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ACTA ONCOLOGICA: Review paper for DBCG 40-year anniversary

Concurrent new drug prescriptions and prognosis of early breast cancer: Studies using the Danish Breast Cancer Group clinical database

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Abstract

Myriad reports suggest that frequently used prescription drugs alter the viability of breast cancer cells in pre-clinical studies. Routine use of these drugs therefore may impact breast cancer prognosis, and could have important implications for public health. The Danish Breast Cancer Group (DBCG) clinical database provides high quality prospectively collected data on breast cancer diagnosis, treatment, and routine follow-up for breast cancer recurrence. Individual-level linkage of DBCG data to other population-based and medical registries in Denmark, including the Danish National Prescription Registry, has facilitated large population-based pharmacoepidemiology studies. A unique advantage of using DBCG data for such studies is the ability to investigate the association of drugs with a cancer-specific outcome (breast cancer recurrence) rather than breast cancer mortality—which may be misclassified—or all-cause mortality. Here we summarize findings from pharmacoepidemiological studies, based on DBCG data, on the association between routinely used prescription drugs and risk of breast cancer recurrence. Our findings suggest that concurrent use of glucocorticoids, ACE inhibitors, aspirin, NSAIDs, selective COX-2 inhibitors, digoxin, and opioids has little impact on breast cancer recurrence. Similarly, patients who use SSRIs concurrently with tamoxifen treatment are not at increased risk of recurrence. In contrast, post-diagnostic use of simvastatin, a lipophilic statin, correlates with a decreased risk of breast cancer recurrence, providing a rationale for a prospective randomized clinical trial investigating simvastatin as an adjuvant therapy for breast cancer. As a whole, findings of pharmacoepidemiological studies based on DBCC data provide reassurance to physicians and healthcare personnel who provide supportive care during and after cancer (including prescriptions for comedications) and to breast cancer survivors for whom the risk of breast cancer recurrence is a major concern.

INTRODUCTION

Breast cancer is the most common malignancy among women worldwide. In 2017, about 4,900 women in Denmark will be diagnosed with breast cancer (1). The dissemination of increasingly effective adjuvant therapies has enlarged the pool of breast cancer survivors (2).

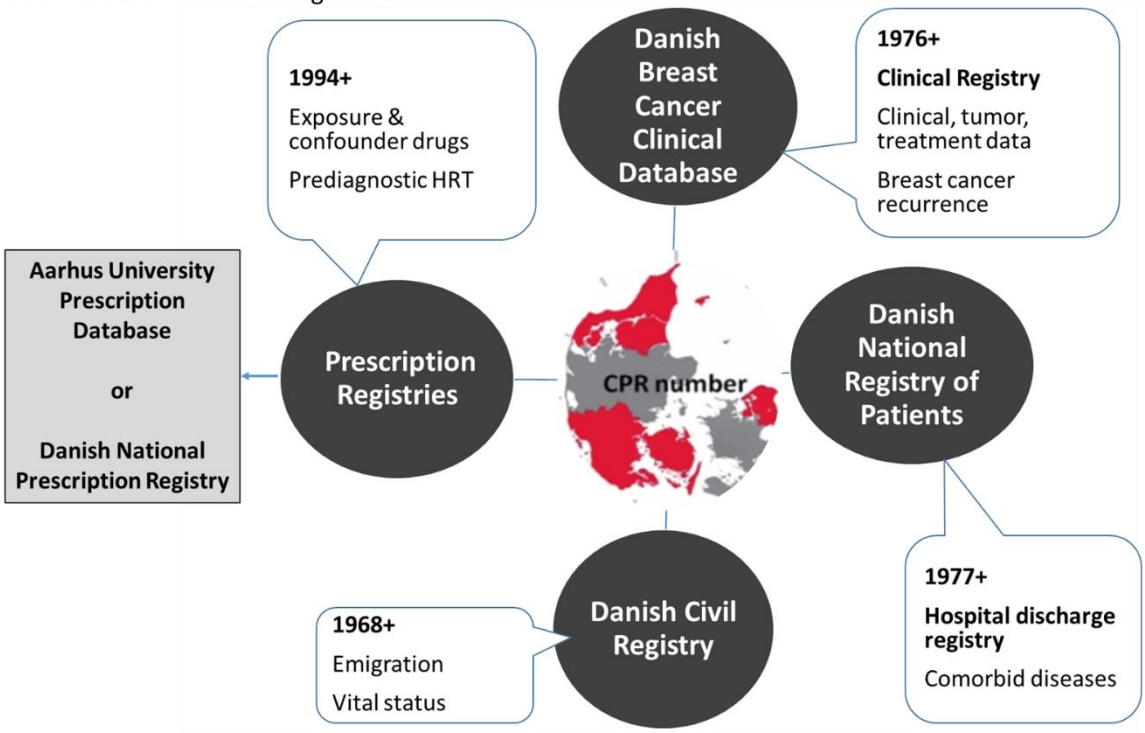
Denmark has a strong tradition and history of high quality registries with prospectively collected data. For 40 years, the Danish Breast Cancer Group (DBCG) clinical database has routinely registered data on breast cancer patients diagnosed in Denmark (3,4). The DBCG data quality and validity are high (5). The database records menopausal status, date and type of surgery, tumour characteristics, cancer treatment, and follow-up, including routine registration of breast cancer recurrence. For all patients who undergo breast cancer surgery, the DBCG registers data on follow-up examinations to detect recurrent disease. These examinations occur semi-annually during the first five years after diagnosis and annually the next five years (6). The DBCG records the civil personal registration (CPR) number, facilitating individual-level data linkage across Denmark's population-based registries (Figure), including the Danish National Prescription Registry (7).

