Statins and Breast Cancer: An Overview of the Current Situation

Sohun Moonindranath, Huiling Shen*

Department of Oncology, The Affiliated People’s Hospital, Jiangsu University, Zhenjiang, China

Email: shenhuiling0826@163.com

Received 5 November 2015; accepted 23 January 2016; published 26 January 2016

Copyright © 2016 by authors and Scientific Research Publishing Inc.
This work is licensed under the Creative Commons Attribution International License (CC BY).
http://creativecommons.org/licenses/by/4.0/

Abstract

Statins [(3-hydroxy-3-methylglutaryl-coenzyme A reductase, HMG-CoA reductase, abbreviated HMGCR) inhibitors] inhibit cholesterol synthesis and are commonly used in the treatment and prevention of cardiovascular diseases. Preclinical and clinical studies have shown that the drug can be effective in several cancers including breast cancer which is the second most frequent cancer in the world and the commonest one among women. In breast cancer cell lines statins reduce proliferation, increase apoptosis, decrease invasion and sensitize them to radiation. Clinical trials in breast cancer patients have shown positive outcome in terms of decreased recurrence rate, decreased mortality and positive role as neoadjuvant agent. They may have a particular role in treatment-resistant cases like triple-negative or inflammatory breast cancer which have a poorer prognosis. There is also evidence of their potential use in metastatic bone disease from breast cancer. When statins inhibit 3-hydroxy-3-methylglutaryl CoA reductase which is the rate-limiting enzyme of the mevalonate pathway, the levels of mevalonate as well as its downstream products are decreased. Hence cancer growth is inhibited by reduced prenylation of CAAX proteins, N-Glycosylation of growth factor receptors and synthesis of membrane and steroid among others. Also statins are relatively cheap and can contribute to decrease the high cost of cancer treatment. However studies till now have not shown any association with decreased breast cancer incidence. In addition there are doubts regarding safety of statins when used over a prolonged period of time. Although statins are relatively safe with myotoxicity and hepatotoxicity being their major side effects, evidence regarding issues like drug interactions with anti-cancer drugs is lacking.

Keywords

Statins, HMG CoA Reductase Inhibitors, Breast Cancer

*Corresponding author.
1. Introduction

In 2012 there was approximately 1.67 million new breast cancer cases diagnosed which makes it the second most frequent cancer in the world after lung cancer (25% of all cancers) and the commonest cancer among women. It is the most common cancer in women irrespective of the level of development of the region, with slightly more cases in less developed (883,000 cases) than in more developed (794,000) regions. There is approximately a four-fold variation of incidence rate across the globe, with rates ranging from 27 per 100,000 in Middle Africa and Eastern Asia to 96 in Western Europe [1]. In our hospitals the management of breast cancer is multi-disciplinary, involving surgery, radiotherapy, chemotherapy, hormonal therapy and use of immunotherapeutic agents with the treatment decision depending on the stage of the cancer. Although many options are available in the management of this disease, breast cancer has a high mortality rate. Patient management is affected by many hurdles. Indeed in initially 90% of primary breast cancers and 50% of metastases the drug regimen is effective but unfortunately treatment is stopped due to drug toxicity and drug resistance by many mechanisms including interruption of the apoptotic signalling pathway [2]. In addition cancer treatment is expensive, notably immunonontherapeutic agents, so that not every patient can afford the ideal treatment regimen, especially in developing countries. Thus the need for effective, safe and cost-effective alternatives is necessary.

Statins inhibit the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR, HMGCoAR) which catalyses the conversion of 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) to mevalonic acid, the rate-limiting step in the mevalonate pathway that ultimately yields cholesterol [3]. But statins exert pleiotropic actions beyond their cholesterol lowering capacity. In coronary heart disease they stabilize the atherosclerotic plaque, reduce vascular inflammation and decrease the short term recurrent ischaemia in acute coronary syndromes [4]-[7]. They may be used in some autoimmune diseases and have an immunomodulatory role after organ transplantation [8] [9]. Other effects include the stimulation of the bone marrow and antiproliferative effects on smooth muscle cells [10] [11].

The potential beneficial role of statins in cancer management is particularly exciting. In breast cancer there is both pre-clinical and clinical evidence to support their possible benefits. Unfortunately other studies yielded less optimistic results. So this review summarises the evidence for and against the use of statins in breast cancer, raises some issues and provides some suggestions regarding their use in the management of breast cancer patients.

2. Statins Pharmacology

As shown in Figure 1 statins target the enzyme HMG-CoA Reductase which is the rate limiting step in the pathway. Statins bind to HMGCR with 1000 fold more affinity than HMG CoA thus competitively inhibiting the enzyme. Hence synthesis of mevalonate as well as the downstream products is inhibited with many consequences as illustrated. Also shown is the site of action of biphosphonates, a common drug prescribed in breast cancer patients with bone metastasis to prevent bone resorption. Its importance will be mentioned later.

