain the observed differences between studies conducted *in vivo* and *in vitro* [Sloan *et al.* 2010]. In ovarian cancer models, β -AR stimulation has been consistently shown to promote tumour growth [Thaker *et al.* 2006; Landen *et al.* 2007; Lee *et al.* 2009]. This effect, as noted, is associated with tumour cell β -AR expression, mediated through the β_2 -AR and inhibited by the β -blocker propranolol (β_1/β_2 -AR nonselective) [Thaker *et al.* 2006; Landen *et al.* 2007; Lee *et al.* 2009]. Similar results have been observed in pancreatic and oesophageal cancer [Liu *et al.* 2008; Zhang *et al.* 2009].

Tumour metastasis

Several *in vivo* breast cancer studies have shown that β -AR signalling is involved in the pathogenesis of breast cancer metastases [Melamed *et al.* 2005; Benish *et al.* 2008; Avraham *et al.* 2010; Sloan *et al.* 2010]. In these studies either stress-induced or pharmacological β -AR stimulation resulted in up to a 30-fold increase in metastasis to distant sites, including the lymph nodes and lung. β -Blockers (propranolol, nadolol; β_1/β_2 -AR-nonselective) inhibited these prometastatic effects by between 50% and 100%. Greater inhibition was also obtained by combining these β -blockers with prostaglandin synthesis inhibitors (cyclooxygenase [COX] 1 and COX2 inhibitors, e.g. indomethacin) and immune stimulants. [Melamed *et al.* 2005; Benish *et al.* 2008; Avraham *et al.* 2010]. The prometastatic effects of β -AR signalling have also been demonstrated in melanoma

and ovarian, lung and prostate cancer [Palm *et al.* 2006; Thaker *et al.* 2006; Glasner *et al.* 2010]. β -AR signalling promotes the development of tumour metastases through the regulation of several key steps in the pathogenesis of metastasis. These include tumour vascularization, invasion, migration, survival in circulation and the evasion of tumour immune responses [Lutgendorf *et al.* 2010].

Cell death

Preclinical studies have demonstrated conflicting effects of β -AR signalling in the regulation of tumour cell apoptosis and anoikis. Carie and colleagues demonstrated that the β_2 -AR agonist ARA-211 induced breast tumour cell apoptosis *in vitro* and tumour regression *in vivo* [Carie and Sebti, 2007]. However, Sastry and colleagues determined that signalling via the β_2 -AR reduces the sensitivity of prostate cancer cells to apoptosis [Sastry *et al.* 2007]. Sood and colleagues also showed that the β -AR agonists epinephrine and norepinephrine protected ovarian tumour cells from anoikis and that this effect was inhibited by the β_1/β_2 -nonselective antagonist propranolol [Sood *et al.* 2010]. Two further studies have also shown that inhibition of β_2 -AR signalling by propranolol or a β_2 -adrenergic receptor-specific antagonist in combination with gemcitabine induces apoptosis in pancreatic cancer cells [Zhang *et al.* 2009; Shan *et al.* 2011]. In these studies the β_1 -AR-selective antagonist metoprolol had the least effect on apoptotic rate [Zhang *et al.* 2009].

Angiogenesis

β -AR signalling has been shown to increase the *in vitro* [Madden *et al.* 2011; Park *et al.* 2011; Shi *et al.* 2011] and *in vivo* [Thaker *et al.* 2006; Sloan *et al.* 2010] expression of vascular endothelial growth factor (VEGF) and interleukin (IL)-6, key pro-angiogenic factors, in a number of breast tumour models. This stimulation of VEGF expression by β -AR signalling is proportional to β -AR expression [Madden *et al.* 2011], dose-dependent [Park *et al.* 2011] and inhibited by propranolol [Park *et al.* 2011]. There have, however, been discrepancies between the results from *in vitro* and *in vivo* studies of β -AR signalling and VEGF expression [Thaker *et al.* 2006; Madden *et al.* 2011]. It has been suggested that these discrepancies may be attributed to *in vivo* VEGF production by β -AR-expressing cells in the