Several frequently used prescription drugs alter breast cancer cell growth. The prospect of improving breast cancer prognosis through use of affordable drugs with relatively benign side effects has great appeal. Conversely, the potential for such medicines to worsen prognosis has critical implications for treatment of breast cancer and comorbidities, and for cancer-related healthcare costs.

Here, we present findings from selected pharmacoepidemiological studies that linked data from the DBCG to population-based prescription registries in Denmark. The studies aimed to investigate the impact of routinely prescribed drugs on the risk of breast cancer recurrence and

mortality. We discuss findings for each drug in the context of the existing literature and highlight the clinical implications of observed associations.

Figure: The Civil Personal Registration (CPR) number facilitates individual-level linkage of DBCG data to other population-based and medical registries in Denmark.



METHODS

Search strategy:

We included observational studies that linked DBCG data to the following population-based prescription databases in Denmark: the Danish National Prescription Registry (8), the Aarhus University Prescription Database (AUPD) (9), and the Danish National Health Service Prescription Database (10). Study data, design, and analytic strategy are described in the individual research papers. We provide brief synopses.

Study design & study population:

Except for two studies, all used a cohort design, including patients diagnosed with breast cancer registered in DBCG. Three cohort studies included patients diagnosed between 1996 and 2003 with follow-up through 2008 (11-13). Later the cohorts were expanded to include patients diagnosed between 1996 and 2008 with follow-up through July 2013(14-16). Patients diagnosed with metastatic breast cancer were excluded from all studies. Follow-up began on the date of breast cancer primary surgery, as recorded in DBCG, and ended on the date of breast cancer recurrence, death, ten years, or end of follow-up.

Our studies of SSRIs, tamoxifen inhibition, and breast cancer recurrence used a case-control design, nested in the population of breast cancer patients diagnosed during 1985-2001, registered in the DBCG, who resided in the former Danish counties of North Jutland, Aarhus, Viborg, and Ringkøbing. We subsequently included women diagnosed during 1996-2001, registered in DBCG, who resided in Jutland. We included (1) ERα+/T+: ERα+ patients treated with tamoxifen for >=1 year, and (2) ERα–/T–: ERα– patients not treated with tamoxifen, who survived >=1 year. "*Cases"* had recurrence within ten years of diagnosis. "*Controls"* did not have a recurrence when their matched case recurred. We matched one control to each case based on ERα+/T+ or ERα–/T–, menopausal status, breast cancer surgery date, county, and stage. We identified 541 ERα+/T+ cases and 541 matched controls, and 300 ERα–/T– cases and 300 matched controls.

