MINI-REVIEW

Are Beta Blockers New Potential Anticancer Agents?

Shahid Akbar[1]*, Mansour Saleh Alsharidah[2]

Abstract

β-Blockers have been one of the most widely used and versatile drugs for the past half a century. A new potential for their use as anti-cancer drugs has emerged in the past few years. Various retrospective case control studies have been suggestive that use of β-blockers before the diagnosis of cancer could have preventive and protective effects against non-small cell lung carcinoma, melanoma, and breast, pancreatic and prostate cancers. Experimental and clinical observations are still inconclusive with some inconsistent findings. However, indications are pointing toward a positive role of some β-blockers against certain forms of cancers. This mini review is an effort to present the up to date published results of case-control studies and experimental findings.

Keywords: Beta - blockers - adrenoceptors - anticancer - breast - ovarian - pancreatic - prostate

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Introduction

Since their arrival on the clinical scene, β-adrenoceptors (β-ARs) antagonists or β-blockers as they are commonly known, have proved to be one of the most versatile and widely used drugs in clinical practice. Although dichloroisoproterenol (DCI) was the first β-blocker synthesized by Elli Lilly, it was pronethalol that was the first β-blocker tested for clinical use, but due to the finding that it was carcinogenic in mice it was never approved for clinical use. The first β-blocker, propranolol that was free of carcinogenic activity and entered into clinical practice in 1964 for the treatment of angina pectoris was introduced by Sir James Black (Dr. Black received the Nobel Prize for his invention in 1988 and was knighted by the Queen of England in 2000). It was a revolutionary drug that created a new category of drugs for the treatment of cardiovascular diseases.

Since their introduction, β-blockers have gone a sea change both in terms of their nature and properties and their therapeutic uses. Propranolol was a non-selective antagonist that competitively blocked both β1 and β2 adrenergic receptors, and thus produced certain adverse effects due to β2 receptors blockade, such as potentiation of effects of hypoglycemic drugs, causing bronchoconstriction in sensitive individuals and masking warning signs of hypoglycemia (mainly β1 effects). It was also a highly lipophilic drug that crossed the blood brain barrier and produced CNS adverse effects. Atenolol, a hydrophilic and β1-selective (cardioselective) β-blocker that did not cross into the CNS and did not produce adverse effects due to β2 receptors blockade, was approved for clinical use in 1976 and changed the dynamics of treatment of cardiovascular diseases once again. The breadth of β-blockers use since their introduction has expanded from the treatment of angina pectoris to include hypertension, cardiac arrhythmias, myocardial infarction, prophylaxis of migraine headaches, essential tremors, situational anxiety, cardiac manifestations of thyrotoxicosis, etc., and even heart failure for which their use was contraindicated for almost a quarter of a century. Now β-blockers, especially bisoprolol, carvedilol and metoprolol, are considered beneficial in heart failure cases and are credited to reduce morbidity and mortality of heart failure patients (Packer et al., 1996; Hunt et al., 2005).

However, the observation that β-blockers produced an anticancer effect and improved survival of cancer patients opened a new front of investigations of the role of β-blockers in various cancers. In fact it was the serendipitous discovery of anti-angiogenic activity of propranolol that was observed in cases of severe infantile capillary hemangiomas that regressed completely with the use of propranolol (Leaute-Labreze et al., 2008), that served the forerunner for observational and retrospective case-control studies of cancer patients who used β-blockers. Meanwhile, Fitzgerald (2009) put forth the hypothesis that norepinephrine was an etiological factor for a number of cancers and he presented his arguments in a following publication (Fitzgerald, 2010), urging for retrospective studies to find a link between cancer and norepinephrine. Although, β-blockers are being regularly used in the treatment of hemangiomas, we have left them out from the purview of this review.

This mini review covers what has so far been reported in the scientific literature about the influence of β-blockers against different forms of cancers and how a limited number of experimental studies reconcile with clinical observations.

*[1]Department of Pharmacology, College of Pharmacy, [2]Department of Physiology, College of Medicine; Qassim University, Buraidah, Saudi Arabia *For correspondence: shahidakbar@sbcglobal.net*

Putative Role of Catecholamines in Cancer (*in vitro* and *in vivo* studies)

It has been observed that all cancers on which β-blockers have shown a suppressive effect express β-ARs (Perez-Sayans et al., 2010). β-ARs signaling pathways play a significant role in cell proliferation, differentiation and cell migration (Herlenius and Lagercrantz, 2001; Kim et al., 2008). β-ARs stimulation by norepinephrine (noradrenaline)(NE) and epinephrine (adrenaline), known as stress hormones, acting through cAMP/PKA signaling pathways, is pro-angiogenic and pro-metastatic in ovarian tumors (Masur et al., 2001; Drell et al., 2003); this has been suggested as the link between stress and cancer (Cole and Sood, 2012). Both the synthesis and release of norepinephrine and epinephrine are regulated by nicotinic acetylcholine receptors (α7nAChRs)(Schuller, 2009). Interestingly, the inhibitory neurotransmitter γ-aminobutyric acid (GABA) also serves as an inhibitor of β-ARs stimulation-mediated signaling cascade by blocking activation of adenylyl cyclase via inhibitory G-protein-coupled $GABA_B$ receptors (Wojcik and Neff, 1984; Schuller et al., 2008). Epinephrine increases proliferation of lung adenocarcinoma cells in vitro, which is mediated by increase in intracellular cAMP (Park et al., 1995). Several other in vitro and in vivo studies have shown that catecholamines promote tumor cell growth and metastases by promoting production of vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMP2 and 9) and interleukins (IL-6, IL-8) which are inhibited by β-blockers (Sood et al., 2006; Yang et al., 2006; Yang et al., 2009; Quoc Lu'o'ng and Nguyen, 2012). Epinephrine also stimulates proliferation of human colon adenocarcinoma HT-29 cells with enhanced expression of COX-2 and VEGF. This proliferative effect is blocked by β1-selective blocker atenolol and β2-selective blocker ICI 118,551 (Wong et al., 2011). Administration of isoproterenol (a nonselective β-ARs agonist) increased metastases 22-fold in a mouse model of breast cancer (Sloan et al., 2010). Human prostate cancer cells show an increase in cAMP level in response to β-ARs agonists in a descending order from terbutaline to isoproterenol to epinephrine to norepinephrine. The nonselective β-blockers, propranolol and CGP 12177 block this activity 80-96%, which suggests a predominant role of β2-adrenoceptors in these cell types (Nagmani et al., 2003). Norepinephrine significantly increases β2-ARs expression, while propranolol inhibits the NE-induced over-expression of β2-ARs (Shang et al., 2009). NE-augmented metastases of human prostate carcinoma cells in a mouse model of prostate cancer were also inhibited by propranolol (Palm et al., 2006). Oral squamous cell carcinoma expresses β2-ARs that are significantly correlated with cervical lymph nodes metastasis, tumor size and clinical stage of the tumors. Organs rich in catecholamine contents, such as adrenal medulla and brain, also serve as chemoattractants to cancer cells and serve as sites for metastasis (Schouten, 2002).