tumour stroma (i.e. macrophages) [Thaker *et al.* 2006]. This suggestion has subsequently been confirmed [Sloan *et al.* 2010]. *In vivo* studies have associated β -AR-induced increases in VEGF production with significant increases in breast tumour vasculature [Thaker *et al.* 2006; Sloan *et al.* 2010]. These studies have focused on the role of β_2 -AR signalling in breast tumour angiogenesis, but have not ruled out the possibility that other members of the β -AR family may also play a role. Studies in other tumour types have, however, shown that the effects of adrenergic signalling are mediated primarily through the β_2 -AR [Liu *et al.* 2008; Zhang *et al.* 2010]. The stimulatory effects of β -AR signalling on VEGF expression have been observed in ovarian [Lutgendorf *et al.* 2003; Thaker *et al.* 2006; Lee *et al.* 2009], nasopharyngeal [Yang *et al.* 2006], melanoma [Yang *et al.* 2009], oesophageal [Liu *et al.* 2008], multiple myeloma [Yang *et al.* 2008], prostate [Park *et al.* 2011] and pancreatic [Guo *et al.* 2009; Zhang *et al.* 2010] tumour models. Also of interest has been the recent chance discovery that the nonselective β -blocker propranolol is an effective treatment for infantile haemangioma, a common benign tumour occurring in 5–10% of infants [Schiestl *et al.* 2011]. It has been suggested that the observed benefits of treatment are due in most part to the inhibition of VEGF production by propranolol [Storch and Hoeger, 2010].

Migration and invasion

In vitro breast cancer models have shown that the β -AR agonist norepinephrine exerts both chemokinetic and chemoattractive effects on breast tumour cells [Drell *et al.* 2003; Lang *et al.* 2004]. In these studies, norepinephrine exposure positively influenced the number and direction of migrating tumour cells. Similar findings have been reported for several other tumour types, including ovarian, colon, prostate and pancreatic cancers [Masur *et al.* 2001; Lang *et al.* 2004; Sood *et al.* 2006; Zhang *et al.* 2010]. *In vivo* studies of these promigratory and pro-invasive effects have also demonstrated an association between norepinephrine exposure, increased invasiveness, nodal involvement and the development of metastasis [Palm *et al.* 2006; Sood *et al.* 2006]. It has been shown that these effects are mediated through the β -AR pathway, primarily the β_2 -AR, and are inhibited by nonselective β -blockers, for example propranolol [Masur *et al.* 2001; Drell *et al.* 2003; Lang *et al.* 2004; Palm *et al.* 2006; Sood *et al.*

2006; Zhang *et al.* 2010]. Similar inhibitory effects have not been uniformly observed with the use of β_1 -AR-selective antagonists such as atenolol [Masur *et al.* 2001; Drell *et al.* 2003; Lang *et al.* 2004; Zhang *et al.* 2010]. β -AR signalling regulates the migratory and invasive capacity of tumour cells through alterations in tumour gene expression and the upregulation of matrix metalloproteinase (MMP) expression (MMP-2, MMP-9) [Sood *et al.* 2006; Landen *et al.* 2007; Zhang *et al.* 2010]. Pharmacological blockade of these MMPs has been shown to inhibit the effects of β -AR signalling on tumour cell invasive potential [Sood *et al.* 2006].

Immune response

β -AR signalling plays an important role in the regulation of tumour-directed immune responses. Two studies have demonstrated, using *in vivo* breast tumour models, that β -AR agonists suppress natural killer cell activity in a dose-dependent manner, resulting in a 10-fold increase in the number of tumour cells retained in the lungs and a similar rise in the number of consequent lung metastases [Melamed *et al.* 2005; Benish *et al.* 2008]. Further confirmation of these results was obtained in studies demonstrating that the perioperative use of propranolol and a COX2 inhibitor regulates the immune response, reduces the risk of postoperative tumour metastasis and improves recurrence-free survival rates in mice undergoing primary tumour excision [Avraham *et al.* 2010; Glasner *et al.* 2010]. β -AR signalling also appears to regulate the prometastatic effects of the tumour immune response. Sloan and colleagues used an *in vivo* model of breast cancer to demonstrate that either stress-induced or pharmacological adrenergic stimulation resulted in a considerable increase in the development of metastases [Sloan *et al.* 2010]. This effect was mediated through β_2 -AR signalling, which promoted the infiltration of macrophages into the primary tumour parenchyma and induced a prometastatic gene expression signature. Macrophages were shown to be the intratumoral target of this β_2 -AR signalling, which resulted in the increased expression of macrophage-derived factors, including COX2, MMP-9 and VEGF, the last of which was associated with a threefold increase in tumour blood vessel density. Treatment with the β -blocker propranolol inhibited macrophage infiltration, tumour spread to distant tissues and the vascularization of tumours.

