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Statins and breast cancer prognosis: evidence and opportunities

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SUMMARY

Much preclinical and epidemiologic evidence supports anticancer effects of HMG-CoA reductase inhibitors (statins). Epidemiologic evidence does not support an association between statin use and reduced breast cancer *incidence*, but does support a protective effect of statins—particularly simvastatin—on breast cancer prognosis. We argue that the current evidence base is sufficient to justify a clinical trial of breast cancer adjuvant therapy with statins. We advocate for such a trial to be initiated without delay. If a protective effect of statins on breast cancer recurrence is supported by trial evidence, then the indications for a safe, well-tolerated, and in expensive treatment can be expanded to improve outcomes for breast cancer survivors. We discuss several design

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CONTRIBUTORS

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CONFLICTS OF INTEREST

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opportunities—including candidate predictive biomarkers of statin safety and efficacy—and offer solutions to key challenges to enrolment, follow-up, and analysis of such a trial.

INTRODUCTION

Many *in vitro* and animal studies suggest that statin drugs suppress breast cancer progression. In human subjects, little evidence supports a protective effect of statins on breast cancer *incidence*, but consistent evidence supports a protective effect on disease *recurrence*. The case for adjuvant breast cancer therapy with statins is unlikely to be advanced by new observational epidemiology studies, so now requires evidence from a randomised trial. Our purposes herein are to provide a review of statin pharmacology, summarize the evidence for statin effects on breast cancer incidence and recurrence, describe why a clinical trial is the next necessary step, and evaluate key challenges and design opportunities germane to such a trial.

STATIN PHARMACOLOGY

Statins were discovered in 1976 with the isolation of mevastatin from *Penicillium* fungus.¹ Several analogues were later marketed (Table 1), all of which lower LDL cholesterol (LDL-C) concentrations in blood by inhibiting hydroxymethylglutaryl-coenzyme A reductase (HMGCoAR). HMGCoAR catalyses the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonic acid, the rate-limiting step in the mevalonate pathway that ultimately yields cholesterol (Figure 1).² Statins bind to the active site of HMGCoAR with approximately 1,000-fold greater affinity than HMG-CoA itself, resulting in strong competitive inhibition of the enzyme and arrested production of downstream compounds.² In addition to LDL-C, these compounds include farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP), which we discuss below.

All statins are administered orally, where upon 30 to 85% of the ingested dose is absorbed. The absorbed fraction undergoes extensive first-pass hepatic uptake, mediated by the organic anion transport protein 1B1 (OATP1B1).^{2,3} Simvastatin and lovastatin are administered as lactones, requiring *in vivo* hydrolysis by non-specific carboxyesterases to active beta-hydroxy acids; all other statins are administered in the active form.⁴

Bioavailabilities range between 5% and 75% for the various statin compounds (Table 1). With the exception of pravastatin (which undergoes sulphation), biotransformation occurs through cytochrome P450-mediated oxidation reactions, in which the polymorphic *CYP3A4* and *CYP2C9* enzymes play dominant roles (Table 1). More than 90% of circulating statins are protein-bound except for pravastatin, which is ~50% protein-bound (Table 1). Figure 2 illustrates the disposition of statins, using simvastatin as an example.

Statin drugs differ from one another in several important ways that might impact the degree to which they exert antineoplastic effects. Past studies have focused on differences in solubility, classifying statins dichotomously into hydrophilic and lipophilic varieties. This classification may be an over simplification given the continuum of relative organic/aqueous solubility values reported for each drug (Table 1). Moreover, two measures of relative solubility can be employed for this purpose. The distribution coefficient (logD) measures

relative concentrations of ionized and un-ionized species in organic and aqueous phases, and is therefore pH-dependent. The partition coefficient (logP) accounts only for the un-ionized form of the drug. Table 1 shows that solubility ranking by logD at physiologic pH would produce a different ordered list of statins than solubility ranking by logP. Furthermore, neither of these measures accounts for the potency or effectiveness of the corresponding drugs. The more hydrophilic statins are largely confined to the liver, whereas the more lipophilic compounds readily permeate extrahepatic tissues.⁵ Lipophilic statins are therefore hypothesized to have the greatest potential to exert pleiotropic effects—that is, extrahepatic effects on endpoints other than LDL-C lowering.

