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Statins: a role in breast cancer therapy?

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Abstract. Borgquist S, Bjarnadottir O, Kimbung S, Ahern TP (Aarhus University Hospital, Aarhus C, Denmark; Lund University, Lund, Sweden; and The University of Vermont, Burlington, VT, USA). Statins: a role in breast cancer therapy? (Review). *J Intern Med* 2018; **284**: 346–357.

Statin drugs have been used for more than two decades to treat hypercholesterolemia and as cardio-preventive drugs, resulting in a marked decrease in cardiovascular morbidity and mortality worldwide. Statins halt hepatic cholesterol biosynthesis by inhibiting the rate-limiting enzyme in the mevalonate pathway, hydroxymethylglutaryl-coenzyme A reductase (HMGCR). The mevalonate pathway regulates a host of biochemical processes in addition to cholesterol production. Attenuation of these pathways is likely responsible for the myriad benefits of statin therapy beyond cholesterol reduction – the so-called *pleiotropic effects* of statins. Chief amongst these purported effects is anti-cancer activity. A considerable body of preclinical, epidemiologic and clinical evidence shows that statins impair proliferation of breast cancer cells and reduce the risk of breast cancer recurrence. Potential mechanisms for this effect have been explored in laboratory models, but remain poorly understood and require further investigation. The number of clinical trials assessing the putative clinical benefit of statins in breast cancer is increasing. Currently, a total of 30 breast cancer/statin trials are listed at the global trial identifier website clinicaltrials.gov. Given the compelling evidence from performed trials in a variety of clinical settings, there have been calls for a clinical trial of statins in the adjuvant breast cancer setting. It would be imperative for such a trial to incorporate tumour biomarkers predictive of statin response in its design and analysis plan. Ongoing translational clinical trials aimed at biomarker discovery will help identify, which breast cancer patients are most likely to benefit from adjuvant statin therapy, and will add valuable clinical knowledge to the field.

Keywords: breast cancer, cholesterol, endocrine therapy, HMGCR, statins.

Breast cancer

Breast cancer is globally the most common malignancy amongst women, contributing more than 25% of the total number of new cancer cases diagnosed (www.wcrf.org). The number of breast cancer cases has steadily increased over the last few decades, although annual incidence rates vary greatly worldwide, from 19.3 per 100 000 women in Eastern Africa to 89.7 per 100 000 women in Western Europe (www.who.int). Worldwide, breast cancer ranks as the fifth most frequent cause of cancer death, and in the female population, it is the second most frequent cause of cancer death [1]. In parallel with the incidence rates for breast cancer, the prevalence of overweight and obesity has rapidly risen. Overweight/obesity is often associated with the metabolic syndrome and increases the risk of a number of diseases, including hypercholesterolemia and breast cancer [2]. Not only does overweight/obesity influence breast cancer incidence [3, 4], it also worsens prognosis following breast cancer [5]. The epidemiological and clinically manifested linkage between overweight/obesity and breast cancer is increasingly clear [6], although important gaps exist in our knowledge. A common comorbidity of overweight/obesity is hypercholesterolemia, and one knowledge gap is, for example, the impact of cholesterol on the progression of breast cancer and on the effectiveness of adjuvant endocrine therapy.

Molecular basis for statin use as breast cancer therapeutic agents

Statins are routinely used to treat hyperlipidaemia, but may also have antineoplastic effects. The target for statins, HMGCR, is a transmembrane glycoprotein found in the endoplasmic reticulum in all cells.