Prescription data:

The Danish National Prescription Registry, maintained by Statistics Denmark, has registered all prescriptions dispensed at Danish pharmacies since 1995. Recorded data include the redemption date, prescribed drug [classified using Anatomical Therapeutic Chemical (ATC) codes], and fill quantity (see Appendix for list of ATC codes) (8). For the cohort studies, prescription drug data

were ascertained from the Danish National Prescription Registry. Via Statistics Denmark, the prescription data was linked from the Prescription Registry to the clinical cohort. For each drug, users were individuals who redeemed at least one prescription following breast cancer diagnosis. In all studies, medication use was modeled as a time-varying exposure, updated daily and lagged by one year, to avoid reverse causation and immortal person-time bias (17).

For one case-control study (18), we ascertained information on prescriptions from the AUPD (9). The AUPD has received and merged prescription data from the former Danish counties of North Jutland, Aarhus, Ringkjøbing, and Viborg (since 1989, 1996, 1998, and 1998, respectively). Since 2007, data in the AUPD is merged with data from the community pharmacies of the Central and North Denmark Region. The database records prescriptions dispensed at pharmacies for drugs that receive general or conditional reimbursement.

Outcomes:

We obtained recurrence and vital status data from DBCG, which routinely follows patients for the development of recurrent disease up to ten years after primary diagnosis (5). The DBCG defines breast cancer recurrence as any local, regional, or distant recurrent breast cancer, or contralateral breast cancer diagnosed during follow-up. Specific details on the site of recurrent breast cancer are also recorded.

Statistical analyses:

Descriptive characteristics of the study populations were outlined. In the cohort studies, Cox regression models quantified the association of each prescription drug with rates of recurrence

and all-cause mortality. In the case-control studies, conditional logistic regression estimated the association of SSRI use with recurrence.

RESULTS

Statins:

Statins (hydroxy-3-methylglutaryl coenzyme A—HMG-CoA reductase inhibitors) inhibit the rate-limiting step of cholesterol biosynthesis. Statins lower serum cholesterol and prevent atherosclerotic disease. Statins are well-tolerated. They target lipid metabolism, but exert pleiotropic effects including mevalonate inhibition, which impacts cell growth, signal transduction, differentiation, and apoptosis (19). Statins thus modulate several physiological processes essential to cancer initiation and promotion. Although statins do not impact *breast cancer incidence*, observational data suggests the anti-cancer effects of statins in preclinical studies extend to modifying *cancer outcomes*.

We investigated the association of post-diagnostic statin use and breast cancer recurrence. Among over 18,000 Danish breast cancer patients registered in DBCG, we observed 20% lower rate of recurrence among users of lipophilic statins, primarily simvastatin (13). In accordance with our *a priori* hypotheses, we observed no decrease in recurrence rates associated with hydrophilic statin use. The decreased rate of recurrence among users of lipophilic statins was observed for ipsilateral, contralateral, and regional lymph node recurrences, but not for bone metastases. The decreased rate of recurrence was robust to stratified analyses, though slightly stronger for ER+ than ER- tumours, consistent with two previously published small studies (20,21). Lower risks of recurrence/mortality in lipophilic statin users have been observed in a further four (22-25) out of five (26) observational studies.

The Breast International Group 1-98 (BIG 1-98) double-blind randomized clinical trial compared tamoxifen, letrozole, or a sequence of the two drugs in 8,010 postmenopausal patients – 1,396 patients were included via DBCG (27). A *post-hoc* observational study within BIG 1-98 investigated the survival benefit of cholesterol-lowering drugs during endocrine therapy among 1,700 breast cancer patients (28). Findings suggested that patients with ER+ breast tumours who used cholesterol-lowering medications had lower rates of recurrence compared with non-users. However, the BIG 1-98 trial was not designed to investigate the efficacy of cholesterol-lowering medication among breast cancer patients.

Candidate biomarkers that may modify the effect of statins on tumour growth include HMG-CoA reductase expression (29), as well as several polymorphic genes encoding enzymes that metabolize statins (30).