Pasquier et al. (2011) reported dose-dependent anti-proliferative and anti-angiogenic effects of propranolol in several human cancer and normal cell lines in Metrogel assays. Propranolol, though, exhibited synergistic, additive or antagonistic effects on cell proliferation in different cell lines, when used in combination with 5-fluorouracil or paclitaxel. It also produced a very significant and sustained antitumor effects and increased survival of experimental breast cancer-bearing animals with these combinations. A subset of breast adenocarcinomas expresses β-ARs that regulate a downstream arachidonic acid-mediated signal transduction pathway (Plummer et al., 2004). However, Perez Pinero et al., (2012) recently reported a contradictory finding that activation of β-ARs by nonselective β-ARs agonist isoprenaline (isoproterenol) and β2-selective agonist salbutamol (albuterol) decreases proliferation of breast cancer cells, and the inhibitory effect of these agonists was antagonized by propranolol.

Nicotine stimulates gastric cancer cells growth through activation of β-ARs and downstream up-regulation of COX-2 (Shin et al., 2007). Similar increase in proliferation and up-regulation of β-ARs and COX-2 expression was observed by chloroform extract of cigarette smoke in human esophageal squamous carcinoma EC 109 cells (Li et al., 2009) and by epinephrine of HKESC-1 cells (Liu et al., 2008). Both the stimulatory action on cells proliferation and COX-2 expression are abolished by β1-selective and β2-selective β-ARs antagonists. 4-(methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is a highly carcinogenic nitrosamine which is a tobacco component formed after nitrosation of nicotine. NNK is an agonist for both β1-ARs and nAChRs (Schuller and Orloff, 1998) and thus activates cAMP-dependent pathway and additionally stimulates the release of norepinephrine/epinephrine by binding to alpha7nAChRs (Al-Wadei et al., 2009). NNK stimulates the proliferation of human lung adenocarcinoma cells and thus, provides the link between smoking and smoking-associated cancers (Schuller, 2010). NNK-induced pancreatitis is a risk factor for pancreatic ductal adenocarcinoma (PDAC), which is one of the deadliest cancers and is usually unresponsive to existing therapy. Pancreatic cancer cells express both β1- and β2-ARs but predominantly β2-ARs and overexpress COX-2 and 5-lipoxygenase enzymes (Weddle et al., 2001). Stimulation of pancreatic cancer cells by NE results in cell proliferation and migration and increase in the expression of MMP-2, MMP-9 and VEGF, which are completely abolished by propranolol (Guo et al., 2009; Huang et al., 2012). The β-ARs stimulation effect in pancreatic cancer cells is reported to be mediated through cAMP, protein kinase A (PKA) and mitogen-activated protein kinase (MAPK). ICI 118,551, a β2-ARs antagonist, significantly suppresses cell invasion and proliferation by inhibiting cAMP/PKA and Ras, and significantly alters VEGF, COX-2, MMP-2 and MMP-9 expression. Propranolol significantly suppresses cell invasion and proliferation in comparison to metoprolol (Zhang et al., 2010). ICI 118,551 also significantly induces pancreatic carcinoma cell GI/S phase arrest and causes cells death but not the β1-selective metoprolol (Zhang et al., 20011), and potentiates the anti-proliferative and apoptotic effects of gemcitabine on human pancreatic cancer cells (Shan et al., 2011). β2-Selective antagonist, butoxamine causes significantly more apoptosis of pancreatic cancer cells than propranolol

and the least is caused by metoprolol (Zhang et al., 2009). Propranolol also inhibits proliferation of human gastric adenocarcinoma cell lines (SGC-7901 and BGC-823), induces apoptosis in both cell lines, decreases the level of nuclear factor kB and down-regulates VEGF, COX-2, MMP-2 and MMP-9 expression (Liao et al., 2010a,b). Schuller and Al-Wadei (2012) suggested role of β-ARs stimulation in the growth of pulmonary adenocarcinomas and pancreatic ductal adenocarcinomas, as both cell types share the ability to release cAMP-dependent bicarbonate. Involvement of β3-adrenoceptors in human colon cancers has also been suggested as β3-ARs mRNA expression is twice as much in cancer tissue as in the normal tissue (Perrone et al., 2008).

Emotional and psychological stresses evoke excessive release of epinephrine/norepinephrine and intrusive thoughts, such as after the diagnosis of cancer, which can exacerbate and prolong adrenergic sympathetic system activation. Users of β-blockers in newly diagnosed breast and colorectal cancer patients are reported to have 32% fewer intrusive thoughts (Lindgren et al., 2013). Likewise, excessive catecholamines are released during perioperative period of the surgery of primary tumor, due to anxiety and fear of the surgery, the disease and death that can facilitate the progression of preexisting micro-metastases and may initiate the new ones (Neeman et al., 2012), and are suspected of enhancing the chances of postsurgical cancer recurrence (Glasner et al., 2010). Observational studies also suggest that surgery *per se* can increase the risk of cancer in patients without a history of clinical cancer and this is attributed to catecholamine surge due to the stress of surgery (Goldstein and Mascitelli, 2011). Norepinephrine levels of ovarian tumors are high with the advanced stage and higher grade of the tumor, and even higher in patients who lack social support, a significant factor for depressed mood, anxiety and stress (Lutgendorf et al., 2011). Even in animals subjected to stress, the tumor growth is augmented which is completely prevented by pretreatment with propranolol (Hasegawa and Saiki, 2002). Thus, a positive correlation between the level of stress hormones and growth of various cancers is overwhelmingly suggestive.