HMGCR activity controls the mevalonate pathway, which in addition to cholesterol produces steroid-based hormones and non-sterol isoprenoids (Fig. 1) [7, 8]. Inhibition of hepatic HMGCR causes reduced intracellular cholesterol levels in hepatocytes. This in turn triggers up-regulation of low-density lipoprotein cholesterol (LDL-C) receptors to scavenge cholesterol from the serum to support cell growth and division. Serum levels of LDL-C consequently plummet, reducing the rate of adverse cardiovascular events in statin-treated individuals [9]. Cellular cholesterol levels and HMGCR activity are maintained *via* tightly regulated feedback mechanisms, whereas extracellular serum cholesterol concentrations vary [10]. In addition to reducing LDL-C production, blocking the mevalonate pathway interrupts synthesis of the isoprenoids geranylgeranyl pyrophosphate (GGPP) and farnesyl pyrophosphate (FPP) [7, 8]. Isoprenylation of proteins by GGPP and FPP enables subcellular localization and intracellular trafficking of membrane-associated proteins that are essential for the cell [11]. GGPP and FPP post-translationally prenylate a host of proteins – including the oncogene products Ras, Rac and Rho – to enable their full function [11–13]. The isoprenoids demonstrate tumour-suppressive properties as regulators of important processes in cancer such as proliferation, migration and angiogenesis [7, 14]. Comprehensive analysis of statin-induced changes in tumour cell lipid profiles may reveal the dominant pathways through which statins attenuate tumour promotion [15].

Highly proliferative cells (such as cancer cells) must rapidly produce lipid bilayer membranes, requiring increased cholesterol biosynthesis [16]. Whilst the cholesterol biosynthesis pathway is tightly regulated in normal cells, it may be dysregulated in cancer cells [17]. It has been implied that HMGCR is a metabolic oncogene, and that dysregulation of the mevalonate pathway promotes transformation [18]. In addition, high mRNA levels of HMGCR and other mevalonate pathway genes were associated with impaired prognosis for breast cancer patients [18]. This finding was recently validated in two large breast cancer datasets [19].

The mevalonate pathway is a possible therapeutic target for tumours with mutations of the tumour suppressor p53 [20, 21]. The p53 protein, encoded by the *TP53* gene, is dubbed 'the guardian of the genome' due its tumour-suppressing activities. These activities, triggered by DNA damage, include activation of DNA repair mechanisms, initiation of growth arrest at the G1/S boundary and induction of apoptosis if repair fails. The mevalonate pathway is both necessary and sufficient for the phenotypic effects of mutant p53 on breast tissue architecture, and mutant p53 associates with sterol gene promoters [20]. In a three-dimensional culture model, mutant p53 up-regulated mevalonate pathway genes in breast cancer cells, leading to disordered, invasive morphology [20]. In the same model, depletion of mutant p53 by RNA interference caused reversion to normal morphology. Remarkably, the addition of clinically achievable concentrations of simvastatin to the culture system resulted in marked reductions in tumour cell growth, induction of apoptosis and reversion to normal morphology in the various breast cancer

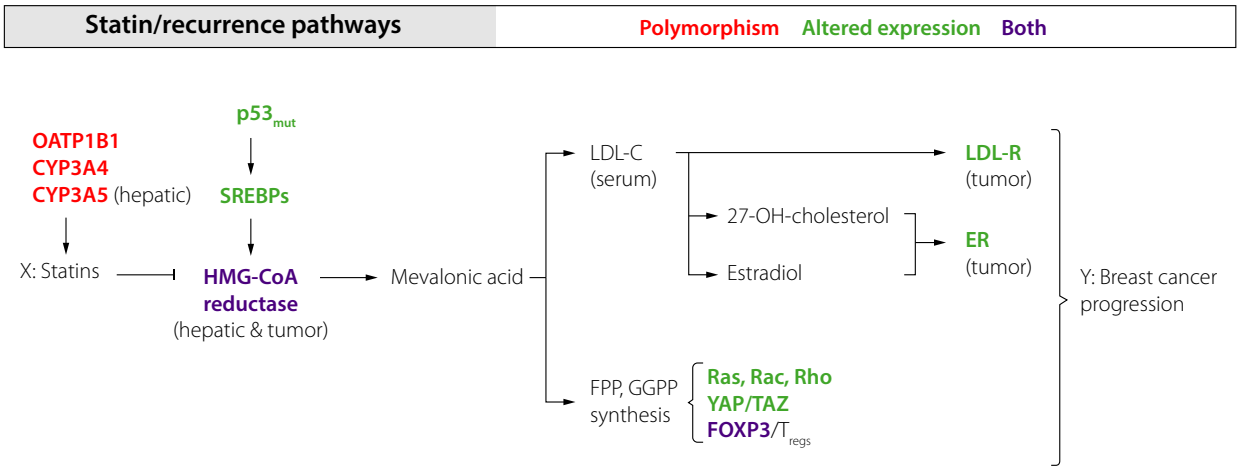

Fig. 1 *Pathways and potential predictive biomarkers that may mediate breast tumour response to statin therapy.*