STATIN PLEIOTROPY

Statins have proved effective for the primary and secondary prevention of coronary heart disease (CHD);⁶ recent evidence indicates a host of other statin effects that may be independent of LDL-C. The best-characterized of these pleiotropic effects concern vascular health (e.g., reduced thrombogenesis, atherosclerotic plaque stabilization, and improved endothelial function),⁷ but more recent studies have reported beneficial effects on the immune and skeletal systems and on the primary and secondary prevention of cancer.^{8,9} Statins are relatively safe, well-tolerated, and inexpensive. A proven preventive effect of statins on breast cancer recurrence would yield a cost-effective, low-toxicity option for adjuvant therapy that could be made available to breast cancer survivors in the very near term.

Putative anti cancer mechanisms of statins parse into the following categories: (1) inhibition of proliferation by systemic cholesterol reduction, (2) stimulation of anti-tumour immune surveillance, (3) inhibition of tumour-associated HMGC_oAR activity, and (4) interruption of oncogenic signalling by prenylation-dependent proteins.^{10–14} A 2011 Mendelian randomisation study did not support the hypothesized anticancer effect of systemic cholesterol reduction.¹⁵ However, a recent preclinical study implicated 27-hydroxycholesterol—a cholesterol metabolite whose plasma concentration correlates with that of total cholesterol—in breast tumour promotion through ER stimulation.¹⁶

Cholesterol-independent mechanisms involve the depletion of FPP and GGPP, two intermediate compounds in the mevalonate pathway (Figure 1). FPP is an isoprenoid produced from mevalonate, and is the starting material for synthesis of both cholesterol and GGPP (Figure 1). FPP and GGPP post-translationally prenylate multiple proteins to ensure their proper intracellular localization and function.¹⁷ Notably, members of the RAS oncogene superfamily depend upon prenylation for successful placement in the plasma membrane.¹⁸ Reduced prenylation is also central to the immunomodulatory effects of statins, which can result in both suppressed inflammation (preventing formation of a cancer-promoting milieu of growth factors and cytokines) and an enhanced anti-tumour response from both the innate and adaptive arms of the immune system.^{11,19} Disrupting protein prenylation through FPP and GGPP depletion is therefore an attractive chemoprevention tactic.¹⁸

THE ANTICANCER POTENTIAL OF STATINS: PRECLINICAL EVIDENCE

Preclinical studies have employed a variety of breast cancer cell lines and animal models to better understand the mechanisms linking mevalonate inhibition to anticancer effects. These studies consistently report anti-tumour effects of lipophilic statins. Simvastatin inhibits DNA binding of the NF-kappa-B transcription factor, reduces expression of the anti-apoptotic protein bcl-xL and increases transcription of phosphatase and tensin homolog (PTEN), which represses the oncogenic phosphatidylinositol-3-kinase (PI3K) pathway.²⁰ Furthermore, oral simvastatin impairs growth of human breast tumour xenografts in mice by increasing PTEN expression and inducing apoptosis.²⁰ Lipophilic statins, but not the hydrophilic pravastatin, reduce breast cancer cell proliferation by deactivating NF-kappa-B and the AP-1 transcription factor, especially in cell lines with constitutively active RAS or overexpressed HER2.²¹ A number of other studies report statin-mediated attenuation of PI3K signalling and deactivation of NF-kappa-B; some directly implicate delocalization of prenylated GTPases in the anti-tumour effect.^{22–25} Simvastatin also directly induces apoptosis in breast cancer cells by activating the JNK/CHOP/DR5 pathway.²⁶

STATINS AND BREAST CANCER PREVENTION

Despite compelling preclinical evidence for anticancer statin effects, epidemiologic findings are inconsistent with respect to the association between statin use and breast cancer prevention. Epidemiologic evidence for an association between statin use and breast cancer incidence comes from both observational and experimental studies, though it is important to note that none of the randomised statin trials was designed with breast cancer incidence as the primary endpoint.²⁷ Several meta-analyses of the association between statin use and cancer incidence have been published,^{6,28–33} only two of which focused on breast cancer.^{28,33} Bonovas and colleagues analysed data from 7 randomised trials and 9 observational studies, with a total of 7,858 breast cancer cases. The summary relative risk showed no association between statin use and breast cancer incidence over an average follow-up of ~5 years (RR = 1.02, 95% CI: 0.89, 1.18).²⁸ Undela and colleagues analysed data from 24 observational studies with 76,759 total breast cancer cases, and also saw no association (RR = 0.99, 95% CI: 0.94, 1.04).³³ The remaining meta-analyses reported null associations between statin use and breast cancer risk, even when stratified by statin type and study design.^{6,29–32}