Yet, some believe the cancer survival benefits of statins are attributable to selection and immortal person-time bias (31). Using SEER-Medicare data, Emilsson et al emulated a clinical trial investigating statin initiation up to six months after cancer diagnosis and cause-specific and all-cause mortality up to three years after colorectal, breast, prostate and bladder cancer diagnosis. Although the study had short follow-up, and no data on cancer recurrence, the paper highlights important limitations of the published studies of statins and cancer outcomes. Nonetheless, the analysis grouped all cancer sites together, thus allowing beneficial associations for one cancer site (breast cancer) (13,30) to be masked when averaged with null associations at other cancer sites (colorectal cancer) (32).

Despite the promising observational data, the hypothesis that statin therapy may reduce the risk of breast cancer recurrence has never been examined in a randomized clinical trial.

Aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), and selective COX-2 (sCOX-2) inhibitors:

Aspirin, NSAIDs, and sCOX-2 inhibitors target the cyclooxygenase enzymes, COX-1 and COX-2, which promote angiogenesis and prevent apoptosis. COX-1 expression is ubiquitous; COX-2 is expressed during inflammation and in cancer (33). Laboratory studies suggest that drugs targeting these enzymes inhibit breast cancer cell growth (34)(34-36), but findings from observational studies are inconsistent (37-46). For aspirin, three studies report lower mortality risks (37,39,47); others show no association (38,43-45,48,49). For NSAIDs, decreased mortality risks (39,40,50) and null associations have been reported (41,49,51). Reasons underlying the inconsistent findings include variation in ascertainment of drug exposure (*i.e.*, self-reported versus prescription-based) and confounder adjustment.

Low-dose aspirin reduces the risk of cardiovascular disease, so studies that assessed mortality (37-41,44), rather than the cancer-specific outcome recurrence (37,40), could not distinguish an effect of low-dose aspirin on cancer (via recurrence) from its direct effect on mortality. Importantly, several published aspirin studies did not adjust for statins (20,21,37,39-41,43,47), which are frequently prescribed with aspirin to prevent cardiovascular disease.

Our study of 34,188 breast cancer survivors showed no evidence of decreased recurrence rate associated with *post-diagnostic* aspirin, NSAIDs, or sCOX2 inhibitor use (14). Our results were unchanged in stratified analyses and in analyses examining drug exposure and site-specific cancer recurrence.

Findings from preplanned analyses of pre-diagnostic aspirin use, and *post-hoc* analyses of pre-diagnostic use of NSAIDs and sCOX-2 inhibitors, suggested a slight decreased risk of recurrence. Our findings for pre-diagnostic aspirin use support a previous study by Barron and

colleagues (42). Pre-diagnostic use of these drugs may confer less aggressive tumour phenotypes (52), but these findings are unlikely to be of meaningful clinical relevance.

Despite inconsistent findings from observational studies, a randomized placebo-controlled clinical trial (NCT02804815) is underway to investigate the efficacy of adjuvant aspirin (100mg or 300 mg versus placebo) in breast cancer patients, and in patients with colorectal, gastro-esophageal, and prostate cancers. The results of the trial will become available in 2026.

β-blockers, ACE inhibitors, and ARBs

β-blockers are indicated for hypertension and heart disease. They compete with epinephrine and norepinephrine to bind β-adrenergic receptors (β-AR) 1 and 2, thereby inhibiting the stress response. Physicians have increasingly prescribed selective β-blockers targeting β-AR1, such as atenolol, rather than nonselective β-blockers, such as propranolol, due to their cardioselective properties (53).

Breast tumours express β-ARs and preclinical studies suggest β-blockers prevent angiogenesis and metastasis(54). Accordingly, drugs that inhibit β-ARs may favourably impact cancer survival. Epidemiologic studies note decreased risk of cause-specific mortality and breast cancer recurrence associated with β-blocker use (55,55-58). Propranolol use has been correlated with an 80% decreased rate of breast cancer-specific mortality (57). However, findings are inconsistent (23,54,59), and imprecise (60).

The indications for angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) are similar to those for β-blockers, but also include prevention of renal insufficiency in type II diabetes and chronic kidney disease. These drugs inhibit the renin-angiotensin-aldosterone system (RAAS)(61). Genetic polymorphisms that increase RAAS

activity increase activation of several biomarkers and pathways essential to tumourigenesis. RAAS polymorphisms correlate with increased risk of breast cancer(62). Thus ACEis and ARBs may prevent breast cancer progression. However, observational studies show decreased (63), null (64,65), and increased (23,66) risks of breast cancer progression or mortality associated with ACEis or ARBs.