cell lines tested [20]. The beneficial effects of simvastatin were negated when the mevalonate pathway products GGPP and FPP were simultaneously added to the culture medium. The p53 effect is likely modulated by sterol regulatory element-binding proteins (SREBPs), and tied to the YAP/TAZ effectors of the Hippo signalling pathway [22]. YAP/TAZ activity is also controlled by Rho GTPases, which are dependent on prenylation for activation [23]. Therefore, overexpression of genes encoding p53, SREBPs, mevalonate pathway genes and the YAP/TAZ transcriptional regulators may identify breast tumours that will be sensitive to statin treatment.

A large number of *in vitro* and *in vivo* cancer studies with statins have been performed (Table 1), with many more underway. So far, these models have shown that statins decrease proliferation and increase apoptosis of breast cancer cells [18, 24]. The biological mechanisms for these actions are not yet fully elucidated. Our previous work demonstrated that HMGCR is differentially expressed in human breast cancer samples and holds prognostic value [25, 26]. HMGCR may also predict tumour response to endocrine treatment [27], as well as to statin treatment, in a recent phase II clinical trial (ClinicalTrials.gov Identifier: NCT00816244) [28]. Other *in vitro* studies demonstrated substantial statin-induced increases in HMGCR expression [29], and atorvastatin induced HMGCR up-regulation when assessed with a novel, well-validated monoclonal HMGCR antibody [19]. Additionally, *in vivo* studies suggest that HMGCR activity is higher in mammary tumours compared with normal mammary glands, and that tumours are resistant to feedback regulation by sterols [30].

If statins do target the mevalonate pathway in cancer cells within a tumour, the lowering of intracellular cholesterol may lead to lowered intra-tumoural autocrine hormone production, as cholesterol is fundamental for all steroid hormone synthesis. Interestingly, one study has reported that atorvastatin and its metabolites are detectable in human breast samples following oral administration [31], indicating that direct inhibition of HMGCR may occur in breast tumours. Most relevant for an endocrine responsive disease such as oestrogen receptor (ER)-positive breast cancer, statin treatment reduces levels of the cholesterol metabolite 27-hydroxy cholesterol (27HC) [32]. 27HC acts as an ER ligand, potentiating ER-dependent tumour growth [33–36]. Interestingly, 27HC can agonize both the ER and the liver X receptor (LXR) to drive breast tumour proliferation [33, 34], and it promotes metastasis through interactions with myeloid immune cells [37]. The cholesterol biosynthesis pathway was recently shown to be up-regulated in ER-positive breast cancer cell lines that are resistant to oestrogen deprivation [38, 39], suggesting that dysregulation of cholesterol biosynthesis may be a mechanism of endocrine resistance in hormone receptor-positive breast cancer [38, 39]. Chronic oestrogen deprivation in ER-positive breast cancer cells seems to stabilize the epigenetic activation of the mevalonate pathway and cholesterol biosynthesis [39], and this leads to the accumulation of other ligands (such as 27HC), which potentiate ER signalling in the absence of oestrogen, consequently driving the activation of genes that promote a proliferative and invasive cell phenotype [39].

To summarize, cancer cells depend on cholesterol for continued growth and survival. Therefore, attenuating cholesterol biosynthesis seems to be a promising anti-cancer strategy. Of note, rapidly proliferating cancer cells have an increased cholesterol demand to enable cell membrane synthesis [16, 40]. By lowering plasma levels of cholesterol and 27HC, their availability for use by cancer cells is consequently lowered. Additionally, direct inhibition of HMGCR by statins depletes intratumoural reserves of isoprenoids, which are key regulators of cancer cell proliferation and metastasis. Ongoing studies are exploring additional roles that cholesterol, cholesterol metabolites and statins play in breast tumour promotion.