Members of the statin family include simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin and rosuvastatin. After oral administration, 30% to 85% of the ingested dose is absorbed in the intestine. The absorbed fraction undergoes extensive first-pass hepatic uptake, mediated by the organic anion transport protein 1B1 (OATP1B1) [3] [12]. Thus only 5% - 30% of statins and their hepatic metabolites reach the systemic circulation. All the statins, except simvastatin and lovastatin, are administered in the \( \beta \)-hydroxy acid form, which is the form that inhibits HMG-CoA reductase. Simvastatin and lovastatin are administered as inactive lactones that must be transformed in the liver to their respective \( \beta \)-hydroxy acids, simvastatin acid (SVA) and lovastatin acid (LVA) In the plasma, more than 95% of statins and their metabolites are protein bound, with the exception of pravastatin and its metabolites, which are only 50% bound [13].

After statins are ingested peak plasma concentration is reached after 1 - 4 hours. The half-life of the parent compounds varies. It is usually 1 - 4 hours except for atorvastatin and rosuvastatin (half-life 20 hours) and simvastatin (half-life 12 hours) [14]. The longer half-life of atorvastatin and rosuvastatin may contribute to their greater cholesterol-lowering efficacy [15]. All statins are biotransformed in the liver which excretes more than 70% of statin metabolites, with subsequent elimination in the feces [16]. Inhibition by other drugs of OATP1B1, which transports several statins into hepatocytes and inhibition or induction of CYP3A4 by a variety of pharmacological agents explains the drug-drug interactions involving statins [17].

Statins differ in their solubility. The more hydrophilic ones (for example lovastatin) are largely confined to
the liver, whereas the more lipophilic compounds (for example simvastatin, atorvastatin) readily permeate extra-hepatic tissues [18]. Thus hydrophilic statins inhibit cholesterol synthesis primarily in the liver but this leads to increased cholesterol synthesis in extra hepatic tissues. On the other hand lipophilic statins act both on hepatic and extra-hepatic tissues and hence exert more pleiotropic effects. The difference in solubility might explain why many studies have shown greater efficacy of lipophilic agents as anti cancer agents compared to hydrophilic agents.

2.1. Evidence Supporting the Beneficial Role of Statins in Breast Cancer

Many breast cancer cell lines and animal models have been used to elucidate the role of statins in tumorogenesis. It has been observed that statins, especially lipophilic ones, consistently exert anti tumor effects by inhibiting proliferation and invasion and promoting apoptosis and usually act by one or a combination of these three mechanisms. The beneficial role was further confirmed in clinical studies.

2.1.1. Inhibition of Proliferation

Increased cell proliferation following excessive proliferative signaling is one of the hallmarks of cancer. Statins prevent breast cancer from proliferating by interfering with these pathways in various ways.

Fritz et al. [19] suggested statins exerted their action by inhibiting RhoA-like GTPases certain of which are expressed more in breast tumors than in the normal tissue of the same person. The amount of RhoA-like proteins correlates with the prognostic factors like histological grade and proliferation index. They are members of the RAS oncogene superfamily and need to undergo prenylation to be successfully incorporated in the plasma membrane [20]. Statins deplete FPP and GGPP and disrupt protein prenylation and thus inhibit proliferation of cancer cells.
In the study by Keyomarsi et al. [21], MCF-7 cells treated with lovastatin showed inhibition of DNA synthesis and their growth was arrested in the early G1 phase, with mevalonate reversing this effect. Campbell et al. [22] implicated the role of nuclear factor kappa B (NFkB), a transcription factor which when activated induces proliferation and decreases apoptosis. They found that lipophilic statins inhibited proliferation in susceptible breast cancer cell lines by deactivating NFkB. Breast cancer cells with activated Ras or ErbB2 pathways had higher endogenous levels of activated NF-kB than those overexpressing estrogen receptor, and proved to be more sensitive to statins. Thus statins may prove beneficial in the treatment of triple negative breast cancer in which they also cause depletion of intracellular iron levels via NO-dependent pathways and upregulation of antioxidant defence mechanisms which mediate anti-proliferative and anti-invasive effects [23].

Confirmation of the anti-proliferative effects of statins was seen in phase 2 trials in which they decreased the Ki-67 expression in breast cancer tissues. The monoclonal antibody, Ki-67, reacts with a human nuclear antigen present in all cycling (G1, S, G2 and M) cells but is absent in serum starved quiescent (G0) cells [24] [25]. It is used to assess the proliferative status of a breast cancer. In these trials histopathology reports of patients with invasive breast cancer treated with atorvastatin before operation showed decreased Ki-67 expression in post surgical samples [26]. Similar results were obtained in DCIS and stage 1 breast cancer patients treated with fluvastatin [27]. Feldt et al. [28] confirmed the findings when they compared tissue samples from patients with invasive breast cancer treated with atorvastatin before surgery. In addition they proposed the anti-proliferative mechanism to be up-regulated expression of the tumor suppressor p27 and down-regulated expression of the oncogene cyclin D1 which is over expressed in up to 50% of all primary breast cancers, with amplification of the cyclin D1 gene, CCND1, being one of the reasons [29]. Cyclin D1 increases the expression of genes associated with proliferation. It interacts with CDK4 and CDK6, leads to phosphorylation and thereby inactivation of the Rb-protein and its G1-maintaining function, hence leading more cells to transit from G1 to S phase [30] [31]. On the other hand p27 (also known as Kip1) is a CDK inhibitor which is involved in the regulation of the G0-to-S-phase transition. It interacts with CDK2-cyclin E, CDK4/6-cyclin D, and CDK2-cyclin A complexes, thereby counteracting the actions of cyclins [32] [33]. Breast tumors have decreased p27 expression and hence show greater proliferative potential, have higher grade and are characterized by HER2 amplification, estrogen receptor (ER) and progesterone receptor (PR) negativity [33] [34].