β -Blockers in breast cancer: pharmacoepidemiological studies

Six recently published pharmacoepidemiological studies have examined the association between β -blocker exposure and breast cancer progression. In the first of these studies, published in October 2010, Powe and colleagues reviewed medical records to identify female patients with stage I and II breast cancer presenting to the Nottingham City Hospital, UK, between 1987 and 1994 [Powe *et al.* 2010b]. These patients were then classified into one of three subgroups: women with a history of hypertension receiving a β -blocker for at least 1 year prior to diagnosis ($n = 43$, β_1 -AR-selective 74%, β_1/β_2 -AR-non-selective 26%); women with a history of hypertension at the time of breast cancer diagnosis receiving other antihypertensive drug treatment for at least 1 year prior to diagnosis ($n = 49$); and normotensive women ($n = 374$) not on any anti-hypertensive drugs. Women receiving β -blocker treatment for less than 1 year were excluded from the study. The time to distant metastasis formation and breast cancer-specific survival was compared between all three groups using multivariate analyses. These demonstrated a 57% reduced risk of metastasis development (hazard ratio [HR] 0.43; 95% confidence interval [CI] 0.20–0.93) and a 71% reduction in the risk of breast cancer-specific mortality after 10 years (HR 0.29; 95% CI 0.12–0.72) after adjusting for tumour size, stage and grade in women taking any β -blocker compared with those who were not.

In a subsequent study by Ganz and colleagues the authors examined associations between any β -blocker exposure and/or angiotensin converting enzyme inhibitor (ACEi) exposure and breast cancer outcomes [Ganz *et al.* 2011]. The Life After Cancer Epidemiology (LACE) cohort was used to identify 1779 women enrolled from the Kaiser Permanente Northern California Cancer Registry with a diagnosis of early-stage invasive breast cancer between 1997 and 2000. β -Blocker and ACEi exposure in the year before and after breast cancer diagnosis was identified for each patient in this cohort from pharmacy dispensing records. They identified 407 women who filled at least one prescription for a β -blocker or an ACEi during this period. This number comprised 66 patients who filled a prescription for both, 137 who filled a prescription for an ACEi only and 204 who filled a prescription for a β -blocker only (β_1 -AR-selective 82%, β_1/β_2 -AR-nonselective 18%). The time to breast cancer recurrence,

breast cancer-specific mortality and overall mortality was compared between exposed and unexposed groups using delayed-entry Cox proportional hazards models adjusted for age, race, tumour stage, hormone receptor status, chemotherapy and hormonal therapy use, body mass index, hypertension and diabetes. In comparison with unexposed women, women taking β -blockers had a nonsignificant 14% reduction in the risk of breast cancer recurrence (HR 0.86; 95% CI 0.57–1.32) and a nonsignificant 24% reduction in the risk of breast cancer-specific mortality (HR 0.76; 95% CI 0.44–1.33). There was, however, no reduction in all-cause mortality (HR 1.04; 95% CI 0.72–1.51). ACEi exposure was unexpectedly associated with a significant increase in breast cancer recurrence and cause-specific mortality.

Four further studies were published in 2011 [Barron *et al.* 2011; Melhem-Bertrandt *et al.* 2011; Sendur *et al.* 2011; Shah *et al.* 2011]. In the study by Melhem-Bertrandt and colleagues, the authors used the Breast Cancer Management System Database at The University of Texas MD Anderson Cancer Center to identify 102 women with invasive breast cancer, treated with neoadjuvant chemotherapy from January 1995 to May 2007 who also reported taking a β -blocker (β_1 -AR-selective 89%, β_1/β_2 -AR non-selective 11%) and 1311 patients taking no β -blockers. There was no difference in the rate of pathological complete response between women taking and not taking β -blockers. Relapse-free survival and overall survival were also compared between the two groups. Women taking β -blockers had a 48% reduction in the risk of breast cancer recurrence (HR 0.52; 95% CI 0.31–0.88) and a nonsignificant 36% reduction in the risk of death (HR 0.64; 95% CI 0.38–1.07) after adjusting for age, stage, race, body mass index, comorbidities and medication usage. In further subgroup analyses β -blocker use was associated with a 70% reduction in breast cancer recurrence (HR 0.30; 95% CI 0.10–0.87) among patients with TNBC ($n = 377$) and a nonsignificant 65% reduction in mortality (HR 0.35; 95% CI 0.12–1.00). β -Blocker use had no significant association with relapse-free survival and overall survival among women with ER-positive ($n = 826$) breast cancer. The study authors suggest that the relatively short follow-up time in their study (median follow-up 55 months) may have limited the ability to detect an association in this population.