Breast cancer risk reduction by statins

The positive association between overweight and obese body constitutions on risk of postmenopausal breast cancer has been demonstrated by several studies [3, 6, 41–43]. The biological underpinnings of the observed association between obesity and breast cancer are not completely understood; both in terms of effects from the local micro-environment on progression [44], and also regarding breast cancer initiation (an area that has hardly been explored) [45]. Overweight-associated alterations in circulating cholesterol might partly explain the association between obesity and breast cancer [46]. Evidence for an association between cholesterol and cancer incidence is not consistent [47–49]. Some epidemiological studies previously

Table 1 *Key experimental data linking statin treatment to decrease proliferation and cell death induction in cancer*

Reference	Research findings	Tumour type
Campbell *et al.* [67]	Cancer cells with activated Ras or ErbB2 pathways and low oestrogen receptor expression were more susceptible to statin-induced anti-proliferative and pro-apoptotic signals. Statin sensitivity also correlated with endogenous levels of activated nuclear factor kappaB (NF-kappaB)	Breast
Wong *et al.* [68]	Half of a panel of 17 genetically distinct multiple myeloma cell lines displayed significant sensitivity to statin-induced apoptosis. Addition of mevalonate, geranylgeranyl PPi, farnesyl PPi, completely or partially rescued the sensitive cells from the statin-induced apoptosis, thus highlighting the importance of isoprenylation in this process	Multiple myeloma
Clendening *et al.* [18]	Overexpression of HMGCR accentuates growth of transformed and non-transformed cells *in vitro* and in mice. This occurs via mechanisms including cooperation with RAS to drive cell transformation	Breast, colorectal
Clendening *et al.* [69]	Statin treatment inhibits proliferation and induced apoptosis in a subset of primary myeloma cells. Dysregulation of the mevalonate pathway may distinguish between sensitive and resistant cells	Multiple myeloma
Garwood *et al.* [70]	Preoperative treatment with high dose (80 mg day^{-1}) or low dose (20 mg day^{-1}) fluvastatin for 3–6 weeks showed measurable biologic activity by reducing tumor proliferation and increasing apoptosis in high-grade, stage 0/1 primary tumours	Breast
Bjarnadottir *et al.* [28]	Preoperative treatment with high dose (80 mg day^{-1}) atorvastatin for 2 weeks showed measurable biologic activity by reducing tumor proliferation in HMGCR-expressing primary tumours	Breast
Freed-Pastor *et al.* [20]	Genome-wide expression analysis revealed that p53 mutants significantly upregulate the mevalonate pathway. Treatment with statins and sterol biosynthesis intermediates reveal that the mevalonate pathway is both necessary and sufficient for the phenotypic effects of mutant p53 on breast tissue architecture implicating the mevalonate pathway as a therapeutic target for tumours bearing mutations in p53	Breast

Table 1 (*Continued*)

Reference	Research findings	Tumour type
Nelson *et al.* [33]	Cholesterol through its conversion to 27-hydroxycholesterol increased ER-dependent cell and tumor growth. These effects were attenuated by treatment with statins and CYP27A1 inhibitors	Breast
Sorrentino *et al.* [22]	Statin treatment prevented YAP/TAZ nuclear localization and transcriptional responses which are necessary to promote tissue proliferation and organ growth thus revealing a link between mevalonate-YAP/TAZ axis which is required for proliferation and self-renewal of breast cancer cells	Breast
Pandyra *et al.* [17]	Blocking the sterol-feedback loop initiated by statin treatment, by co-inhibiting SREBP2 significantly potentiates the anti-tumour activity of statins	Breast, Lung

indicated lower cancer incidence amongst statin users [50, 51], although the results have been inconsistent across studies [52–55]. Our recent update from the large, prospective Nurse's Health Study (NHS) showed no association between different statin exposures and risk of invasive breast cancer [56]. Results from a prominent meta-analysis were null [54]. Notably in the NHS, statin use was not associated with *increased* risk of invasive breast cancer, regardless of histological type. Nonetheless, development of a subset of breast cancer – presumably subtypes highly dependent on functional cholesterol metabolism – may possibly be obstructed by treatment with cholesterol-lowering agents. This hypothesis stresses the need for a much more sophisticated approach to modelling risk of breast cancer molecular subtypes.