2.1.2. Induction of Apoptosis
Failure of apoptosis is another hallmark of cancer cells. Statins increase cancer cells apoptosis by complex mechanisms.

One of the mechanisms may involve c-Jun N-terminal kinases (JNKs). The JNKs, JNK1, JNK2, and JNK3, form one subfamily of the mitogen-activated protein kinase (MAPK) group of serine/threonine protein kinases [35]. Koyuturk et al. [36] showed that statins activate JNK-signalling pathway leading to apoptosis in breast cancer cells irrespective of whether they express ER or p53, or not. Inhibition of JNK activation is responsible for resistance to drugs like cisplatin and vinblastine and so statins can help overcome chemoresistance in these cases [37] [38].

In their study simvastatin induced cell-cycle arrest, initiated apoptosis and activated cellular signaling activity of JNK in both MDA-MB 231 (ER-negative and expressing mutant p53) and MCF-7 (ER -positive and expressing wild-type p53), independent of the absence or presence of estradiol. p53 does not influence the action of simvastatin which decreased proliferation and induced apoptosis without altering the levels of either mutant p53 in ER-negative MDA-MB-231 cells or wild-type p53 in ER-positive MCF-7 cells.

JNK signaling was also implicated by Gopalan et al. [39]. They showed that simvastatin activated the JNK/CHOP/DR5 pathway thus directly inducing apoptosis of breast cancer cells. The authors showed that simvastatin up-regulated expression of death receptor-5 (DR5), CCAAT/enhancer binding protein homologous protein (CHOP) and phosphorylated c-Jun N-terminal kinase (pJNK) in human breast cancer cell lines. The pro-apoptotic action of simvastatin was significantly inhibited by siRNA knockdown of DR5, CHOP or JNK. To confirm the action of the statin, the authors added mevalonate and GGPP which consequently suppressed the activation of JNK/CHOP/DR5 pro-apoptotic pathway by simvastatin.

Ghosh-Choudhury et al. [40] brought forward a complex interaction to show how simvastatin prevented growth of MDA-MB-231 human breast cancer cell. They concluded that the primary target of simvastatin is nodal transcription factor NFkB and Akt. Simvastatin inhibits NFkB with 2 consequences, firstly reduced transcription and expression of its target antiapoptotic protein BclXL and secondly derepressed the expression of
S. Moonindranath, H. L. Shen

respectively translocate Ras breast cancer cell line MDA-MB-231 by preventing the synthesis of cholesterol precursor FPP and GGPP which interacted by statins via inhibition of the specific cell signaling pathways. The ability of cancer to invade local tissues and metastasise to distant organs has been shown to be counteracted by statins via inhibition of the specific cell signaling pathways.

Bone complications include pathological fractures and spinal cord compression following vertebral body collapse. The ability of cancer to invade local tissues and metastasise to distant organs has been shown to be counteracted by statins via inhibition of the specific cell signaling pathways. Also, signal transduction involved in various cellular processes is regulated by Ras and RhoA, including cell motility. Absence of RhoA from the cell membrane following its delocalization to the cytosol causes actin fibers to be disorganized and focal adhesion sites to disappear. GGPP but not FPP reversed inhibition of invasion and metastasis produced by RhoA inactivation. Moreover, the authors showed that cerivastatin inactivated NfxB in a RhoA inhibition-dependent manner, resulting in a decrease in urokinase and matrix metalloproteinase-9 expressions, which are important for cell migration.

Denoyelle et al. [42] suggested that the statin cerivastatin inhibited invasion and metastasis in the aggressive breast cancer cell line MDA-MB-231 by preventing the synthesis of cholesterol precursor FPP and GGPP which respectively translocate Ras and Rho to the cell membrane and thus prevent cell proliferation and migration. Also, signal transduction involved in various cellular processes is regulated by Ras and RhoA, including cell motility. Absence of RhoA from the cell membrane following its delocalization to the cytosol causes actin fibers to be disorganized and focal adhesion sites to disappear. GGPP but not FPP reversed inhibition of invasion and metastasis produced by RhoA inactivation. Moreover, the authors showed that cerivastatin inactivated NfxB in a RhoA inhibition-dependent manner, resulting in a decrease in urokinase and matrix metalloproteinase-9 expressions, which are important for cell migration.