Few studies have captured the effect of long-term statin use on breast cancer incidence. The meta-analysis by Undela and colleagues included a long-term statin exposure category, but the actual duration of exposure in the individual studies was quite variable, ranging from 3 years up to 10 years. Although the association with long-term use remained null in the meta-analysis (RR = 1.03, 95% CI: 0.96, 1.11),³³ the individual study with the longest duration of statin use (> 10 years) reported an imprecisely measured 20% reduced risk of breast cancer (RR = 0.8, 95% CI: 0.5, 1.4).³⁴ In contrast, a recent study that assessed long-term statin use (> 10 years) showed a positive association with both invasive lobular and ductal carcinoma (OR = 1.97, 95% CI: 1.25, 3.12; and OR = 1.83, 95% CI: 1.14, 2.93, respectively).³⁵ The increased risk was limited to individuals who used lipophilic statins for 10 years, and was driven by use of atorvastatin.³⁵

STATINS AND BREAST CANCER PROGNOSIS

Several of the primary preventive mechanisms described above are also relevant to secondary prevention, and additional mechanisms have been proposed by which statins may directly improve breast cancer prognosis. In a perioperative trial, high-dose (80 mg/day) neoadjuvant fluvastatin therapy, compared with low-dose therapy (20 mg/day), reduced breast tumour proliferation and increased the rate of apoptosis.³⁶ These markers of prognosis were compared between biopsy and subsequent excision specimens in women with DCIS or stage I breast cancer, and changes were particularly apparent in high grade tumours. A similar trial observed a reduction in Ki67-measured proliferation rate associated with two weeks of atorvastatin at 80 mg/day, limited to the breast tumours that expressed HMGC α R.³⁷ While it is reasonable to expect that an anti-tumour benefit of statin therapy would be limited to tumours expressing HMGC α R, it is also important to realize that HMGC α R expression was associated with small tumour diameter, lower histologic grade, ER α and ER β expression, and lower baseline proliferation rate.³⁸

As a second possible mechanism, *in vitro* and in murine xenografts, simvastatin stimulated production of a variant of the p53 transcription factor and diminished the potential to form bone metastases.³⁹ This mechanism motivated the hypothesis that an effect may be limited to protection against metastases to bone, the most common site of breast cancer metastasis. Other evidence implicates the p53 pathway. A 3-dimensional breast cancer cell culture model showed that mutant p53 up-regulated the mevalonate pathway to induce an invasive phenotype.⁴⁰ Addition of simvastatin to the culture medium caused reversion to normal morphology, while the malignant phenotype persisted when both simvastatin and GGPP were present in the medium.⁴⁰

Epidemiologic evidence of the association between statin use and breast cancer prognosis is scarce, and the hypothesis that statin therapy reduces the risk of breast cancer recurrence has never been subjected to a randomised clinical trial. We restrict our manuscript to statins' association with the prognosis of invasive breast carcinoma. One study has evaluated statins' association with inflammatory breast cancer prognosis.⁴¹

The initial report of a protective effect of statin use came from a U.S. cohort,⁴² in which the adjusted hazard ratio associating statin use with risk of recurrence equalled 0.67 (95% CI: 0.39, 1.13). Follow-up for an average of five years began approximately two years after breast cancer diagnosis, and data on medication use came from the pharmacy records of the Kaiser Permanente health plan. Ninety-eight percent of statin prescriptions were for lipophilic statins (84% lovastatin), and statin use was initiated after diagnosis, with an average exposure duration of two years over the follow-up period. Recurrences were verified by medical record review.