Potential future studies of statins in relation to breast cancer incidence should explore effects in an appropriately powered primary prevention trial amongst high-risk women. Such a trial would benefit from translational studies where the biological relevance of statins to prevent breast cancer is understood. To investigate the biological processes of statins as a primary preventive drug in experimental models have yet not been investigated in relevant models involving normal breast epithelial cells and stromal cells, which will be critical for understanding the potential role of statins in breast cancer initiation, and therefore primary prevention.

Statins and breast cancer prognosis

The U.S. National Cancer Institute estimated that there were over 2.7 million breast cancer survivors living in the United States in 2009 [57]. Statins are inexpensive and well-tolerated drugs, taken long term by about one-third of older US adults, so a beneficial effect of statins on breast cancer outcomes would have important public health impact. There is considerable evidence for a protective effect of statin use against recurrence amongst survivors of nonmetastatic breast cancer (Fig. 2). One study of about 2000 breast cancer survivors observed an imprecise protective association between statin use and recurrence (HR = 0.67, 95% CI: (0.39, 1.13) [58]. This association was measured with greater precision in a cohort of 18 769 Danish breast cancer survivors, in which statin users had a reduced rate of recurrence compared with never users (HR = 0.73, 95% CI: (0.60, 0.89) [59]. Since publication of these studies, 11 others have measured the association in a variety of source populations [60]. A systematic review and meta-analysis reported a summary relative risk associating statin use with breast cancer recurrence of 0.64 (95% CI: (0.53–0.79) [60]. Another meta-analysis showed that statin use was associated with lower breast cancer-specific mortality (lipophilic statins) and all-cause mortality (lipophilic and hydrophilic statins) [61]. A third meta-analysis of observational studies showed that postdiagnostic statin use was associated with lower cancer-specific mortality in breast cancer,