Alonso et al. [43] investigated the effect of lovastatin on the F3II sarcomatoid mammary carcinoma, a highly invasive and metastatic murine tumor model. They showed that lovastatin prevented tumor cell attachment and migration in vitro while in vivo it significantly increased the time for tumors to appear and reduced tumor formation and metastatic dissemination to the lungs from established mammary tumors. Addition of mevalonate but not equivalent concentrations of FPP blocked these actions thus confirming the role of statins.

In the subtopic of prevention of cancer invasion and metastasis it is worth mentioning the work by Rachner et al. [44] which reveals the potential role of statins in the management of metastatic bone lesions in breast cancer. Bisphosphonates like zoledronic acid are licensed to treat bone metastasis in breast cancer. The authors showed that both atorvastatin and zoledronic acid effectively inhibit the Wnt inhibitor DKK-1 in breast cancer cells MDA-MB-231, MCF-7 and T47D and inhibit WNT3A induced OPG (a potent inhibitor of osteoclast activity) production in osteoblasts in vitro and inhibit osteoblast differentiation. However lower concentrations of atorvastatin than zoledronic acid was sufficient to suppress DKK-1 by the same proportion. More recently Gobel et al. [45] suggested that even lower concentration of statin and zoledronic acid significantly suppressed DKK-1 if both the drugs are used together, with simvastatin being most potent statin. In the triple negative MDA-MB-231 cells each drug potentiated each other as far as their DKK-1 suppressing activity was concerned. In hormone-negative and highly osteotropic breast cancer cell lines, there is significant expression of DKK-1 which does not depend on tumor grade or stage. In triple-negative breast cancer, which is associated with an unfavourable outcome and high risk of recurrence, high levels of DKK-1 is a negative prognostic marker [46]. Breast cancer patients with metastatic bone lesions usually show increased DKK-1 levels [47]. Thus statins may prove to be a more effective alternative than bisphosphonates when used alone or in combination in preventing bone resorption by bone metastases from breast cancer.

2.1.3. Inhibition of Invasion and Metastasis

In advanced cases of breast cancer tumor cells usually metastasize to bone (commonest site), liver and lung. Bone complications include pathological fractures and spinal cord compression following vertebral body collapse. The ability of cancer to invade local tissues and metastasise to distant organs has been shown to be counteracted by statins via inhibition of the specific cell signaling pathways.

The role of ionizing radiation (IR) in cancer treatment is to kill cancer cells at the site of the tumor and its vicinity where the probability of microscopic spread is highest. Statins may be useful in radiotherapy by exerting radiosensitizing effects [48] [49]. One of the factors influencing the sensitivity of cells to ionizing radiation is the phase of the cell cycle in which they are [50] [51]. Cells located in late G1 and G2-M phases of the cell cycle are most sensitive to ionizing radiation-induced cell death, whereas cells located in the S phase are the most resistant. Since HMG-CoA reductase inhibitors arrest cells in late G1 phase, they sensitize cancer cells to radiotherapy.

Co-administration of statins with radiation may be particularly useful to reduce local recurrence rate among patients with inflammatory breast cancer (IBC). Lacerda et al. [52] did both an in vitro study and a retrospective
clinical study to support this association. They reported that simvastatin promoted radiosensitization of cancer stem cells of IBC and non-IBC triple-negative cell lines but it radioprotects stem cells of non-IBC cell lines. In their clinical study, among the 519 IBC patients treated with postmastectomy radiation (PMRT), 53 used a statin. In statin users there was a higher local recurrence-free survival (LRFS) and thus better local control.

According to some studies radiation therapy effects may be paradoxical because if on one hand it kills most of the cells in the primary tumor on the other hand it increases the metastatic potential of surviving tumor cells. The mechanism involved in the pro-metastatic trans-effect of IR is likely to be its effect on endothelial cells which promote the extravasation of circulating tumor cells. Hamalukic et al. [48] thus recommended the concomitant use of statins and radiation therapy to prevent this adverse effect of ionizing radiation after showing that pre administration of lovastatin antagonized the IR stimulated extravasation and metastasis. When human endothelial cells (EC), tumor cells (TC) (MCF-7 and T47D mammary carcinoma cells) or both were exposed to IR this increased TC-EC adhesion in vitro. However IR-stimulated TC-EC adhesion was blocked by the HMG-CoA reductase inhibitor which decreases TC-EC interaction both in vitro by inhibiting activation of NFkB and the blocking of the Rac1-regulated and NF-kB-dependent expression of E-selectin following TNFa or IR exposure of endothelial cells [53] [54]. The results were confirmed in vivo [55]. Moreover, radiotherapy induces inflammation and subsequent fibrosis in normal tissue as acute or delayed side effect and statins decrease the normal tissue damage [55]-[58]. Lovastatin had the same anti-metastatic effect whether it was given before or after radiation treatment. Thus we can use lovastatin before radiotherapy to prevent its pro-metastatic effect and continue its use after radiotherapy for an extended period of time to help normal tissue healing without adversely affecting metastasis.

2.1.5. Clinical Trials Suggest Statins Decrease Recurrence Rates and Improve Breast Cancer Prognosis

Table 1 summarises the results of some important clinical trials aimed to see whether statin use affects breast cancer recurrence and prognosis.