In a cohort of 18,733 breast cancer patients registered in DBCG, we observed no evidence of a protective effect of β-blockers, ACEis, or ARBs on breast cancer recurrence (12). The null associations remained robust regardless of selectivity or lipophilicity of β-blockers and the timing or intensity of drug use.

In a meta-analysis, Raimondi *et al.* summarized the association of β-blockers, ACEis, and ARBs with progression in breast cancer patients (67). They concluded that β-blocker use correlated with longer disease-specific survival, while ACEis or ARBs had little impact on breast cancer survival. However, several of the included studies comprised small samples and some were prone to immortal person-time bias (21), which can inflate the magnitude of a protective association. Notably, the studies that reported null findings had the largest sample sizes and highest number of exposed patients who developed the outcome (12,23,58,68). A recent study reported dramatically improved progression-free survival in patients with advanced HER-2 negative breast cancer who participated in the ROSE/TRIO-012 study (69). The study has many limitations precluding any inference of a truly beneficial effect, most importantly the strong potential for the decreased risk of progression-free survival to have arisen from immortal person-time bias.

These findings provide reassurance to cancer survivors and their physicians that use of β-blockers, ACEis, or ARBs is unlikely to exacerbate cancer progression.

Glucocorticoids

Synthetic glucocorticoids mediate immunosuppressive effects and are indicated for acute and chronic inflammatory diseases. In breast cancer cells, glucocorticoid treatment induces a less invasive phenotype in ER-negative cells compared with untreated ER-negative cells or ER-positive cells (70). While glucocorticoid use does not correlate with breast cancer incidence(71), they may help tumour cells evade immune detection, thus aid cancer progression.

Using the DBCG database, we conducted the first and only large population-based study to investigate the association between prescriptions for glucocorticoids and risk of breast cancer recurrence (11). We found no evidence of an association between prescriptions for systemic, inhaled, or intestinal-acting glucocorticoids and risk of recurrent breast cancer. These findings remained robust in stratified analyses—providing reassurance to patients and physicians about the safety of these drugs.

Opioids

Opioids are central to pain management, but they inhibit key elements of cell-mediated immunity—the primary defense against cancer (72). Preclinical studies suggest that high-dose opioids inhibit angiogenesis, metastasis, and induce apoptosis. Morphine, a strong opioid, does not initiate tumourigenesis, but research suggests it promotes cancer progression. Tramadol has similar analgesic properties to morphine, but research in patients undergoing surgery for uterine carcinoma shows it can activate natural killer cells in the postoperative period (73). Thus, opioids may modify cancer progression, but the direction of this association is not clear.

Opioid use is increasing (74), particularly in cancer survivors (75). Studies have primarily investigated recurrence risk associated with perioperative opioid use. Most (76-78), but not all (79,80), have concluded that morphine-based systemic anaesthesia correlates with increased recurrence risk compared with non-systemic anaesthesia.

Our study linking DBCG data with population-based prescription data in Denmark is the first study to investigate the impact of opioid use on cancer recurrence (15). Our study population included 34,188 patients with non-metastatic breast cancer followed for up to ten years after their primary diagnosis. We explored the following topics: impact of opioid strength; cumulative dose according to morphine equivalents; immunosuppressive effects; and chronicity of use, to model the impact of chronic long-term opioid use on recurrence risk. Except for the strongly immunosuppressive drugs, our findings show no evidence of an association between opioid use and breast cancer recurrence. Among patients who used strongly immunosuppressive drugs, we observed decreased recurrence, but increased mortality, likely attributable to channeling bias (81).

Thus, opioids do not appear to modify cancer progression. This is important to the increasing number of cancer survivors for whom post-cancer pain is a major concern.