Clinical Observations and Retrospective Studies

In vitro studies cannot always be extrapolated to expected results in humans, and human studies are essential to verify and establish the veracity of a phenomenon or an effect. However, observational studies reported so far about the beneficial effects of β-blockers are inconclusive. Most of these retrospective case-control studies have been published in the past few years. Nevertheless, there is a growing body of clinical evidence, based on these studies that use of β-blockers helps in reducing the tumor progression, formation of metastases, recurrence and cancer mortality, and increases chances of disease-free survival from various types of cancers. Over 90% of all cancer deaths are due to metastases and not due to the primary cancers, and cancer cells migration from the original site is a prerequisite for metastases (Palm et al., 2006). Norepinephrine increases this locomotion of SW 480 colon carcinoma cells via stimulation of β2-ARs, as the increase is inhibited by nonselective β-blocker propranolol and not by the β1-blocker atenolol (Masur et al., 2001). However, in pancreatic cancer cells, NE reduces the migratory activity, which is hypothesized to be due to an increase in cAMP (Stock et al., 2013).

Several observational studies have suggested a preventive and protective role of β-blockers for certain types of cancer, such as breast (Powe et al., 2010; Ganz et al., 2011), prostate (Perron et al., 2004; Algazi et al., 2006), ovarian (Diaz et al., 2012), melanoma (De Giorgi et al., 2011, 2012) and non-small-cell lung carcinoma (Wang et al., 2013). Even, in diabetic patients a significantly reduced overall risk of cancer has been reported with β-blocker use (Monami et al., 2013). However, in a retrospective study using UK's primary care database, Shah et al. (2011) compared the survival rate of newly diagnosed cancer (solid tumors) patients who were regularly treated with β-blockers before the diagnosis with those who received other antihypertensive drugs, and reported a poor effect of β-blockers on survival. Among the β-blocker users, only 13% of patients were prescribed propranolol and the rest used either atenolol (75%) or other β-blockers. This study was in contrast to a prospective follow up for an average 10 years of patients with cardiovascular disease by Algazi et al. (2004) who reported a reduced risk of cancer in ever-user of β-blockers patients compared to never-users.

Thirty percent of all treated breast cancer patients develop metastases and 90% of breast cancer deaths are due to these metastases (Sporn, 1996). Various authors have so far reported inconsistent observations where some studies even suggested an increase in breast cancer incidence in patients using β-blockers. Use of β-blockers for hypertension before the diagnosis of breast cancer is suggested to significantly reduce metastasis development, tumor recurrence and cancer-related mortality on years of follow up, compared to those who did not use β-blockers. In 49 British women with breast cancer who used β-blockers for hypertension treatment before the diagnosis of breast cancer, metastases, tumor recurrence and cancer-related mortality on 10-years follow-up was significantly less, compared to women who used other antihypertensive drugs or were non-hypertensive control (Powe et al., 2010). Another observational study from Northern California found β-blockers use associated with a lower risk of recurrence and breast cancer-related mortality. Combined use of ACE inhibitors with β-blockers, though, increased the overall mortality (Ganz et al., 2011). Use of β-blockers or other antihypertensive drugs was not found associated with increase in breast cancer in a study of Danish women (Fryzek et al., 2006). However, another prospective observational study in 18,733 Danish women diagnosed with non-metastatic breast cancer reported no reduced risk of cancer recurrence in β-blocker users but a slight increase in recurrence associated with metoprolol and sotalol use (Sorensen et al., 2013). Contrarily, protection by β-blockers was reported by Melhem-Bertrandt et al., (2011) who reviewed records of women diagnosed with triple-negative breast cancer (TNBC) and who were using β-blockers before

they were subjected to chemotherapy. Patients using β-blockers had significantly higher relapse-free survival (but not in estrogen receptor positive cancers) and significant increase in overall survival in TNBC patients in a median 55-months follow-up than those who did not use β-blockers. Similarly, β-blockers use significantly decreased tumor recurrence, metastasis and cancer-related mortality in TNBC-diagnosed postmenopausal Italian women (Botteri et al., 2013). One major issue with these studies was that many of them did not identify the nature of β-blockers used (selective or non-selective), because Irish women who used propranolol before the diagnosis of breast cancer had a significantly less risk of local tumor invasion or nodal or metastatic involvement at diagnoses than those who did not use β-blockers or used β1-receptor selective atenolol (Barron et al., 2011).

Another aspect of β-blockers use in breast cancer patients is to reduce chemotherapy-induced heart failure. In the first 3 months of post-trastuzumab therapy period, use of β-blockers was associated with significantly increased hypertension and reduction in left ventricular ejection fraction (LVEF) compared to those who did not use β-blockers, and the deleterious effect more than doubled if β-blockers were combined with ACE inhibitors or ARBs. However, the LVEF recovered during the 3-12 months post-trastuzumab therapy (Oliva et al., 2012). Contrarily, Seicean et al. (2013) reported a protective effect of β-blockers on anthracycline and trastuzumab therapy-induced heart failure in breast cancer patients.