In the U.S. cohort by Kwan et al. [59] breast cancer patients less than 3 years after breast cancer diagnosis were prescribed statins and followed for a period of 5 years. They found that statins decreased the rate of recurrence and the longer the duration of use of the statins, the more was the reduced recurrence rate. Ninety-eight percent of statin prescriptions were for lipophilic statins (84%).

This result was confirmed by Ahern et al. [60] from Denmark. According to their study 18,769 invasive breast cancer patients were prescribed statins and were followed for a median of 6.8 years after diagnosis. They found that out of 100 women who used only simvastatin for a follow-up period of 10 years, breast cancer recurred in approximately 10 of them. Thus lipophilic statins decreased the breast recurrence rate in stage 1 to 3 breast cancer while hydrophilic statins did not seem to affect the recurrence rate. The chief strengths of this study are its large size, prospective design, and the use of high-quality prescription and clinical registry data.

Chae et al. [61] did a retrospective cohort of 703 stage II/III breast cancer patients who were prescribed statins (60% and 17% of patients received atorvastatin and simvastatin respectively). They concluded that use of any statin for ≥6 months was associated with a lower recurrence rate. The low hazard ratio (0.4) is likely to be an exaggeration due to the inclusion of immortal person-time in the rate denominator for statin-exposed subjects [62] [63].

The German study by Nickels et al. [64] observed a non-significant reduced risk of recurrence and breast cancer-specific mortality in 3024 stage I-III breast cancer patients in a median follow-up of 5.3 years. The result might have been significant if in the design of the study attention was given to statin and non-statins lipid lowering agents and counting patients who were already using statin at time of selection in the unexposed comparison

<table>
<thead>
<tr>
<th>Study by</th>
<th>Year</th>
<th>Number of patients</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kwan et al. [78]</td>
<td>1997 - 2000</td>
<td>1945</td>
<td>0.67</td>
<td>0.39, 1.13</td>
</tr>
<tr>
<td>Ahern et al. [21]</td>
<td>1996 - 2003</td>
<td>18,769</td>
<td>0.7</td>
<td>0.57, 0.86</td>
</tr>
<tr>
<td>Chae et al. [20]</td>
<td>1999 - 2005</td>
<td>703</td>
<td>0.4</td>
<td>0.24, 0.67</td>
</tr>
<tr>
<td>Nickels et al. [79]</td>
<td>2001 - 2005</td>
<td>3024</td>
<td>0.83</td>
<td>0.54, 1.24</td>
</tr>
<tr>
<td>Boudreau et al. [80]</td>
<td>1990 - 2008</td>
<td>4216</td>
<td>0.82</td>
<td>0.62, 1.08</td>
</tr>
</tbody>
</table>
group. Boudreau et al. [65] worked on the association between common medications used in cardiovascular disease (which include statins) and second breast cancer events (SBCE). Again they suggested a reduced risk of SBCE with statin use in women who were diagnosed with stage I or II breast cancer. The majority of statins used in their study was also lipophilic.

2.1.6. Statins as Effective Neoadjuvant Therapy

The work by Garwood et al. [27] shows promise regarding the use of statins as neoadjuvant therapy for breast cancer. They tried to find whether patients with in situ and invasive breast cancer could benefit from taking lipophilic statins on a short-term basis. Women with a diagnosis of DCIS or stage 1 breast cancer who were due for surgery were treated with fluvastatin. Patients were randomly given high dose (80 mg/day) or low dose (20 mg/day) fluvastatin for 3 - 6 weeks before surgery. Tissue (diagnostic core biopsy/final surgical specimen), blood, and magnetic resonance images before treatment were compared with those after treatment. Anti-proliferative and pro-apoptotic actions of statins (determined by Ki-67 and CC3 respectively) was more significant in high grade tumors than in low grade tumors. On the other hand, MRI showed that the median tumor volume after treatment decreased by 12.7% which was not statistically significant. Nevertheless the results are promising because they provide clinical evidence that statins could be the answer to the treatment of resistant ER-negative high grade breast cancers. It provides solid ground for further research on the effect of other statins for different treatment times which may have better outcome on tumor shrinkage.

Similarly Bjarnadottir et al. [26] investigated the effects of statins in neoadjuvant setting and tried to clarify the relationship between statins and their effects on tumor proliferation and HMGCR expression. They tried to see whether HMGCR expression could be used as a tool to predict whether a breast cancer could show beneficial response if treated with a statin as a neo adjuvant treatment. High-dose atorvastatin (80 mg/day) was prescribed to 50 patients with primary invasive breast cancer 2 weeks before surgery. Ki67 and HMGCR immunohistochemical expression was compared in paired samples before and after statin treatment. They concluded that atorvastatin treatment significantly up-regulated HMGCR in 68% of the paired samples with evaluable HMGCR expression. Anti-proliferative action of atorvastatin was not significant in the paired samples but significant in tumors expressing HMGCR in the pre-treatment sample. Furthermore, post-treatment Ki67 expression and HMGCR expression showed an inverse correlation (rs = -0.42; P = 0.03). Thus patients with breast cancers expressing HMGCR appear to be ideal candidates for statin neoadjuvant therapy in whom statins are more likely to decrease proliferation. Nevertheless it is important to point out that HMGCR expression is associated with smaller tumour diameter, lower histologic grade, ERα and ERβ expression, and lower baseline proliferation rate [66].