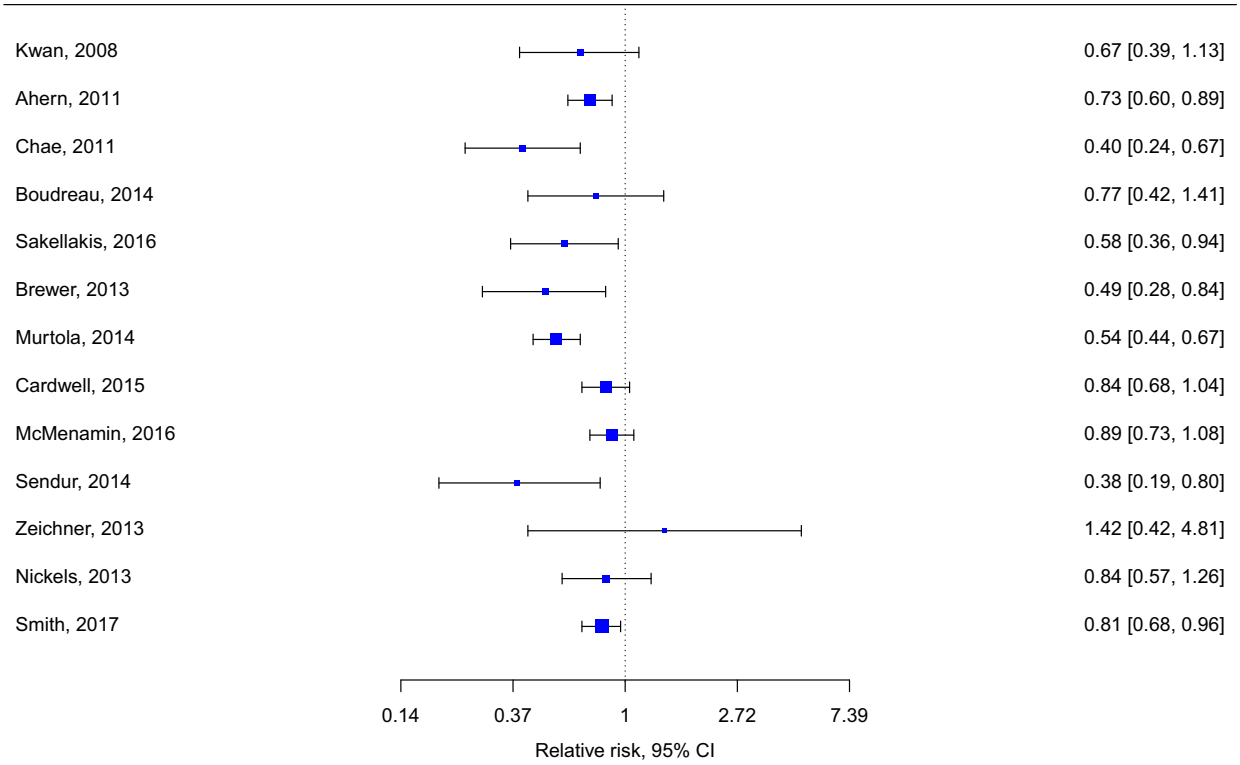

Fig. 2 *The prognostic value of statin treatment in the adjuvant breast cancer setting illustrated by a forest plot of the currently reported studies.*

and prediagnostic statin use was negatively associated with both all-cause and cancer-specific mortality [62].

Statins and response to endocrine therapy in breast cancer

Hypercholesterolemia is an established clinical side effect of aromatase inhibitor (AI) therapy. Given the revelations about the estrogenic cholesterol metabolite 27HC, this phenomenon may counteract the intended effects of AIs [33, 63]. Breast cancer patients experiencing hypercholesterolemia during AI treatment may thus benefit from concomitant cholesterol-lowering treatment to reduce the probability of 27HC-driven ER actions. Tamoxifen, on the other hand, reduces circulating cholesterol levels. The large-scale Breast International Group (BIG) 1–98 study examined the clinical efficacy of tamoxifen and AI, respectively, as adjuvant endocrine therapy. Within the BIG 1–98 study population, we investigated whether initiation of cholesterol-lowering medication (CLM) concomitantly with endocrine therapy in the adjuvant setting was related to prognosis. Initiation of CLM improved disease-free survival (HR = 0.79, 95% CI: (0.66–0.95), breast cancer-free interval (HR 0.76, 95% CI: (0.60–0.97) and distant-recurrence-free interval (HR 0.74, 95% CI: (0.56–0.97). We concluded that CLM during adjuvant endocrine treatment appears to have a favourable impact on clinical outcome in ER positive breast cancer [64]. The beneficial effects of concomitant CLM were apparent for both endocrine drug groups (AI and tamoxifen).

Since cholesterol forms the biochemical scaffold for all steroid hormones (*e.g.* oestradiol), it is likely to play a crucial role in hormone (oestrogen)-dependent breast cancer. Importantly, 27HC, the oxysterol produced from cholesterol, is involved in the regulation of intracellular cholesterol homeostasis [33], but also acts as an endogenous selective oestrogen receptor modulator capable of increasing the growth and metastasis of tumours [63]. Valuable clinical insight into the impact of statin treatment on 27HC in breast cancer patients was

gained through collaboration with the McDonnell Lab at Duke University [32], where biological samples from our "window-of-opportunity" statin trial [19, 28, 65] were analysed. This work demonstrated that statin therapy reduces 27HC in parallel with reductions in LDL cholesterol levels [32]. A significant up-regulation of tumour expression of CYP27A1, the enzyme responsible for the production of 27HC from cholesterol (Fig. 1), was, however, observed in breast tumours following statin therapy. Further investigation revealed noteworthy associations between CYP27A1 expression and adverse tumour characteristics and with poorer breast cancer prognosis in women 50 years and older (presumably postmenopausal women). The revelation that prognosis was worse for older women with high tumour CYP27A1 expression (and, presumably, high 27HC), is of relevance as these will be the breast cancer patients who are prescribed AI treatment; measures to address 27HC levels may improve outcomes for these women.