In the study by Barron and colleagues, we used linked national cancer registry and prescription refill data from Ireland to identify 5801 women with a diagnosis of stage I–IV invasive breast cancer between 2001 and 2006 [Barron *et al.* 2011]. From this population, women taking propranolol only ($n = 70$, β_1/β_2 -nonselective), atenolol only ($n = 525$, β_1 -selective) or no β -blocker ($n = 4738$) at any time in the year prior to diagnosis were identified. Separate matched (ratio 1:2) analyses were conducted to examine associations between the use of propranolol or atenolol and the risk of local tumour invasion at diagnosis (T4 tumour), nodal or metastatic involvement at diagnosis (N2/N3/M1 tumour) and breast cancer-specific mortality. In comparison with nonusers, propranolol users were less likely to present with a T4 tumour (odds ratio [OR] 0.24; 95% CI 0.07–0.85) or N2/N3/M1 tumour (OR 0.20; 95% CI 0.04–0.88). Women taking propranolol at the time of diagnosis ($n = 47$) had an 81% lower risk of breast cancer-specific mortality (HR 0.19; 95% CI 0.06–0.60) after adjusting for age, stage, grade and comorbidity score. No association with invasive tumour characteristics (T4 tumour: OR 1.31; 95% CI 0.91–1.88. N2/N3/M1 tumour: OR 1.10; 95% CI 0.72–1.71) or breast cancer-specific mortality (HR 1.08; 95% CI 0.84–1.40) was observed for patients taking the β_1 -selective antagonist atenolol.

In the study by Shah and colleagues, the authors used the DIN-LINK primary care database in the UK to identify 3462 women with a primary diagnosis of breast ($n = 984$), colorectal ($n = 619$), lung ($n = 436$), oesophagus ($n = 159$), ovarian (148), pancreas ($n = 140$), prostate ($n = 759$), renal ($n = 124$) or stomach ($n = 93$) cancer between 1997 and 2006, and at least two prescriptions for an antihypertensive agent in the year prior to diagnosis [Shah *et al.* 2011]. Patients with coronary heart disease, heart failure, stroke or arrhythmias before cancer diagnosis were excluded, as were patients with a contraindication for β -blocker or other antihypertensive therapy. The 1406 patients taking a β -blocker were compared with 2056 patients taking other antihypertensive therapy. The proportions of all patients taking selective and nonselective β -blockers were 83% and 17%, respectively. Information on selective/nonselective β -blocker use by cancer subtype was not provided. In the breast cancer analysis, there was no difference in overall survival (HR 1.09; 95% CI 0.80–1.49) between patients receiving any β -blocker ($n = 434$) and patients receiving

other antihypertensive medications ($n = 554$) after adjusting for age, sex, year of diagnosis, smoking status, number of medications received in the year before diagnosis, socioeconomic status and national region. However, data on treatment received and prognostic tumour characteristics, such as stage, grade and receptor status, were not available. In addition, the use of patients receiving antihypertensives other than a β -blocker as a comparator group makes the interpretation of the results from this study difficult. This is because there is evidence to suggest that a number of these antihypertensive drugs may also influence breast cancer outcomes [Ganz *et al.* 2011].

In the study by Sendur and colleagues, the authors report the results from an age-matched retrospective analysis of breast cancer outcomes in users ($n = 88$) and nonusers ($n = 456$) of the β_1 -AR-selective antagonist metoprolol [Sendur *et al.* 2011]. There were no significant differences in 3-year disease-free or 5-year overall survival rates between metoprolol users and nonusers. This analysis was, however, not adjusted for relevant prognostic and confounding variables.

Overall, the results from these pharmacoepidemiological studies suggest a potential role for targeting the β -AR pathway in breast cancer patients. There are, however, differences between their results that raise a number of important questions. Firstly, preclinical data indicate that it is β_2 -AR signalling that plays the most prominent role in breast tumour regulation. Yet in the studies by Powe, Ganz and Melhem-Bertrandt and their colleagues the most commonly used β -blockers were β_1 -AR-selective antagonists (74–89%) [Powe *et al.* 2010b; Ganz *et al.* 2011; Melhem-Bertrandt *et al.* 2011]. It has been suggested that the observed associations with these agents may be due to the fact that many β_1 -AR-selective β -blockers have relatively large off-target β_2 -AR receptor affinity, and that even modest β_2 -AR antagonism may be sufficient to inhibit the effects of β_2 -AR signalling [Ganz and Cole, 2011]. However, this assumption is not strongly supported by preclinical studies, which have shown relatively little effect for β_1 -AR antagonists, or the results from our study [Barron *et al.* 2011], in which no effect on breast cancer outcomes was observed for atenolol, a β_1 -AR-selective antagonist with a $\beta_1:\beta_2$ adrenergic receptor affinity of 6:1 [Smith and Teitler, 1999]. It is difficult to draw definitive conclusions about the possible effects of β_1 -AR-selective agents from the studies by Powe,