2.1.7. Statins May Reduce Breast Cancer Mortality

Murtola et al. [67] conducted a cohort study in Finland involving 31,236 newly diagnosed breast cancer patients identified from the Finnish Cancer Registry over the period 1995-2003 and followed them for a median 3.25 years after the diagnosis. They concluded that those patients who used statins were at lesser at risk to die from their disease. Neither the stage of the disease (localized or metastatic breast cancer) nor the time at which statin use was started (before or after breast cancer diagnosis) seemed to affect the beneficial role of statins. In addition the lowered risk correlated with the dose of statin use especially for pre-diagnostic usage. Differences in age, tumor characteristics and treatment selection between statin users and non-users did not alter the risk decrease. Other antilipidaemic drugs like fibrates did not possess the protective effect when given to patients of similar age, tumor and treatment characteristics. Competing causes of death or the likelihood that patient could decrease statin usage at the end of life did not seem to undermine the decreased risk observed. Major strengths of this study include the large number of patients and detailed knowledge on timing, dosage and duration of statin use.

Cardwell et al. [68] tried to determine the relationship between patients taking statins after they were diagnosed with breast cancer and whether this affected cancer-specific or all-cause mortality. Data was taken from a cohort of 17,880 breast cancer patients newly diagnosed between 1998 and 2009 using data from English cancer registries. Their results suggested statins decreased mortality due to breast cancer (fully adjusted HR = 0.84, 95% CI = 0.68 - 1.04) and all causes (HR = 0.84, 95% CI = 0.72 - 0.97). These associations were more marked for simvastatin (HR = 0.79, 95% CI = 0.63 - 1.00) and (HR = 0.81, 95% CI = 0.70 - 0.95) respectively. Unfortunately the results may be misleading because of the weakness of the associations involved and attenuation seen in some sensitivity analyses.

More recently Zhong et al. [69] conducted a meta-analysis which concluded that patients who used statins
both before and after their cancer was diagnosed survived longer. There was a decrease in both cancer and non-cancer specific mortality in colorectal, prostate and breast cancer. In breast cancer they concluded a HR = 0.73, 95% CI = 0.62 - 0.86. Limitations of the study included outcome other than mortality (all-cause and cancer specific) for example cancer recurrence, low statistical power of subgroups due to smaller number of patients, failure to analyze those patients who were on statin before cancer diagnosis and who continued using statins, failure to consider unmeasured factors related to statin and immortal time bias in the included studies.

### 2.1.8. Statins in Inflammatory Breast Cancer

Inflammatory breast cancer is a rare but the most lethal type of breast cancer and has a poor prognosis [70] [71]. The cohort study by Brewer et al. [72] reviewed how statin use and the type of statin used affected the progression-free survival (PFS), overall survival (OS) and disease-specific survival (DSS) in 723 patients diagnosed with primary IBC in 1995-2011 and treated at The University of Texas MD Anderson Cancer Center. Statin users were defined as being on statins at the initial evaluation. They found that H-statins were associated with significantly improved PFS compared with no statin (hazard ratio = 0.49; 95% confidence interval = 0.28 - 0.84; P < 0.01); OS and DSS P-values were 0.80 and 0.85, respectively. For L-statins vs no statin, P-values for PFS, DSS, and OS were 0.81, 0.4, and 0.74, respectively. Thus H-statins significantly improved PFS. Another inference is the usefulness of hydrophilic statins. It questions the superior effectiveness of lipophilic statins as compared to hydrophilic statins. Almost all preclinical and clinical studies have highlighted the efficacy of lipophilic statins in breast cancer but this study is one of the exceptions. It warrants more insight into the potential effectiveness of hydrophilic statins in specific subtypes of breast cancer.

### 2.1.9. Statins Are Cost Effective Drugs

Treating cancer patients involves a lot of costs. Patients not only have to pay for the drugs but also laboratory tests, diagnostic and therapeutic procedures, imaging tests, radiotherapy, hospitalization and surgery. Although cancer drugs are effective the fact that they are expensive makes it a deterrent to treatment. Indeed 11 of the new cancer drugs approved in 2012 were priced above $100,000 annually and 20% - 30% copayment can make them unaffordable even for well-insured patients. In many cases patients stop treatment while in some cases treatment is not started. This leads to complications in the patient, management of which may be more difficult and costlier. To make things worse health insurance companies are unwilling to reimburse a significant portion of the expenses. Statins have the potential to lower the cost of breast cancer management and allow patients to get quality cancer care at an affordable price. There is a big variation in the price of statins depending on the setting but low-intensity generic statins are now widely available from discount retailers which hence makes the drug more accessible. In one study the authors assumed universal access to statins at $4 per month in an attempt to determine the cost-effectiveness of cheap statin generics in the primary prevention of coronary artery disease [73].