AIs have now been used in postmenopausal breast cancer treatment for more than a decade. However, updated knowledge on the interaction between endocrine treatment and obesity/hypercholesterolemia is needed to ensure that breast cancer patients with lipid-associated comorbidities, such as obesity and hypercholesterolemia, receive optimal endocrine treatment.

Predictive factors for statin response in breast cancer

The well-characterized molecular and clinical heterogeneity of breast cancer warrants that for every novel drug showing efficacy against this disease, specific treatment predictive biomarkers should be identified to enable the precise selection and treatment of only those patients who may derive clinical benefit from the treatment. As such, the search for statin treatment predictive markers in breast cancer has been the subject of many studies (Table 2). HMGCR has been shown to be overexpressed in about 80% of breast tumours, and its expression is correlated with less aggressive tumour phenotype and longer recurrence-free survival [25–27]. In the aforementioned clinical phase II trial when 50 breast cancer patients were treated preoperatively with 80 mg day^{-1} atorvastatin for 2 weeks, tumour levels of Ki67 (a proliferation marker) decreased from presurgical biopsy to resected tumour only if the tumour expressed HMGCR [28, 65], suggesting a predictive role for HMGCR for efficacy of statin treatment in breast cancer. HMGCR was not only differentially expressed across tumours from breast cancer patients, but was also associated with improved prognosis amongst ER-positive breast cancer patients, whereas ER-negative patients seemed to have better outcomes when HMGCR was absent [25, 26]. Several other mevalonate pathway biomarkers have been associated with breast tumour response to statins *in vitro* and in animal models. However, no study has comprehensively evaluated the network comprised of these individual factors, and how it is perturbed by statin exposure to alter recurrence risk. Randomized trials are now warranted to clarify the potential beneficial effects of statins in breast cancer management in the adjuvant and metastatic setting. In October 2016, the first trial with statins in metastatic breast cancer was launched, with the hypothesis that HMGCR expression will identify tumours that will respond to statin treatment (ClinicalTrials.gov Identifier: NCT02958852).

Exploring transcription profiles associated with breast cancer sensitivity to statin treatment is another method that has been explored to discover genes or gene signatures that are predictive of statin treatment sensitivity. In one such study based on *in vitro* experiments with atorvastatin in a collection of breast cancer cell lines, we aimed to uncover transcriptional differences associated with statin response in breast cancer [19, 65]. The strongest discriminants between the breast cancer cells associated with statin sensitivity at the transcriptional level were the expression of the oestrogen receptor and a gene set enriched for genes involved in the cholesterol biosynthesis pathway. Following statin treatment, the less-sensitive cells exhibited the classical response of up-regulating the expression of genes in the cholesterol biosynthesis pathway *via* the normal negative feedback loop resulting from the statin-induced inhibition of HMGCR. This classical response was, however, weaker in the sensitive cells, suggesting that these cells may possess an inherent defect in this pathway. This cholesterol biosynthesis gene set showed potential for identifying tumours that experience reduced proliferation upon statin treatment, albeit in a small cohort of patients. Further studies using similar and more advanced approaches are necessary to identify robust biomarkers for identifying patients most likely to derive benefit from the addition of cholesterol-

Table 2 *Candidate predictive biomarkers linking statin exposure to breast cancer recurrence risk*