Median progression-free survival of β-blocker users of epithelial ovarian cancer was significantly higher than nonusers of β-blockers (27 months *vs* 17 months), with overall disease-specific survival to be 56 months and 48 months, respectively (Diaz et al., 2012). However, no significant decrease in mortality by β-blockers was observed in ovarian cancer patients in a Danish study (Johannesdottir et al., 2013). Also, patients with recurrent ovarian cancer and undergoing chemotherapy had no significant difference in median progression-free survival or overall survival among β-blockers users and nonusers (Heitz et al., 2013). In a Canadian retrospective study, use of β-blockers for an extended period of time (>1 year) reduced risk of prostate cancer, whereas calcium channel blockers and ACE inhibitors did not influence the prostate cancer risk (Perron et al., 2004). β-blocker use also reduced prostate cancer (PCa)-specific mortality in patients who had androgen-deprivation therapy, but otherwise it did not affect PCa-specific mortality (Grytli et al., 2013). In patients with high-risk or metastatic disease at the time of diagnosis, β-blockers use reduced PCa-specific mortality in Norwegian patients, independent of the use of aspirin or statins (Grytli et al., 2014). A British data-based study, though, reported a lowered risk of developing prostate cancer in patients who used captopril; other ACE inhibitors did not share this property (Ronquist et al., 2004). A 10% reduction in prostate cancer risk associated with the use of β-blockers and ACE inhibitors was reported by Rodriguez et al. (2009). A similar protective effect with slower tumor progression and decreased mortality was observed in advanced colon cancer patients who used ACEIs/ARBs with β-blockers (Engineer et al., 2013). However, other observational studies did not find any protective effect of β-blockers in colorectal cancer patients (Jansen et al., 2012; Hicks et al., 2013) except in stage IV colorectal cancer patients where β-blocker users had a significantly longer overall and cancer-related survival than non-users (Jensen et al., 2014).

β-blockers use by patients suffering from non-small-cell lung carcinoma (NSCLC) and undergoing radiotherapy had a significantly improved distant metastasis-free survival, disease-free survival and overall survival compared to nonusers of β-blockers (Wang et al., 2013). Even in a short follow-up (17.8 months) of only 35 patients of NSCLC with metastases, who used β-blockers during chemotherapy, mainly metoprolol (80%), had a significantly better survival than nonusers (19.25±2.87 months *vs* 13.20±2.37 months)(Aydiner et al., 2013). A univariate analysis found use of nonselective and selective β-blockers during the perioperative period to reduce recurrence-free and overall survival of patients with NSCLC, but in a multivariate analysis, this was not found to be true (Cata et al., 2014). However, propranolol use decreased the risk for hepatocellular carcinoma (HCC) by more than 50% in 3-years follow-up and by more than 80% after 5-years follow-up in patients who suffered from compensated viral C (HCV) cirrhosis and were prescribed propranolol for esophageal varices (Nkontchou et al., 2012).

Use of β-blockers, but not other antihypertensive drugs, significantly improved disease-free and overall survival of patients with malignant melanoma (De Giorgi et al., 2012). One year or more use of β-blockers decreased progression of thick malignant melanoma by 90% and none of the 30 users of β-blockers died over a median 2.5-years follow-up, whereas 24 out of 91 untreated patients died during the same period, there was a 36% risk reduction for each year of β-blocker use (De Giorgi et al., 2011). An extended follow-up of 4-years of more melanoma patients (79 patients) using β-blockers, usually for hypertension, confirmed that each year of β-blockers use reduced the risk of death by 38% compared to nonusers. Similar protection was not afforded by the use of other antihypertensive drugs (De Giorgi et al., 2013). In a Danish study with a median follow-up of 4.9-years and a median β-blocker use within 90 days of melanoma diagnosis, both melanoma deaths and all-cause mortality were decreased (Lemeshow et al., 2011). However, a Dutch study found no significant effect of β-blockers use, either duration or dosage, on survival of melanoma patients who started using β-blockers after melanoma diagnosis (Livingstone et al., 2013).

Suggested Mechanism(s) of Action of Anticancer Effects

Multiple cellular processes are suggested to be involved in the initiation, progression and metastases of cancers through β-receptors stimulation. β-ARs stimulation leads to increased cAMP formation and activation of PKA/CREB, which cause pro-oncogenic effects by inhibition of apoptosis, angiogenesis, invasion and metastasis (Al-Wadei et al., 2012). Administration of

epinephrine or metaproterenol in rats suppresses natural killer (NK) cells activity (Shakhar and Ben-Eliyahu, 1998; Ben-Eliyahu et al., 2000). Excessive perioperative release of catecholamines and prostaglandins causes post-surgery immune suppression by decreasing (NK) cells cytotoxicity (Benish et al., 2008). The trauma of surgery suppresses cell-mediated immunity proportional to the extent of surgery and damage to tissue (Shakhar and Ben-Eliyahu, 2003; Goldfarb and Ben-Eliyahu, 2006). This perioperative stress and the resulting increase in stress hormones, epinephrine and norepinephrine, has not yet been recognized clinically to have any bearing on post-surgical fate of the tumor. However, various animal studies have shown that stress responses affect the recurrence and survival. Surgery reduces the NK cell cytotoxicity, circulating lymphocyte concentrations and increases corticosterone levels and COX-2 expression, which are inhibited by pretreatment with propranolol and etodolac, a COX-2 inhibitor (Glasner et al., 2010). Mice implanted with Lewis lung carcinoma and subjected to rotational stress show increased lung metastasis, which are prevented by pretreatment with reserpine but not by α-adrenoceptor blocker phenoxybenzamine or β-blocker propranolol (Perissin et al., 1996). Surgical stress also significantly increased the ovarian tumor weight, microvessels density and expression of vascular endothelial growth factor (VEGF) in mice after intraperitoneal tumor cell injection; propranolol treatment blocked these effects (Lee et al., 2009). Tumor necrosis factor-alpha (TNFα) is involved in the generation of cytotoxic T lymphocyte (CTL) activity and inhibition of CTL generation by norepinephrine (NE) involves inhibition of TNFα production; propranolol inhibits both NE-induced decrease in TNFα and inhibition of CTL generation (Kalinichenko et al., 1999).