### 2.2. Evidence Not Supporting Use of Statins

#### 2.2.1. Meta-Analyses Reveal No Relationship between Statins and Breast Cancer Incidence

Since randomized statin trials did not have breast cancer incidence as the primary endpoint [74], epidemiologists have used observational and experimental studies to conduct meta-analyses. Unfortunately they have shown no relationship between statin use and breast cancer risk. Table 2 summarises the results of some of these studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Risk ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonovas et al.</td>
<td>2005</td>
<td>1.03</td>
<td>0.93 - 1.14</td>
</tr>
<tr>
<td>Dale et al.</td>
<td>2006</td>
<td>1.02</td>
<td>0.97 - 1.07</td>
</tr>
<tr>
<td>Browning et al.</td>
<td>2007</td>
<td>1.01</td>
<td>0.79 - 1.30</td>
</tr>
<tr>
<td>Kuoppala et al.</td>
<td>2008</td>
<td>1.04</td>
<td>0.74 - 1.9</td>
</tr>
<tr>
<td>Baigent et al.</td>
<td>2010</td>
<td>1.07</td>
<td>0.84 - 1.38</td>
</tr>
<tr>
<td>Unde et al.</td>
<td>2012</td>
<td>0.99 (statin use)</td>
<td>0.96 - 1.11 (long term statin use)</td>
</tr>
</tbody>
</table>
Among these the studies by Bonovas and Undela focused on breast cancer specifically while others focused on cancers in general including breast cancer. Randomised clinical trials are essential to determine the chemopreventive potential of statins and whether they are superior to tamoxifen which at present is the only drug licensed as a chemopreventive agent for women at high risk for breast cancer (women more than 35 years and with a 5-year predicted risk of breast cancer equal to or more than 1.67% according to the Gail model).

2.2.2. Potential Carcinogenicity of Statins

With statins being the most commonly prescribed drug in the world, we must ensure they are safe both on short and long term bases. There are mixed opinions regarding the potential of statins to cause cancer.

According to the meta analysis conducted by Bjerre et al. [81], statins did not seem to increase the risk of fatal and non fatal cancers over a 5 year period. Another meta analysis by Hebert et al. [82] involved 16 individual trials with 29000 patients with an average follow up of 3.3 years concluded that neither non-CVD deaths nor cancer incidence were significantly increased. The meta-analysis by Law et al. [83] showed no evidence that a low serum cholesterol significantly increased cancer mortality but it did increase the risk of haemorrhagic stroke. The Scandinavian Simvastatin Survival Study (4S) followed patients on a period of 8 years to see the protective role of statins in the secondary prevention of coronary heart disease. Again there was no decrease in overall mortality (relative risk, 0.70; P 0.00002) with no significant difference in cancer deaths (relative risk, 0.73; P 0.087).

However, some think statins can trigger cancer formation directly by possessing intrinsic carcinogenic property and indirectly by curbing serum cholesterol. According to some studies it may be possible that all-cause mortality and serum cholesterol in men may be related by a U-shaped association [84]. Newman et al. [85] found that HMG-CoA reductase inhibitors and fibrates caused cancer in rodents but as far as human beings are concerned results were inconclusive and they suggested long term follow up and careful post marketing surveillance. Human cohort studies showed that low cholesterol levels were associated with an increase in cancer deaths [84] [86]. However confounding variables like the effect of preexisting cancer and the retrospective nature of the studies warrants further research [87].

Other schools of thought selectively blame the hydrophilic but not the lipophilic statins to cause cancer. For example pravastatin is a relatively hydrophilic statin which leads to increased mevalonate production in extrahepatic cells including breast and since elevated mevalonate synthesis has been reported in malignant breast cancer, one can make the link [88]-[91]. In contrast, the lipophilic statins like simvastatin and lovastatin inhibit HMG-CoA reductase activity equally well in hepatic and extrahepatic cells and thus lack the carcinogenic potential [92]-[94].

Interestingly McDougall et al. [95] investigated the relationship between long-term statin use and breast cancer risk. They found that use of atorvastatin for more than 10 years almost doubled the risk of invasive ductal carcinoma and invasive lobular carcinoma in a population based case-control study. They raised the possibility of a short term protective effect of statins but promotion of breast carcinogenesis following chronic lowering of serum cholesterol. By far the major strength of this study is the long term follow up. Almost all statin studies lasted less than 10 years. Thus it is important to design long term studies to ensure that statin use may not ironically increase breast cancer risk and will not be useful as a breast cancer chemopreventive agent.