A second, much larger, cohort study of Danish breast cancer patients yielded very similar results. The adjusted hazard ratio associating use of simvastatin with recurrence equalled 0.70 (95% CI: 0.57, 0.86).⁴³ Breast cancer patients were followed from diagnosis for up to ten years (median = 6.8 years). Data on prescriptions came from the national prescription registry, and data on recurrences were registered with high validity^{44,45} by the Danish Breast

Cancer Cooperative Group (DBCG). The protective association was limited to users of lipophilic statins, 92% of whom took simvastatin. The study was large enough to examine effect modification by site of recurrence. The plurality of events (33%) were metastases to bone, for which there was no strong protective association with use of simvastatin, contrary to preclinical findings³⁹ (HR = 0.91; 95% CI: 0.65, 1.3). The protective association was more uniformly observed for ipsilateral and contralateral breast recurrences, and regional lymph node recurrences, and was slightly stronger among ER-positive cases.⁴³

In a retrospective cohort of 703 stage II/III breast cancer patients diagnosed at a single U.S. medical centre between 1999 and 2005, use of any statin for ≥ 6 months was associated with a lower recurrence rate (adjusted HR = 0.48; 95% CI: 0.28, 0.82).⁴⁶ Atorvastatin represented 60% of statin prescriptions in this cohort, and simvastatin was the next-most prevalent drug (17%). The stronger protective association reported by this study is likely an exaggeration resulting from inclusion of immortal person-time in the rate denominator for statin-exposed subjects.^{47,48}

The authors of a German study of 3,024 non-metastatic breast cancer cases diagnosed between 2001 and 2005 reported a lower breast cancer recurrence rate in users of lipid-lowering medications (HR = 0.83, 95% CI: 0.54, 1.24), which is consistent with the earlier findings.⁴⁹ Key limitations of this study—which could readily account for its nearer-null association—include the investigators' inability to isolate statin exposure from other antilipidaemic exposures, and their inclusion of former users in the unexposed comparison group.

Most recently the association was measured in a U.S. cohort of 4,216 women who were diagnosed with stage I or II breast cancer while enrolled in the Group Health healthcare delivery system. Post-diagnosis use of lipophilic statins was associated with a lower rate of breast cancer recurrence (HR = 0.76, 95% CI: 0.54, 1.05), but use of hydrophilic statins was not (HR = 1.01, 95% CI: 0.37, 2.76).⁵⁰

No study of the association between statin use and breast cancer recurrence has stratified by the primary tumour's expression of HMGC α R, which correlates with favourable prognostic markers. In a study of the association between breast tumour HMGC α R expression and recurrence-free survival conducted among patients diagnosed between 1988–1992 when statin prescriptions were rare, breast cancer patients whose tumours expressed HMGC α R had a lower rate of recurrence than those whose tumours did not express HMGC α R, even after adjustment for other prognostic markers (HR = 0.64, 95% CI: 0.43, 0.94).¹³ This protective association was limited to the women whose tumours also expressed ER α (HR = 0.47, 95% CI: 0.30, 0.73). A subsequent study, also conducted in the pre-statin era, replicated these results and extended them to show that tamoxifen was more effective in women with ER α -positive tumours that also expressed HMGC α R.⁵¹

A CLINICAL TRIAL OF ADJUVANT BREAST CANCER THERAPY WITH STATINS: JUSTIFICATION AND DESIGN ISSUES

We are not the first to advocate for a clinical trial of statins in the breast cancer adjuvant setting.^{52,53} Such a trial is not only overdue, but is one of the few remaining options to substantially improve the human evidence concerning this treatment question. Typically, a large body of preclinical data would be backed by numerous replicative observational studies demonstrating consistent associations in different populations. Presently, five observational studies support a protective effect of statins on breast cancer recurrence,^{42,43,46,49,50} and these are reinforced by experimental studies of statin effects on breast tumour biomarkers.^{36,37} The largest epidemiologic study of the association to date was nested in a nationwide Danish source population, from which more than 18,000 survivors were enrolled and followed for recurrence using the DBCG registry. Tumour, treatment, and follow-up data in this registry were of the quality typically achieved by clinical trials,^{44,45} and the near-complete enrolment of breast cancer cases from the source population minimized the possibility of selection bias. We are not aware of another epidemiologic resource than can substantially improve upon the DBCG cohort with respect to its size, lack of selection, data quality, and drug exposure detail. While new observational evidence would be welcome—particularly studies addressing breast cancer-specific mortality or the candidate predictive biomarkers discussed below—postponing a trial to await such evidence is unlikely to be a rewarding strategy.