Unlike normal cells, metastatic cancer cells do not undergo programmed cell death (apoptosis) called anoikis after detaching from their surrounding extracellular matrix. In *in vitro* studies, three β-blockers (carvedilol, nebivolol and propranolol) potentiated the anti-angiogenic, anti-mitochondrial, anti-mitotic and pro-apoptotic effects of vincristine, and significantly increased tumor regression in a TH-MYCN mouse model of neuroblastoma, resulting in a four-fold increase in median survival when treated in combination with vincristine (Pasquier et al., 2013). Overexpression of arachidonic acid-metabolizing enzymes, COX-2 and lipoxygenase, has been reported in breast, lung, pancreas and colon cancers, which is believed to be under β-adrenergic control (Cakir et al., 2002). Almost three-fourths of patients with primary breast cancer and more than 90% with positive lymph nodes metastases overexpress COX-2, compared to 0% in those with fibroadenoma or benign breast disease (Jana et al., 2012). However, various clinical observations pointed to the involvement of β2-receptors than β1-recptors, because users of β1-selective blockers did not show the protective effect of β-blockers (Barron et al., 2011). Pulmonary adenocarcinoma, the most common histologic type of lung cancer, can be reproduced in hamsters by nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a tobacco component. NNK-induced pulmonary adenocarcinomas are multiplied if they are chronically exposed to epinephrine, through increased cAMP, and significantly inhibited by propranolol injection prior to each NNK injection (Schuller et al., 2000).

Conclusions

The jury is still out to firmly establish the nature of β-blockers, selective or nonselective, or any specific ones and the cancers they could be beneficial in. Some investigators have even disputed the reported beneficial effects of β-blockers on grounds that the benefits observed in these patients are due to the simultaneous use of aspirin by cancer patients and not by the use of β-blockers *per se* (Holmes and Chen, 2012; Holmes et al., 2013). However, β-blockers use was shown to reduce prostate cancer-specific mortality in Norwegian patients, independent of the use of aspirin or statins (Grytli et al., 2014). The debate is likely to continue for some time until more corroborative retrospective studies are reported, as prospective, double-blind studies are not possible under this scenario when β-blockers use before the diagnosis of cancer is reported to be protective rather than their use after the diagnosis. Therefore, reliance on retrospective case-control studies is the only option available at this time. Also, presence of comorbidities other than hypertension should be taken into account when analyzing the effects of β-blockers on various forms of cancers. We are of the opinion, though, that these agents could surprise the scientific and medical community once again and protection from cancer might be added to their repertoire of approved clinical use.

References

Algazi M, Plu-Bureau G, Flahault A, Dondon MG, Lê MG (2004). Could treatments with beta- blockers be associated with a reduction in cancer risk? *Rev Epidemiol Sante Publique*, **52**, 53-65 (in French).

Algazi M, Plu-Bureau G, Flahault A, Dondon MG, Lê MG (2006). Is beta-blocker treatment associated with a decrease in the risk of cancer. *Lett Drug Des Discov*, **3**, 653-61.

Al-Wadei HA, Al-Wadei MH, Schuller HM (2009). Prevention of pancreatic cancer by the beta-blocker propranolol. *Anticancer Drugs*, **20**, 477-82.

Aydiner A, Ciftci R, Karabulut S, Kilic L (2013). Does beta-blocker therapy improve the survival of patients with metastatic non-small cell lung cancer? *Asian Pac J Cancer Prev*, **14**, 6109-14.

Barron TI, Connolly RM, Sharp L, Bennett K, Visvanathan K (2011). Beta-blocker and breast cancer mortality: a population- based study. *J Clin Oncol*, **29**, 2635-44.

Ben-Eliyahu S, Shakhar G, Page GG, Stefanski V, Shakhar K (2000). Suppression of NK cell activity and of resistance to metastasis by stress: a role for adrenal catecholamines and beta-adrenoceptors. *Neuroimmunomodulation*, **8**, 154-64.

Benish M, Bartal I, Goldfarb Y, et al (2008). Perioperative use of beta-blocker and COX-2 inhibitors may improve immune competence and reduce the risk of tumor metastasis. *Ann Surg Oncol*, **15**, 2042-52.

Botteri E, Munzone E, Rotmensz N, et al (2013): Therapeutic effect of β-blockers in triple-negative breast cancer postmenopausal women. *Breast Cancer Res Treat*, **140**, 567-75.

Cakir Y, Plummer HK 3rd, Tithof PK, Schuller HM (2002). Beta-adrenergic and arachidonic acid-mediated growth regulation