Digoxin

Cardiac glycosides, including digoxin and digitoxin, inhibit the Na+/K+ ATPase pump, and treat congestive heart failure and atrial fibrillation. Preclinical research highlights anti-cancer effects of cardiac glycosides, including pro-apoptotic effects and topoisomerase II inhibition, a target of several cancer therapies. Observational research suggests that prescription use of cardiac glycosides correlates with increased risk of breast cancer (82-84). This questions the

safety of cardiac glycoside use by breast cancer survivors. Digoxin use correlates with better prognostic features in cancer (85). However, prior to the publication of a study using DBCG data, only one study had reported on the impact of digoxin use on breast cancer prognosis. Among 175 patients followed for 22.3 years, Stenkvist observed a lower breast cancer-specific mortality rate (6%) associated with use of digitalis (digoxin) before breast cancer diagnosis compared with non-users (mortality rate = 34%) (86). However, in this small study only 2 out of 32 patients died from breast cancer.

In 2013, Biggar *et al.* investigated the association between prescription use of digoxin and tumour characteristics, and breast cancer relapse among 34,085 breast cancer patients registered in DBCG (16). Better prognostic features (higher frequency of ER+ tumours, lower histologic grade, and less advanced stage at diagnosis) were observed among women who used digoxin, but overall digoxin use did not correlate with breast cancer relapse. These findings have since been confirmed in a UK-based study by Karasneh *et al.* (87).

Selective Serotonin Reuptake Inhibitors

Two-thirds of breast cancer patients have tumors that express estrogen receptor alpha (ERα), and are candidates for adjuvant endocrine therapy. Tamoxifen reduces the risk of breast cancer recurrence by about 50%. It is the only endocrine therapy recommended for ERα+ premenopausal breast cancer patients, and an important alternative or sequential treatment to aromatase inhibitors for postmenopausal patients. Tamoxifen effectiveness is often tempered by the development of tamoxifen resistance, defined clinically as breast cancer recurrence. No biomarkers of resistance beyond the absence of ERα have been identified (88). Cytochrome P450 (CYP) enzymes catalyze tamoxifen metabolism to 4-hydroxy tamoxifen and 4-hydroxy-N-

desmethyl tamoxifen (endoxifen) (89). Tamoxifen metabolism is inhibited when women carry variant alleles leading to enzymatic impairment, or are concomitantly prescribed drugs that inhibit or compete for CYP2D6 (89).

SSRIs are used to treat depression and vasomotor symptoms due to menopause or side effects of tamoxifen. Women who use SSRIs and tamoxifen can have low serum endoxifen concentration, similar to women who carry no functional CYP2D6 allele (90,91). Such women may have increased risk of breast cancer recurrence. Many studies have investigated the association between drug-induced inhibition of tamoxifen and breast cancer recurrence or mortality. Their findings are heterogeneous, with effect estimates ranging from a 0.3-fold decreased risk to a 3-fold increased risk of recurrence or death (89). Reasons for the heterogeneity of the findings are not clear and are reviewed elsewhere (89,92-94). Nonetheless, no single study characteristic can explain the inconsistency. A recent very large and methodologically strong pharmacoepidemiological study found a null-association between concomitant use of the SSRIs fluoxetine and paroxetine, both strong CYP2D6 inhibitors, and mortality among breast cancer patients receiving tamoxifen (95).

Contrary to our hypothesis, our nested case-control study of early-stage breast cancer patients registered in the DBCG showed no evidence that citalopram or other SSRIs diminish tamoxifen effectiveness in reducing breast cancer recurrence (18,96-98). Furthermore, use of SSRIs was not associated with recurrence risk in ER-negative breast cancer patients who received no tamoxifen, indicating no contraindication for use of these drugs after breast cancer diagnosis.

To be effective, tamoxifen and its metabolites must compete with estrogen for ER binding. Yet all existing clinical epidemiology studies of tamoxifen inhibition have considered the profile of tamoxifen metabolites. For this reason, in collaboration with DBCG, we have established a

cohort of approximately 6000 premenopausal breast cancer patients, in whom estrogen concentrations are much higher than in previously studied post-menopausal patients. We will investigate tamoxifen metabolites, refining existing knowledge with comprehensive genotyping and incorporating comedications that inhibit the metabolism. Importantly, this design improves the current research paradigm, since associations are most likely (given endogenous estrogen) in premenopausal women. The drug is also the guideline-recommended therapy for premenopausal women.