A future trial of statins in the breast cancer adjuvant setting will face a number of design challenges including choice and dose of statin intervention, which predictive biomarkers to evaluate or incorporate into the randomisation scheme, and how to address prevalent and incident hypercholesterolemia among trial enrollees.

Choice of statin for the treatment arm

Current evidence indicates that simvastatin, one of the most lipophilic statins, would be the best candidate for the treatment arm.^{20,26,39,42,43,54} Although simvastatin is associated with incident myopathies (including rhabdomyolysis), the elevated risk is most pronounced with high-dose treatment (80 mg/day), which would be unnecessary in an adjuvant breast cancer trial.⁵⁵ All statins are associated with myopathy, so selecting another drug would not avoid these events in the intervention group.⁵⁶ Selecting another drug would also ignore the fact that most evidence for a statin effect on breast cancer recurrence comes from largely simvastatin-treated women. In order to improve the objectivity of drug selection, we propose the use of a novel quantity that we call the “pleiotropic potential” which was inspired by the lipophilic efficiency (LipE) parameter.⁵⁷ LipE is the difference between a compound's pIC_{50} value (the negative logarithm of the IC_{50} in molar units) and its log partition or distribution coefficient (logP or logD). This quantity assists medicinal chemists in selecting high-potency drug candidates that are no more lipophilic than necessary, since excessive lipid solubility usually conveys higher toxicity risk. In the context of pharmaceutical development, a large LipE value is a desirable trait for a drug candidate. However, it stands to reason that harnessing statins for breast cancer recurrence prevention would require both high potency and high lipid solubility. In Table 1 we report values of the pleiotropic

potential for each statin, calculated as the sum of the compound's pIC^{50} and $\log P$. Ranking compounds based on their pleiotropic potentials suggests that simvastatin, in addition to being the top choice based on epidemiologic evidence, would also be the best intervention from a pharmacokinetic perspective. These arguments for simvastatin efficacy in a breast cancer adjuvant trial outweigh ethical concerns over rare myopathies that are associated with an unnecessarily high dose of the drug.

As with any trial, anticipated side-effects require active follow-up and scrutiny by a Data and Safety Monitoring Board, with pre-specified stopping rules. In addition to myopathies, a statin trial should collect data on adverse events related to immunosuppression and insulin resistance,^{58–60} which may include incident infectious diseases, second primary cancers, changes in fasting insulin levels from baseline, and failure of glucose tolerance tests.

Candidate predictive biomarkers of simvastatin safety and efficacy

Simvastatin is actively transported into hepatocytes by the OATP1B1 transporter (Figure 2), which is encoded by the *SLCO1B1* gene. Single nucleotide polymorphisms (SNPs) in *SLCO1B1* reduce expression or activity of the transporter, causing increased extrahepatic simvastatin concentrations. The rs4149056 variant [minor allele frequency (MAF) = 12.3%]⁶¹ results in a 221% increase in simvastatin area under the curve (AUC) comparing homozygous variant individuals with homozygous wild-types.⁶² While this increased extrahepatic exposure may potentiate an anticancer effect of simvastatin, it is also associated with increased myopathy risk as a function of simvastatin dose. At 40 mg/day, myopathy risk in simvastatin users is increased 2.6-fold for each additional minor allele; at 80 mg/day, the risk is increased 4.5-fold for each additional minor allele.^{4,63} There is no published evidence of similar *SLCO1B1* variant associations among users of low-dose simvastatin (20 mg/day). Carriers of rs4149056 variant alleles are therefore at increased risk of simvastatin toxicity and might warrant exclusion from a trial, due to both ethical concerns and their greater propensity to disenroll. However, greater extra hepatic simvastatin levels might also make carriers most likely to experience a prognostic benefit from simvastatin treatment, in which case exclusion from the trial would be unethical. The trade off between increased myopathy risk and greater treatment benefit could be managed by periodically assessing creatinine kinase levels of women in the intervention arm. Secondary analyses should then assess modification of the simvastatin effect by rs4149056 genotype.

