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Poster MSR128

Swedish Nationwide Register Data as a Low-Cost Resource to Detect Drug-Repurposing Signals: A Study on De Novo Metastatic Breast Cancer Patients

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KEY FINDINGS & CONCLUSIONS

- It is feasible to identify potential candidates for drug repurposing utilizing Swedish nation-wide health registers data
- Five drug repurposing hypotheses were generated based on drug exposure-mediated survival signals
- This study sets up a new low-cost model of mining Swedish Registers for drug repurposing signals
- Careful selection of patient cohort and more detailed information on other prognostic factors as confounders is essential to increase the validity of these exploratory results

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BACKGROUND

- The development of a new cancer drug is estimated to cost $648 million [1] to $2.5 billion [2] and takes an average of 9 to 12 years before market availability [3]
- In clinical trials carried out between 2010 and 2020, the probability of approval for a cancer drug entering phase 1 was approximately 5% [4]
- Hence, there is a need for methods that reduce costs and improve the probability of clinical development success
- Combining data on multiple cancers, Wu et al. [5] recently highlighted electronic health records as a low-cost resource to accelerate cancer therapeutics by drug repurposing discovery
- While there is a wealth of Swedish registries, this data is yet to be leveraged for drug repurposing studies

OBJECTIVE

The objective of this study was to test this approach on Swedish nationwide register data focusing on breast cancer cases with distant metastasis at initial diagnosis (de novo mBC)

To this end we

1. evaluated the drug candidates identified by Wu et al.
2. generated drug repurposing hypotheses based on prescription drugs given to patients during metastatic breast cancer diagnosis/treatment

Table 1: Clinical development success rates for novel drugs vs. non-new molecular entities (repurposed or modified drug candidates) [4].

	Phase I –> Approval	Phase II -> Approval	Phase III -> Approval	NDA/BLA –> Approval
Novel drugs	6.8%	13.2%	47.4%	89.6%
Non-new molecular entities	13.3%	23.2%	61.8%	91.5%
Increased likelihood of approval	1.96	1.76	1.30	1.02

Footnote: The figures in each cell denote the probabilities of eventual approval upon entering a clinical trial phase
NDA – New Drug Application; BLA – Biologics License Application

METHODS

- Patient level data was extracted from the population based Swedish Health Data Registers, kept and maintained by the National Board of Health and Welfare
- All patients diagnosed with de novo mBC in Sweden between 2010 and 2020 were identified in the Swedish Cancer Register (SCR)
- Data on prescription drug use between 2008 and 2020 was collected from the National Prescribed Drug Register (PDR) and used to estimate burden of prescription medication
- Vital status throughout the follow up period was collected from the National Cause of Death Register (CDR)
- Survival after mBC diagnosis was estimated using the Kaplan-Meier method and Cox proportional hazard models
- For model specification, age at mBC diagnosis and burden of prescription medication were leveraged as proxies for patient's general health
  - Burden of prescription medication was defined as the number of unique prescriptions dispensed before mBC diagnosis. Prescription information, e.g. pack size and defined daily dose, was used to assess the duration of each individual prescription
- Drug repurposing hypotheses were then tested and generated using two different cox proportional hazard models
  - A Cox proportional hazards model that estimated the relative hazard for death after breast cancer with medication given during the first six months after de novo mBC diagnosis and prescription medication burden as covariates
  - A similar Cox proportional hazards model with a medication given during the first six months after de novo mBC diagnosis, prescription medication burden and age at diagnosis as covariates
- Hypotheses were tested and generated using Bonferroni correction

RESULTS

Patients

- A total of 2,106 de Novo mBC patients were identified in the SCR between 2010 and 2020
- Of these, 2,091 (99.3%) were female and 1,394 (66.2%) died during follow up
- The mean age at mBC diagnosis was 69.4 (Q1: 60.2, Q3: 80.6)
- The median survival was estimated at 2.00 years (95% CI: 1.83-2.20 years). A Kaplan-Meier plot of overall survival is presented in **Figure 1**
- Across all patients, a total of 814 unique drugs were dispensed during the first 6 months after mBC diagnosis.
- The average unique number of prescriptions were 8.5 and 13.9, before and after mBC diagnosis, respectively

Model specification

- In two univariate Cox regression models, each unique medication prescribed before mBC diagnosis and each additional year of age at mBC, were associated with an increased hazard of 2.6% ($p<10^{-13}$) and 1.9% ($p<10^{-15}$), respectively
- In a third model, we analyzed the relative hazard of survival as a function of both the burden of prescription medication burden and age at mBC diagnosis. Independently, both factors were associated with survival. Each unique medication prescribed before mBC diagnosis and each additional year of age at mBC, were associated with an increased hazard of 1.7% ($p<10^{-6}$) and 1.8% ($p<10^{-15}$), respectively
- The association of between burden of prescription medication and survival is exemplified and presented in **Figure 2**

Table 2. Assessment of the drug repurposing hypothesis generated by Wu et al.