Candidate biomarker	Prevalence	Univariate hypothesis	Reference
SLCO1B1 rs4149056 variant	0.15	Statin-treated breast cancer survivors who carry the variant allele will have a lower rate of breast cancer recurrence compared with statin-treated survivors who carry the normal allele	Ahern *et al.* [8]
HMG-CoA reductase expression	0.75	Statin-treated breast cancer survivors whose primary tumours express high levels of HMG-CoAR will have a lower rate of breast cancer recurrence than statin treated survivors whose tumours express little or no HMG-CoAR	Borgquist *et al.* [26]
YAP/TAZ expression	0.9	Statin-treated breast cancer survivors whose primary tumours exhibit positive nuclear YAP/TAZ staining will have a lower rate of breast cancer recurrence than statin-treated survivors whose tumours do not exhibit nuclear YAP/TAZ staining	Sorrentino *et al.* [22]
CYP3A4 rs35599367 and *CYP3A5* rs776746variants	0.02 0.31	Statin-treated breast cancer survivors who carry at least one of the CYP3A4/5 variants will have a lower rate of breast cancer recurrence than statin-treated survivors who are homozygous wild type at both loci	Ahern *et al.* [8]
ABCB1 rs2032582 variant	0.45	Statin-treated breast cancer survivors who carry at least one variant allele will have a lower rate of breast cancer recurrence than statin-treated survivors who carry only wild-type alleles	Fiegenbaum *et al.* [71]
DDX20 expression	0.80	Statin-treated breast cancer survivors whose tumours express high levels of DDX20 will have a lower rate of breast cancer recurrence than statin-treated survivors whose tumours express little or no DDX20	Shin *et al.* [72]
LDL receptor expression	0.75	Statin-treated breast cancer survivors whose tumours express high levels of LDL receptor will have a lower rate of breast cancer recurrence than statin-treated survivors whose tumours express little or no LDL receptor	Liu *et al.* [73]

Table 2 (*Continued*)

Candidate biomarker	Prevalence	Univariate hypothesis	Reference
Mutant p53	0.30	Statin-treated breast cancer survivors whose primary tumours express mutant p53 will have a lower rate of breast cancer recurrence than statin-treated survivors whose tumours do not express mutant p53	Freed-Pastor *et al.* [20]
"Cholesterol biosynthesis signature"	0.70	Breast cancer survivors whose primary tumours show low activity of the "cholesterol biosynthesis signature" and receive adjuvant statin treatment will have a lower rate of breast cancer recurrence compared with nonstatin treated or survivors whose tumours have a high "cholesterol biosynthesis signature" activity	Kimbung *et al.* [19]
EMT-associated genes (VIM, CDH1, ZEB1, FN1, and CDH2)	0.88	Statin-treated breast cancer survivors whose tumours express high levels of EMT-associated genes will have a lower rate of breast cancer recurrence than statin-treated survivors with lower EMT-associated genes expressing tumours	Yu *et al.* [74]

lowering medications to their therapeutic regimen for controlling breast cancer.

Clinical breast cancer trials with statins

The number of trials assessing the putative clinical benefit of statins in breast cancer is increasing. A total of 30 trials were listed at the global trial identifier website clinicaltrials.gov at the time of this writing (February 23, 2018). Of these, eight trials are currently recruiting; another two trials are active but not yet recruiting, and nine trials are already complete. The remaining trials have either been withdrawn, are not yet active or were terminated for other reasons (*e.g.* slow accrual). Many of the trials include a translational protocol, reflecting the understanding that the success of novel therapies requires molecular prediction of treatment efficacy. Given the compelling evidence from several trials in a variety of clinical settings, there have been calls for a clinical trial of statins in the adjuvant breast cancer setting [8, 66]. It would be imperative for such a trial to incorporate tumour biomarkers predictive of statin response in its design and analysis plan.

Concluding remarks

Taken together, obesity-associated metabolic disorders such as hypercholesterolemia can have a negative impact on the prognosis of breast cancer patients. This may in particular be of importance in the endocrine treatment setting. Future research activities should evaluate the interplay between host factors (*e.g.* obesity/hypercholesterolemia), treatment factors (*e.g.* statin therapy) and breast cancer progression. If such studies detect a group of patients with less expected clinical efficacy of the standard endocrine drug of choice, this may impact future clinical guidelines for the purpose of improved clinical outcome amongst breast cancer patients. Advanced understanding of the molecular mechanisms of breast cancer response to common prescription drugs such as statins stands to increase the effectiveness with which we treat breast cancer and lead to the development of

new therapies with specific actions against up-regulated molecular pathways.

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Conflicts of interest statement

All authors declare to have no relevant conflict of interest.

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