2.2.3. Are Statins Safe?

The major side effect of statins is myotoxicity [96]. This includes myalgia and elevated serum kinase and rhabdomyolysis. The latter is the most severe form, leading to myoglobunuria and acute renal failure. Between 1987 and 2001, the FDA recorded 42 deaths from rhabdomyolysis induced by statins. Although various hypotheses have been suggested to explain myotoxicity of statins the exact mechanism is still unknown [97]. The risk of myopathy and rhabdomyolysis is increased in conditions like advanced age, hepatic and renal impairment, peri-operative period and systemic illnesses like diabetes mellitus and hypothyroidism. Myopathy and rhabdomyolysis is also worsened by drug interactions. The most common statin interactions occurred with fibrates, especially gemfibrozil (38%), cyclosporine (4%), digoxin (5%), warfarin (4%), macrolide antibiotics (3%), mibeferadil (2%), and azole antifungals (1%) [98]. The mechanism of interaction varies with the drug. For instance gemfibrozil inhibits hepatic uptake by OATP1B1 and transformation by glucuronidase leading to higher plasma concentration of the drug and hence more side effects.

Ubiquinone plays a role in enabling mobility within the phospholipid bilayer of the inner mitochondrial
membrane. Statins can reduce serum ubiquinone level upto 40% resulting in myalgia and signs and symptoms resembling mitochondrial encephalomyopathy, lactic acidosis and stroke-like syndrome [99] [100]. Ubiquinone supplementation has been routinely used to treat statin induced myotoxicity but whether it is an effective treatment still needs further research. Recently Banach et al. [101] did a meta-analysis of available randomized controlled trials and concluded from 6 studies with 302 patients that ubiquinone did not significantly improve statin-induced myopathy. Myotoxicity is the dose-limiting toxicity of HMGCoA reductase inhibitors. If we can elucidate the mechanisms, treat and prevent this adverse effect, we can safely use statins at high doses. However as far as breast cancer management is concerned adding another drug to the already long list of medication coupled with its potential risk to cause even more drug interactions casts doubt about its practical use.

The second major side effect is hepatotoxicity. Statins increase serum liver enzymes in a dose dependent fashion and occur at a reported frequency of 1% - 33% [102]. Patients are more at risk to develop signs and symptoms of liver toxicity in the first three months of their treatment and so monitoring of liver enzymes in this period is crucial [103]. However statins are useful in patients with non alcoholic fatty liver disease like in patients with type 2 diabetes mellitus so that raised liver enzymes should not be a deterrent to start statin therapy. Other side-effects include gastro-intestinal disturbances, sleep disturbance, headache, dizziness, depression, paraesthesia, asthenia, peripheral neuropathy, amnesia, fatigue, sexual dysfunction, thrombocytopenia, arthralgia, visual disturbance, alopecia, and hypersensitivity reactions. In very rare cases statins can cause interstitial lung disease and diabetes mellitus.

Till now there has been no study regarding the interaction between statins and anti cancer drugs. They share common side effects with anticancer drugs, for example hepatotoxicity and it will be interesting to know the grading of these side effects when statins are used together with anti cancer agents. Nevertheless currently statins are considered to be relatively safe drugs.

3. Conclusions

At present there is ample evidence to suggest that statins could be used in breast cancer. But many questions need to be answered like regarding the long term effects, drug interaction with chemotherapeutic agents, the dose to be used (and whether it will be same as that used for lipid lowering) and the biomarkers to be used to measure effect of statins among others. Cancers take time to develop so it can take several years for a side effect to come up. So the earlier we embark on phase 3 randomised controlled trials the better it will be. We need more trials like The NSABP-P5 (National Surgical Adjuvant Breast and Bowel Project) which is a phase 3 prospective randomized controlled trial which started in 2010 mainly to determine the ability of rosvastatin to prevent recurrence of polyp and/or colon cancer in patients operated for colon cancer and its possible side-effects.

In my opinion, randomized controlled trials should now focus on breast cancer in view of the high number of patients, relative ease to take diagnostic samples and the tremendous amount of supporting evidence for each modality of treatment. These trials will focus on many objectives. They will decide whether statins are an effective neo-adjuvant treatment. They will determine whether statins can be used as maintenance therapy in cases of localized disease after the tumour has been surgically removed. In locally advanced or recurrent metastatic disease where surgery is not an option to remove the bulk of the tumor, they will give insight on whether statins can improve the efficacy of commonly used cytotoxic or immunological agents if given in combination depending on synergism results obtained in preclinical studies. Furthermore, they will assess the role of the statins in radiation therapy, how effective they are as radiosensitizers and whether they can help overcome radioresistance. Thus they can limit the dose of anti cancer drugs and radiation therapy reducing their side effects, increasing their efficacy and preventing chemo and radio resistance. They will help us decide whether statins are a better alternative to biphosphonates in reducing bone resorption by metastatic cancer cells. Breast cancer prevention in high risk patients (for example in patients with BRCA 1 and BRCA2 mutations) is an exciting prospect and will be a follow up in case of encouraging results.

Statins are relatively safe, well-tolerated, and inexpensive and would yield a cost-effective, low-toxicity treatment. Since newer generations of statins are more potent, have better toxicity profile, and have fewer drug interactions, we can only be optimistic for a positive outcome in the future.

References


S. Moonindranath, H. L. Shen

JAMA, 295, 74-80. http://dx.doi.org/10.1001/jama.295.1.74