Ganz and Melhem Bertrandt and their colleagues, as all of these studies included both β_1 -selective and β_1/β_2 -nonselective antagonists in the same analyses. Understanding of the relative effects of β_1 -selective and β_1/β_2 -nonselective antagonists therefore requires further clarification and future pharmacoepidemiological studies should, if possible, report their results stratified by β -AR subtype.

The second question raised by the results from these studies regards the possible variation in the effect of β -blockers with respect to ER, PR and HER-2 status. Results from the study by Melhem-Bertrandt and colleagues suggest that the effects of β -blocker exposure are most evident in patients with TNBC [Melhem-Bertrandt *et al.* 2011]. A significant benefit from β -blocker exposure was not observed for ER-positive patients in their study. Unfortunately, the studies by Powe, Ganz and Shah and their colleagues and ourselves did not, or were unable to, distinguish between these different breast cancer subtypes and are thus unable to confirm this observation. The rationale for undertaking a subgroup analysis in TNBC patients was based upon the observation that TNBC patients have a higher prevalence of abdominal obesity and metabolic syndrome, both of which are linked to dysregulation of the sympathetic nervous system and potentially increased β -AR signalling [Melhem-Bertrandt *et al.* 2011]. Further work is required to clarify whether the clinical effects of β -blockers vary according to β -AR expression or ER, PR and HER-2 status.

In addition to these remaining questions, future pharmacoepidemiological studies should address questions regarding associations between breast cancer outcomes and β -blocker dose or duration. Also of interest will be the timing of β -blocker exposure with respect to other anti-cancer treatments, in particular surgery; the presence of synergies with other therapies, such as anti-angiogenic agents [Loges *et al.* 2009]; the possibility that β -blocker exposure is associated with site-specific inhibition of metastasis; and whether associations vary by degree of hypertension.

β -Adrenergic receptor antagonists in breast cancer: clinical studies

There are at least three phase II clinical studies currently assessing the safety and efficacy of β -blockers in breast, colorectal and ovarian cancers [ClinicalTrials.gov identifiers: NCT00502684,

NCT00888797 and NCT01308944]. In the breast study, 460 women with stage I/II breast cancer undergoing surgery are being randomized in a double-blind fashion to receive either propranolol (80 mg/day) and etodolac (nonsteroidal anti-inflammatory drug) or placebo from 2 days before to 3 days after surgery. In addition to laboratory studies and safety data, 5-year disease recurrence will be assessed. The planned colorectal cancer study follows a similar design to this. In the ovarian cancer study, 25 women with stage I–IV invasive epithelial ovarian cancer, primary peritoneal carcinoma or fallopian tube cancer will receive propranolol (80 mg/day) from 2 days before surgery and continue treatment for the duration of postoperative chemotherapy. The study's primary outcome will be safety, but progression-free survival rates and biomarkers of response will also be assessed as secondary outcomes.

Conclusion

Overall, the results from preclinical and pharmacoepidemiological studies support the suggestion that β -blockers could provide a clinical benefit in breast cancer through inhibition of the prostatic effects of β -AR signalling on tumour immune responses and the tumour microenvironment. To date, however, pharmacoepidemiological studies examining associations between β -blocker use and improved breast cancer outcomes have been limited in sample size. Larger observational studies will enable subgroup analyses to be undertaken so that women most likely to benefit from the addition of a β -blocker to their breast cancer regimen can be identified. This information can be used to better inform the design of randomized clinical studies to address questions regarding the type of β -blocker, predictive biomarkers or tumour characteristics, appropriate treatment paradigms and, most importantly, efficacy. The results from these randomized studies will be required before targeting of the β -AR signalling pathway can be considered a therapeutic option for patients with breast cancer.

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Conflict of interest statement

The authors declare no conflict of interest in preparing this article.

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