of human breast cancer cell lines. *Int J Oncol*, **21**, 153-7.
Cata JP, Villarreal J, Keerty D, et al (2014). Perioperative beta-blocker use and survival in lung cancer patients. *J Clin Anesth*, **26**, 106-17.
Cole SW, Sood AK (2012). Molecular pathways: beta adrenergic signaling in cancer. *Clin Cancer Res*, **18**, 1201-6.
De Giorgi V, Grazzini M, Gandini S, et al (2011). Treatment with β-blockers and reduced disease progression in patients with thick melanoma. *Arch Intern Med*, **171**, 779-81.
De Giorgi V, Gandini S, Grazzini M, et al (2012). β-blockers: a new and emerging treatment for melanoma. *Rec Prog Med*, **103**, 11-6.
Diaz ES, Karlan BY, Li AJ (2012). Impact of beta blockers on epithelial ovarian cancer survival. *Gynecol Oncol*, **127**, 375-8.
Drell TL, Joseph J, Lang K, et al (2003). Effects of neurotransmitters on the chemokinesis and chemotaxis of MDA-MB-468 human breast carcinoma cells. *Breast Cancer Res Treat*, **80**, 63-70.
Entschladen F, Drell TL, Lang K, Joseph J, Zaenker KS (2004). Tumour-cell migration, invasion and metastasis: navigation by neurotransmitters. *Lancet Oncol*, **5**, 254-8.
Fitzgerald PJ (2009). Is norepinephrine an etiological factor in some types of cancer? *Int J Cancer*, **124**, 257-63.
Fitzgerald PJ (2010). Testing whether drugs that weaken norepinephrine signaling prevent or treat various types of cancer. *Clin Epidemiol*, **2**, 1-3.
Fryzek JP, Poulsen AH, Lipworth L, et al (2006). A cohort study of antihypertensive medication use and breast cancer among Danish women. *Breast Cancer Res Treat*, **97**, 231-6.
Ganz PA, Habel LA, Weltzien EK, Caan BJ, Cole SW (2011). Examining the influence of beta blockers and ACE inhibitors on the risk for breast cancer recurrence: results from the LACE cohort. *Breast Cancer Res Treat*, **129**, 549-56.
Glasner A, Avraham R, Rosenne E, et al (2010). Improving survival rates in two models of spontaneous postoperative metastasis in mice by combined administration of a beta-adrenergic antagonist and a cyclooxygenase-2 inhibitor. *J Immunol*, **184**, 2449-57.
Goldfarb Y, Ben-Eliyahu S (2006). Surgery as a risk factor for breast cancer recurrence and metastasis: mediating mechanisms and clinical prophylactic approaches. *Breast Disease*, **26**, 99-114.
Goldstein MR, Mascitelli L (2011). Surgery and cancer promotion: are we trading beauty for cancer? *QJM*, **104**, 811-5.
Grytli HH, Fagerland MW, Fosså SD, Taskén KA (2014). Association between use of β-blockers and prostate cancer-specific survival: A cohort study of 3561 prostate cancer patients with high-risk or metastatic disease. *Eur Urol*, **65**, 635-41.
Grytli HH, Fagerland MW, Fossa SD, Taskén KA, Haheim LL (2013). Use of β-blockers is associated with prostate cancer-specific survival in prostate cancer patients on androgen deprivation therapy. *Prostate*, **73**, 250-60.
Guo K, Ma Q, Wang L, et al (2009). Norepinephrine-induced invasion by pancreatic cancer cells is inhibited by propranolol. *Oncol Rep*, **22**, 825-30.
Hasegawa H, Saiki I (2002). Psychosocial stress augments tumor development through beta-adrenergic activation in mice. *Jpn J Cancer Res*, **93**, 729-35.
Heitz F, du Bois A, Harter P, et al (2013). AGO study group; NCIC-CTG study group; EORTC-GCG study group . Impact of beta blocker medication in patients with platinum sensitive recurrent ovarian cancer-a combined analysis of 2 prospective multicenter trials by the AGO Study Group, NCIC-CTG and EORTC-GCG. *Gynecol Oncol*, **129**, 463-6.
Herlenius E, Lagercrantz H (2001). Neurotransmitters and neuromodulators during early human development. *Early Hum Dev*, **65**, 21-37.
Hicks BM, Murray LJ, Powe DG, Hughes CM, Cardwell CR (2013). β-Blocker usage and colorectal cancer mortality: a nested case-control study in the UK Clinical Practice Research Datalink cohort. *Ann Oncol*, **24**, 3100-6.
Holmes MD, Chen WY (2012). Hiding in plain view: the potential for commonly used drugs to reduce breast cancer mortality. *Breast Cancer Res*, **14**, 216.
Holmes MD, Hankinson SE, Feskanich D, Chen WY (2013). Beta blockers and angiotensin-converting enzyme inhibitors' purported benefit on breast cancer survival may be explained by aspirin use. *Breast Cancer Res Treat*, **139**, 507-13.
Huang XY, Wang HC, Yuan Z, Huang J, Zheng Q (2012). Norepinephrine stimulates pancreatic cancer cell proliferation, migration and invasion via β-adrenergic receptor-dependent activation of P38/MAPK pathway. *Hepatogastroenterology*, **59**, 889-93.
Hunt SA, Abraham WT, Chin MH, et al (2005). ACC/AHA 2005 Guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to update the 2001 guidelines for the evaluation and management of heart failure). *Circulation*, **112**, 154-235.
Jana D1, Sarkar DK, Maji A, et al (2012): Can cyclo-oxygenase-2 be a useful prognostic and risk stratification marker in breast cancer? *J Indian Med Assoc*, **110**, 429-33.
Jansen L, Below J, Chang-Claude J, Brenner H, Hoffmeister M (2012). Beta blocker use and colorectal cancer risk: population-based case-control study. *Cancer*, **118**, 3911-9.
Jansen L, Hoffmeister M, Arndt V, Chang-Claude J, Brenner H (2014). Stage-specific associations between beta blocker use and prognosis after colorectal cancer. *Cancer*, **120**, 1178-86
Johannesdottir SA, Schmidt M, Phillips G, et al (2013). Use of ß-blockers and mortality following ovarian cancer diagnosis: a population-based cohort study. *BMC Cancer*, **13**, 85.
Kalinichenko VV, Mokyr MB, Graf LH Jr, Cohen RL, Chambers DA (1999). Norepinephrine-mediated inhibition of antitumor cytotoxic T lymphocyte generation involves a beta-adrenergic receptor mechanism and decreased TNF-alpha gene expression. *J Immunol*, **163**, 2492-9.
Kim MO, Na SI, Lee MY, Heo JS, Han HJ (2008). Epinephrine increases DNA synthesis via ERK1/2s through cAMP, Ca(2+)/PKC, and PI3K/Akt signaling pathways in mouse embryonic stem cells. *J Cell Biochem*, **104**, 1407-20.
Leaute-Labreze C, Dumas de la Roque E, Hubiche T, et al (2008) Propranolol for severe hemangiomas of infancy. *N Engl J Med*, **358**, 2649-51.
Lee JW, Shahzad MM, Lin YG, et al (2009). Surgical stress promotes tumor growth in ovarian carcinoma. *Clin Cancer Res*, **15**, 2695-702.
Lemeshow S, Sorensen HT, Phillips G, et al (2011). β-Blockers and survival among Danish patients with malignant melanoma: a population-based cohort study. *Cancer Epidemiol Biomarkers Prev*, **20**, 2273-9.
Li CI, Malone KE, Weiss NS, et al (2003). Relation between use of antihypertensive medications and risk of breast carcinoma among women ages 65-79 years. *Cancer*, **98**, 1504-13.
Li P, Wu WK, Wong HP, et al (2009). Chloroform extract of cigarette smoke induces proliferation of human esophageal squamous-cell carcinoma cells: modulation by beta-adrenoceptors. *Drug Chem Toxicol*, **32**, 175-81.
Liao X, Che X, Zhao W, et al (2010a). The β-adrenoceptor antagonist, propranolol, induces human gastric cancer cell apoptosis and cell cycle arrest via inhibiting nuclear factor