		Model 1		Model 2	
Drug	Exposed	HR	P-value	HR	P-value
Rosuvastatin	18	0.716	0.232	0.792	0.404
Simvastatin	210	1.011	0.896	0.903	0.256
Amlodipine	238	1.014	0.873	0.907	0.272
Tamsulosin	0	na	na	na	na
Metformin	105	1.042	0.739	1.038	0.756
Omeprazole	828	1.06	0.288	1.152	0.012
Warfarin	64	0.948	0.729	0.816	0.192
Lisinoprol	5	1.147	0.784	0.967	0.946
Metroprolol	332	0.973	0.711	0.871	0.064

Wu et al. generated hypotheses based on 141,676 patients with various cancer types including prostate, breast, lung and colorectal cancers
HR – Hazard Ratio; na – not applicable, Bonferroni adjusted threshold for significance = 0.05/9 *(hypotheses tested = 9)*

Table 3. New drug repurposing hypothesis generated in the de Novo mBC patient population (2010-2020)

		Model 1		Model 2	
Drug	Exposed	HR	P-value	HR	P-value
Replens, vaginal gel	84	0.489	1.84E-05	0.508	5.09E-05
Fluoride mouthwash	113	0.569	3.47E-05	0.626	5.88E-04
Letrozole	804	0.762	1.46E-06	0.642	5.14E-14
Calcium + Vitamin D	614	0.752	5.10E-06	0.763	1.64E-05
Morphine	362	1.436	3.78E-08	1.400	3.89E-07
Furosemide	427	1.459	1.09E-08	1.329	2.16E-05
Fentanyl	182	1.587	1.56E-07	1.572	2.71E-07
Salbutamol and Ipratropium bromide	24	2.535	4.00E-05	2.342	1.72E-04

HR – Hazard Ratio; Bonferroni adjusted threshold for significance = 0.05/814 (hypotheses tested = 814)

Figure 1. Overall survival for the 2,106 diagnosed with de novo mBC in Sweden between 2010 and 2020

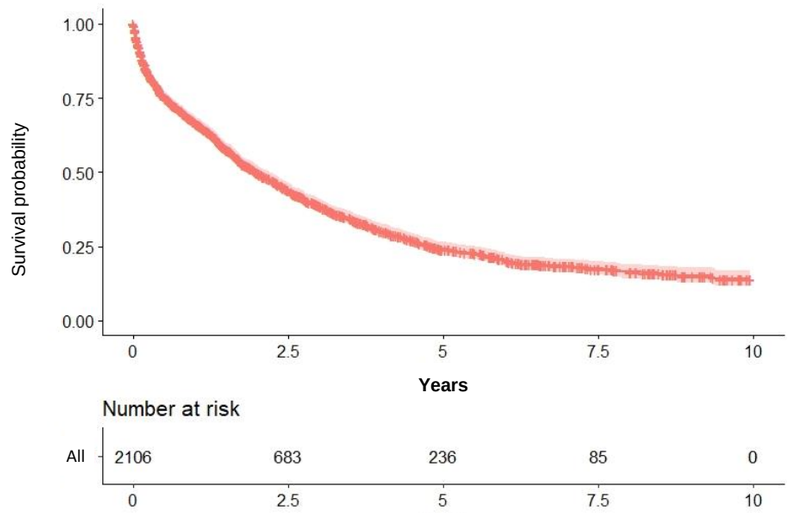
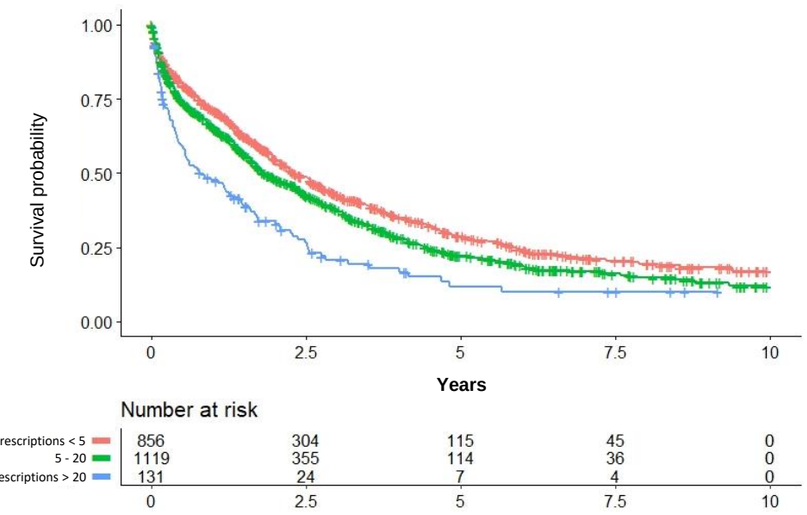


Figure 2. Overall survival stratified by burden of prescription medication



Drug repurposing signals

- The drug repurposing hypotheses derived by Wu et al. were assessed using Model 1 and Model 2. None of the 9 hypotheses were significantly associated with overall survival based on our data (**Table 2**)
- Model 1 and Model 2 were used to generate drug repurposing hypotheses based on the mBC data. All 814 drugs identified during the 6-month period after mBC diagnosis were assessed. The models generated a total of eight drug repurposing hypothesis with a plausible biological rationale for at least 5 of them (Calcium + Vitamin D, morphine, furosemide, fentanyl, salbutamol and ipratropium bromide) (**Table 3**). For the remaining three, there is a lack of plausible explanation (mouthwash) or a treatment-related explanation (letrozole is an anticancer treatment usually prescribed with replens vaginal gel hence a proxy for anti-cancer treatment)
- Notably, while Wu et al. noted the lack of details with regards to exposure information and dosing as a limitation, our study could take these factors into account by leveraging the PDR data

Limitations

- **Causality of drug repurposing hypotheses must be further investigated after identification**
- The approach assumes proportional hazards which has limitations
- Drugs that have been taken before diagnosis, which could potentially have impacted the cancer before it is diagnosed, are not identified optimally with this design
- The methodology does not take homogeneity in sub-group drug-response into account
- We assume that each prescription is taken for a period derived from the package size and recommended daily dose. This assumes that the prescription is consumed according to that schedule, which it, in some cases, may not have been

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