While they are unique isoforms, CYP3A4 and CYP3A5 (CYP3A4/5) share substantial amino acid sequence homology and metabolize many common substrates.^{64–66} Simvastatin is among these substrates, requiring oxidation by CYP3A4/5 for its subsequent elimination (Figure 2). Two SNPs, rs35599367 in *CYP3A4* and rs776746 in *CYP3A5*, impair CYP3A4/5 activity or expression and consequently reduce simvastatin clearance. Carriers of the rs35599367 variant (MAF = 2.2%)⁶⁷ had a stronger lipid-lowering response to simvastatin therapy,^{65,68} but this variant is relatively rare and its association with myopathy risk has not been studied. The rs776746 variant (MAF = 31.2%)⁶⁷ is associated with reduced simvastatin clearance and increased AUC,⁶⁹ but reports disagree about its effect on lipid-lowering response to statins. One study showed greater lipid reduction among carriers of the rs776746 variant allele compared with wild-type,⁷⁰ while another showed no difference between

groups.⁷¹ There is no evidence of increased myalgia risk in carriers of the rs776746 variant.⁷¹ Because current evidence does not suggest a predictive role for these CYP3A4/5 biomarkers in the safety and tolerability of simvastatin therapy, we recommend that they be genotyped only for evaluation as predictive biomarkers in secondary analyses.

As discussed above, joint tumour expression of HMGCoAR and ER α has potential as a predictive biomarker in this setting, and we recommend including HMGCoAR/ER α status as a stratification variable in the randomisation scheme.⁷² Leaving these biomarkers to a post-hoc trial-nested observational study would reduce the precision of stratum-specific association estimates. Related to HMGCoAR expression, assessment of mutant p53 status of the tumour may predict statin response. However, it is unclear whether assessment of mutant p53 expression would add predictive value beyond assessment of HMGCoAR expression.

Evaluation of neoadjuvant statin treatment

Based on supporting evidence from two perioperative studies,^{36,37} we recommend that future trials incorporate neo-adjuvant statin therapy—either as a uniform treatment for all enrollees before randomisation, or as a fully randomised component. Randomising to neo-adjuvant simvastatin or placebo would require a larger enrolment, since subsequent randomisation to adjuvant simvastatin or placebo should be stratified by neo-adjuvant exposure. While this approach requires a larger investment of resources, it permits evaluation of interaction between neo-adjuvant and adjuvant statin therapy, and guards against the possibility that uniform neo-adjuvant treatment would obscure the contrast in recurrence rates between adjuvant treatment arms.

Enrolment and crossover concerns

A further design issue concerns the management of prevalent and incident hypercholesterolemia in the enrolment and follow-up of trial participants. We propose enrolment of breast cancer survivors with LDL-C levels at baseline below <160 mg/dL, who have never been prescribed an antilipidaemic drug, and who are not presently taking a drug for which simvastatin co-prescription is contraindicated (e.g., amiodarone, amlodipine, diltiazem, and verapamil).⁴

After randomisation to statin or placebo, some trial participants will likely discontinue their assigned regimen over long-term recurrence follow-up (e.g., 10 years). Some women in the intervention arm may not tolerate simvastatin therapy and—depending upon their medical indications—will either discontinue statin therapy altogether or switch to a different statin. Some women in the placebo arm may develop indications for statin therapy and go off-protocol to receive that therapy. Such departures from study protocol are common in long-term trials, and can result in post-randomisation confounding. Furthermore, dropout over a lengthy follow-up period can cause selection bias if the propensity to disenroll is a function of both treatment and prognostic factors.⁷³ Confounding is normally addressed by conducting an intent-to-treat (ITT) analysis, classifying exposure according to protocol assignment and preserving the expected baseline balance in confounders. ITT analysis therefore trades a confounded estimate for one that is likely attenuated by exposure

misclassification, perhaps residually confounded by post-randomisation covariate changes, and possibly distorted by selection bias.⁷⁴

We recommend confronting these realities by randomising eligible women to either (1) simvastatin treatment or (2) placebo until statin therapy becomes medically indicated. Under this design, women in the placebo arm who must commence statin therapy for hyperlipidaemia would remain compliant with trial protocol, and the measured effect would contrast compulsory simvastatin treatment with standard-of-care treatment in breast cancer survivors. The trial should collect longitudinal data on treatment, confounders, and prognostic factors after randomisation. These data would permit the application of inverse-probability weighting and/or g-estimation methods to estimate effects adjusted for exposure crossover, post-randomisation confounding, and selection bias.^{74,75}

CONCLUSION

Statins—particularly simvastatin—may reduce the risk of breast cancer recurrence. It is unlikely that new preclinical and observational studies will substantially advance the evidence base that currently supports launching a clinical trial of breast cancer adjuvant therapy with statins. Such a trial should be conducted without delay, and should directly address candidate biomarkers that could identify factors predictive of response to adjuvant statin therapy.