κB signaling. *Oncol Rep*, **24**, 1669-76.
Liao X, Che X, Zhao W, et al (2010b). Effects of propranolol in combination with radiation on apoptosis and survival of gastric cancer cells in vitro. *Radiat Oncol*, **5**, 98.
Lindgren ME, Fagundes CP, Alfano CM, et al (2013). Beta-blockers may reduce intrusive thoughts in newly diagnosed cancer patients. *Psychooncology*, **22**, 1889-94.
Liu X, Wu WK, Yu L, et al (2008). Epinephrine stimulates esophageal squamous-cell carcinoma cell proliferation via beta-adrenoceptor-dependent transactivation of extracellular signal-regulated kinase/cyclooxygenase-2 pathway. *J Cell Biochem*, **105**, 53-60.
Livingstone E, Hollestein LM, van Herk-Sukel MP, et al (2013). β-Blocker use and all-cause mortality of melanoma patients: results from a population-based Dutch cohort study. *Eur J Cancer*, **49**, 3863-71.
Lutgendorf SK, Cole S, Costanzo E, et al (2003). Stress-related mediators stimulate vascular endothelial growth factor secretion by two ovarian cancer cell lines. *Clin Cancer Res*, **9**, 4514-21.
Lutgendorf SK, DeGeest K, Dahmoush L, et al (2011). Social isolation is associated with elevated tumor norepinephrine in ovarian carcinoma patients. *Brain Behav Immun*, **25**, 250-5.
Masur K, Niggemann B, Zanker KS, Entschladen F (2001). Norepinephrine-induced migration of SW 480 colon carcinoma cells is inhibited by beta-blockers. *Cancer Res*, **61**, 2866-9.
Melhem-Bertrandt A, Chavez-Macgregor M, Lei X, et al (2011). Beta-blocker use is associated with improved relapse-free survival in patients with triple-negative breast cancer. *J Clin Oncol*, **29**, 2645-52.
Monami M, Filippi L, Ungar A, et al (2013). Further data on beta-blockers and cancer risk: observational study and meta-analysis of randomized clinical trials. *Curr Med Res Opin*, **29**, 369-78.
Nagmani R, Pasco DS, Salas RD, Feller DR (2003). Evaluation of beta-adrenergic receptor subtypes in the human prostate cancer cell line-LNCaP. *Biochem Pharmacol*, **65**, 1489-94.
Neeman E, Zmora O, Ben-Eliyahu S (2012). A new approach to reducing postsurgical cancer recurrence: perioperative targeting of catecholamines and prostaglandins. *Clin Cancer Res*, **18**, 4895-902.
Nkontchou G, Aout M, Mahmoudi A, et al (2012). Effect of long-term propranolol treatment on hepatocellular carcinoma incidence in patients with HCV-associated cirrhosis. *Cancer Prev Res*, **5**, 1007-14.
Oliva S, Cioffi G, Frattini S, et al.; Italian Cardio-Oncological Network (2012). Administration of angiotensin-converting enzyme inhibitors and β-blockers during adjuvant trastuzumab chemotherapy for nonmetastatic breast cancer: marker of risk or cardioprotection in the real world? *Oncologist*, **17**, 917-24.
Packer M, Bristow MR, Cohn JN, et al; US Carvedilol Heart Failure Study Group (1996). The effect of carvedilol on morbidity and mortality in patients with chronic heart failure, *N Engl J Med*, **334**, 1349-55.
Palm D, Lang K, Niggemann B, et al (2006). The norepinephrine-driven metastasis development of PC-3 human prostate cells in BALB/c nude mice is inhibited by β-blockers. *Int J Cancer*, **118**, 2744-9.
Park PG, Merryman J, Orloff M, Schuller HM (1995). Beta adrenergic mitogenic signal transduction in peripheral lung adenocarcinoma: Implications for individuals with preexisting chronic lung disease. *Cancer Res*, **55**, 3504-8.
Pasquier E, Street J, Pouchy C, et al (2013). β-blockers increase response to chemotherapy via direct antitumour and anti-angiogenic mechanisms in neuroblastoma. *Br J Cancer*, **108**, 2485-94.
Pérez Piñero C, Bruzzone A, Sarappa MG, Castillo LF, Lüthy IA (2012). Involvement of α2- and β2-adrenoceptors on breast cancer cell proliferation and tumour growth regulation. *Br J Pharmacol*, **166**, 721-36.
Perez-Sayans M, Somoza-Martin JM, Barros-Angueira F, et al (2010). Beta-adrenergic receptors in cancer: therapeutic implications. *Oncol Res*, **19**, 45-54.
Perron L, Bairati I, Harel F, Meyer F (2004). Antihypertensive drug use and the risk of prostate cancer (Canada). *Cancer Causes Control*, **15**, 535-41.
Perrone MG, Notarnicola M, Caruso MG, Tutino V, Scilimati A (2008). Upregulation of beta3-adrenergic receptor mRNA in human colon cancer: a preliminary study. *Oncology*, **75**, 224-9.
Plummer HK 3rd, Yu Q, Cakir Y, Schuller HM (2004). Expression of inwardly rectifying potassium channels (GIRKs) and beta-adrenergic regulation of breast cancer cell lines. *BMC Cancer*, **4**, 93.
Powe DG, Voss MJ, Zanker KS, et al (2010). Beta-blocker drug therapy reduces secondary cancer formation in breast cancer and improves cancer specific survival. *Oncotarget*, **1**, 628-38.
Quốc Lu'o'ng KV, Nguyen LT (2012). The roles of beta-adrenergic receptors in tumorigenesis and the possible use of beta-adrenergic blockers for cancer treatment: possible genetic and cell-signaling mechanisms. *Cancer Manag Res*, **4**, 431-45.
Rodriguez C, Jacobs EJ, Deka A, et al (2009). Use of blood-pressure-lowering medication and risk of prostate cancer in the Cancer Prevention Study II Nutrition Cohort. *Cancer Causes Control*, **20**, 671-9.
Ronquist G, Rodriguez LA, Ruigomez A, et al (2004). Association between captopril, other antihyper-tensive drugs and risk of prostate cancer. *Prostate*, **58**, 50-6.
Schouten LJ, Rutten J, Huveneers HAM, Twijnstra A (2002). Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney and lung and melanoma. *Cancer*, **94**, 2698-705.
Schuller HM (2009). Is cancer triggered by altered signaling of nicotinic acetylcholine receptors? *Nat Rev Cancer*, **9**, 195-205.
Schuller HM (2010). Beta-adrenergic signaling, a novel target for cancer therapy? *Oncotarget*, **1**, 466-9.
Schuller HM, Al-Wadei HA (2012). Beta-adrenergic signaling in the development and progression of pulmonary and pancreatic adenocarcinoma. *Curr Cancer Ther Rev*, **8**, 116-27.
Schuller HM, Al-Wadei HA, Majidi M (2008). GABA B receptor is a novel drug target for pancreatic cancer. *Cancer*, **112**, 767-78.
Schuller HM, Orloff M (1998). Tobacco-specific carcinogenic nitrosamines. Ligands for nicotinic acetylcholine receptors in human lung cancer cells. *Biochem Pharmacol*, **55**, 1377-84.
Schuller HM, Porter B, Riechert A (2000). Beta-adrenergic modulation of NNK-induced lung carcinogenesis in hamsters. *J Cancer Res Clin Oncol*, **126**, 624-30.
Seicean S, Seicean A, Alan N, et al (2013). Cardioprotective effect of β-adrenoceptor blockade in patients with breast cancer undergoing chemotherapy: follow-up study of heart failure. *Circ Heart Fail*, **6**, 420-6.
Shakhar G, Ben-Eliyahu S (1998). In vivo beta-adrenergic stimulation suppresses natural killer activity and compromises resistance to tumor metastasis in rats. *J Immunol*, **160**, 3251-8.
Shakhar G, Ben-Eliyahu S (2003). Potential prophylactic measures against postoperative immune-suppression: could