Conclusions

Breast cancer accounts for a significant proportion of cancer deaths in women, and incurs extensive healthcare costs worldwide. Identifying treatments with a beneficial role in breast cancer therapy and few side effects has huge public health implications. Findings from observational pharmacoepidemiology studies are unlikely to change clinical practice in the absence of a clinical trial. However, observational studies help identify patterns of association, pinpointing subcategories of patients likely to benefit from particular treatments, as well as those at risk of harmful treatment effects. Furthermore, adjuvant cancer-directed therapies may be difficult to implement in nations with a low Human Development Index, which incur a substantial proportion of the breast cancer burden (99).

Post-diagnosis statin use consistently correlates with lower recurrence and mortality risk in non-randomized studies. Statins are inexpensive, chemically stable without refrigeration, and have a well-understood safety profile. Their anti-cancer potential among breast cancer survivors in low-resource settings merits consideration, and may also improve cardiovascular health in breast cancer survivors in these nations.

Pharmacoepidemiology studies using DBCG data have noteworthy strengths. Individual-level linkage across Danish databases creates large cohorts nested in a nationwide source population. Tumour, treatment, and follow-up data in the DBCG registry are clinical trial quality (3,4). Selection bias is negligible due to near-complete enrolment of breast cancer cases from the source population. Since Danish legislation does not require informed consent for registry-based studies, pharmacoepidemiology studies are not prone to bias due to self-selection. As well, linkage to the Danish National Prescription Registry provides information on prescriptions redeemed at pharmacies. In Denmark, patients pay a proportion of the cost of each prescription, so those who redeem a prescription are likely to consume the medication. The cohort studies coupling DBCG data to prescription data used lagged post-diagnostic drug exposures to minimise reverse causation, while capturing exposure during etiologically plausible time periods. This lag was generally one year—long enough to allow the drug to impact recurrence, but not so long as to reduce the likelihood of detecting a potential association. Sensitivity analyses altering the exposure lag yielded similar findings, justifying the lag duration.

A major advantage of the DBCG database for pharmacoepidemiology studies is the routine and valid recording of breast cancer recurrence during follow-up. A wealth of evidence indicates the benefit of these prescription drugs to improve quality of life and reduce mortality. Recurrence is a cancer-specific endpoint, so it highlights the direct effect of the drug on cancer, rather than on mortality. A study of statin use among Danish colorectal cancer patients showed a protective effect on cancer-specific and all-cause mortality, but not on recurrence—highlighting the importance of studying recurrence rather than mortality (32).

Several issues are relevant when interpreting the studies discussed above. All the studies ascertained comorbid diseases at the time of breast cancer diagnosis, but lacked information on

the severity of these conditions, which may influence cancer-directed treatment. The comorbidity data relied on comorbidities sufficiently severe to warrant hospital admission or a visit to an outpatient clinic or emergency room. Thus milder conditions, treated by primary care physicians, were unavailable. In several studies, the number of prescriptions was a proxy for cumulative dose, as the actual prescribed drug dose is not available in the Danish National Prescription Registry. Information on in-hospital drug use was also lacking. This may be particularly important for the studies on glucocorticoids, opioids, NSAIDs, and selective Cox-2 inhibitors, all of which are indicated for pain, and for glucocorticoids, used to treat emesis.

Thus, the pharmacoepidemiological studies coupling DBCG data with prescription registry data suggest that use of aspirin, NSAIDs, sCOX-2 inhibitors, ACEis, beta-blockers, ARBs, glucocorticoids, digoxin, SSRIs, and opioids has little effect on breast cancer recurrence. Concerns about recurrence should not impact patient-physician decisions about use of these drugs after breast cancer diagnosis. The lipophilic statin, simvastatin, may be beneficial in breast cancer survivors. Several subsequent observational studies have confirmed the findings DBCG-based statin study findings. The large size of the DBCG-based study makes it unlikely that another observational study can substantially improve upon it. The convincing evidence from the accumulating observational data and *post-hoc* BIG 1-98 analyses provide strong justification for a trial. Such a trial also may provide impetus for research on statins and other cancers, several of which (but not all) may benefit.

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