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SEARCH STRATEGY AND SELECTION CRITERIA

Published works relevant to this Personal View were identified by searching the PubMed database with the string “((hmgcoa reductase inhibitors [MeSH Terms]) OR statin [Text Word]) AND breast neoplasms”. Papers indexed through mid-December 2013 were considered, and no language restriction was applied. Papers most relevant to our discussion points were selected for inclusion. Other papers of interest were identified by reviewing the reference lists of selected papers and, in some cases, searching for citing articles using the Thomson Reuters Web of Science database.

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FIGURE 1.

Statins interrupt the enzymatic reduction of HMG-CoA to mevalonate. This prevents synthesis of cholesterol and two isoprenoids, farnesyl-PP and geranylgeranyl-PP, which post-translationally modify oncogenic proteins. Dashed arrows represent multi-step transitions.

FIGURE 2.

Disposition of simvastatin. Simvastatin lactone (SVL) is absorbed and hydrolysed to simvastatin acid (SVA). SVA enters hepatocytes *via* OATP1B1. Reactions catalysed by CYP3A4/5 yield oxidized compounds (SVOx), which are eliminated.

FIGURE 3.

Published associations between statin use and breast cancer recurrence. Diamonds represent recurrence rate ratio point estimates; grey boxes are proportional to inverse-variance weights. Error lines represent 95% confidence intervals.

Chemical and pharmacological properties of the statins.

Table 1

Lipid solubility									
Origin	Drug name	logD (pH 7.4) ^b	logP ^c	Potency (IC ₅₀), nM ^c	Lipophilic efficiency	Pleiotropic potential	Bioavailability (%) ^d	Percent protein bound ^e	Major metabolic pathway ^g
Natural	Lovastatin	4.1 ^e	4.3	2.7 to 11.1	3.9 [*]	12.5 [*]	5	95	CYP3A4
	Pravastatin	-0.75 to -1.00	-0.2	44.1	7.6	7.2	18	48	Sulfation
	Simvastatin	1.50 to 1.75	4.7	11.2	3.3	12.7	5	95	CYP3A4
Synthetic	Atorvastatin	1.00 to 1.25	4.1	8.2	4.0	12.2	12	>98	CYP3A4
	Cerivastatin ^a	1.50 to 1.75	1.5	10.0	6.5	9.5	60	>99	CYP3A4 ^h
	Fluvastatin	1.00 to 1.25	3.2	27.6	4.4	10.8	10 to 35 ^c	>99	CYP2C9
	Pitavastatin	-1.2 ^e	1.5	6.8 ^c	6.7	9.7	60 ^c	>99	CYP2C9 ⁱ
	Rosuvastatin	-0.33 ^f	-0.3	5.4	8.6	8.0	75 ^c	90	CYP2C9

logD: Distribution constant at pH 7.4; equal to the base 10 logarithm of the ratio of total (ionized + un-ionized) solute concentration in octanol to total solute concentration in water buffered to normal plasma pH.

logP: Partition constant; equal to the base 10 logarithm of the ratio of unionized solute concentration in octanol to unionized solute concentration in water.

Lipophilic efficiency = pIC₅₀ - logP; where pIC₅₀ = -log10(IC₅₀.mol/L)

Pleiotropic potential = pIC₅₀ + logP

^{*} Calculated using the midpoint value of 6.9 for the range of IC₅₀ values.

^a Withdrawn from the market.

^b White CM. A review of the pharmacologic and pharmacokinetic aspects of rosuvastatin. Journal of Clinical Pharmacology. 2002;42(9):963-970. (Unless other citation given.)

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^e ACD predicted values reported by www.chemspider.com.

^f Olsson AG et al. Rosuvastatin: a highly effective new HMG-CoA reductase inhibitor. Cardiovascular Drug Reviews. 2002; 20(4): 303-328.

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