they reduce recurrence rates in oncological patients? *Ann Surg Oncol*, **10**, 972-92.

Shan T, Ma Q, Zhang D, et al (2011). β2-adrenoceptor blocker synergizes with gemcitabine to inhibit the proliferation of pancreatic cancer cells via apoptosis induction. *Eur J Pharmacol*, **665**, 1-7.

Shang ZJ, Liu K, Liang de F (2009). Expression of beta2-adrenergic receptor in oral squamous cell carcinoma. *J Oral Pathol Med*, **38**, 371-6.

Shin VY, Wu WK, Chu KM, et al (2007). Functional role of beta-adrenergic receptors in the mitogenic action of nicotine on gastric cancer cells. *Toxicol Sci*, **96**, 21-9.

Sloan EK, Priceman SJ, Cox BF, et al (2010). The sympathetic nervous system induces a metastatic switch in primary breast cancer. *Cancer Res*, **70**, 7042-52.

Sood AK, Bhatty R, Kamat AA, et al (2006). Stress hormone-mediated invasion of ovarian cancer cells. *Clin Cancer Res*, **12**, 369-75.

Sørensen GV, Ganz PA, Cole SW, et al (2013). Use of β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and risk of breast cancer recurrence: a Danish nationwide prospective cohort study. *J Clin Oncol*, **31**, 2265-72.

Sporn MB (1996). The war on cancer. *Lancet*, **347**, 1377-81.

Thaker PH, Han LY, Kamat AA, et al (2006). Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. *Nat Med*, **12**, 939.

Weddle DL, Tithoff P, Williams M, Schuller HM (2001). Beta-adrenergic growth regulation of human cancer cell lines derived from pancreatic ductal carcinomas. Carcinogenesis, **22**, 473-9.

Wojcik WJ, Neff NH (1984). gamma-Aminobutyric acid B receptors are negatively coupled to adenylate cyclase in brain, and in the cerebellum these receptors may be associated with granule cells. *Mol Pharmacol*, **25**, 24-8.

Wong HP, Ho JW, Koo MW, et al (2011).Effects of adrenaline in human colon adenocarcinoma HT-29 cells. *Life Sci*, **88**, 1108-12.

Yang EV, Sood AK, Chen M, et al (2006). Norepinephrine up-regulates the expression of vascular endothelial growth factor, matrix metalloproteinase (MMP)-2, and MMP-9 in nasopharyngeal carcinoma tumor cells. *Cancer Res*, **66**, 10357-64.

Yang EV, Kim SJ, Donovan EL, et al (2009). Norepinephrine upregulates VEGF, IL-8, and IL-6 expression in human melanoma tumor cell lines: implications for stress-related enhancement of tumor progression. *Brain Behav Immun*, **23**, 267-75.

Yang EV (2010). Role for catecholamines in tumor progression: Possible use for β-blockers in the treatment of cancer. *Cancer Biol Ther*, **10**, 30-2.

Zhang D, Ma QY, Hu HT, Zhang M (2010). β2-adrenergic antagonists suppress pancreatic cancer cell invasion by inhibiting CREB, NFκB and AP-1. *Cancer Biol Ther*, **10**, 19-29.

Zhang D, Ma Q, Wang Z, et al (2011). β2-adrenoceptor blockage induces G1/S phase arrest and apoptosis in pancreatic cancer cells via Ras/Akt/NFκB pathway. *Mol Cancer*, **10**, 146.