Estimating breast cancer incidence using multiple imputation with chained equations (MICE)

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Outline

- Brief background: Breast Cancer and its subtypes
- Motivation and aim: Estimating subtype-specific BC incidence using cancer registry data
- Available data – partly missing information on subtype
- Incidence estimation using multiple imputation with chained equations (MICE)
  - → Why this is a non-standard multiple imputation
- Conclusions

This work was recently published

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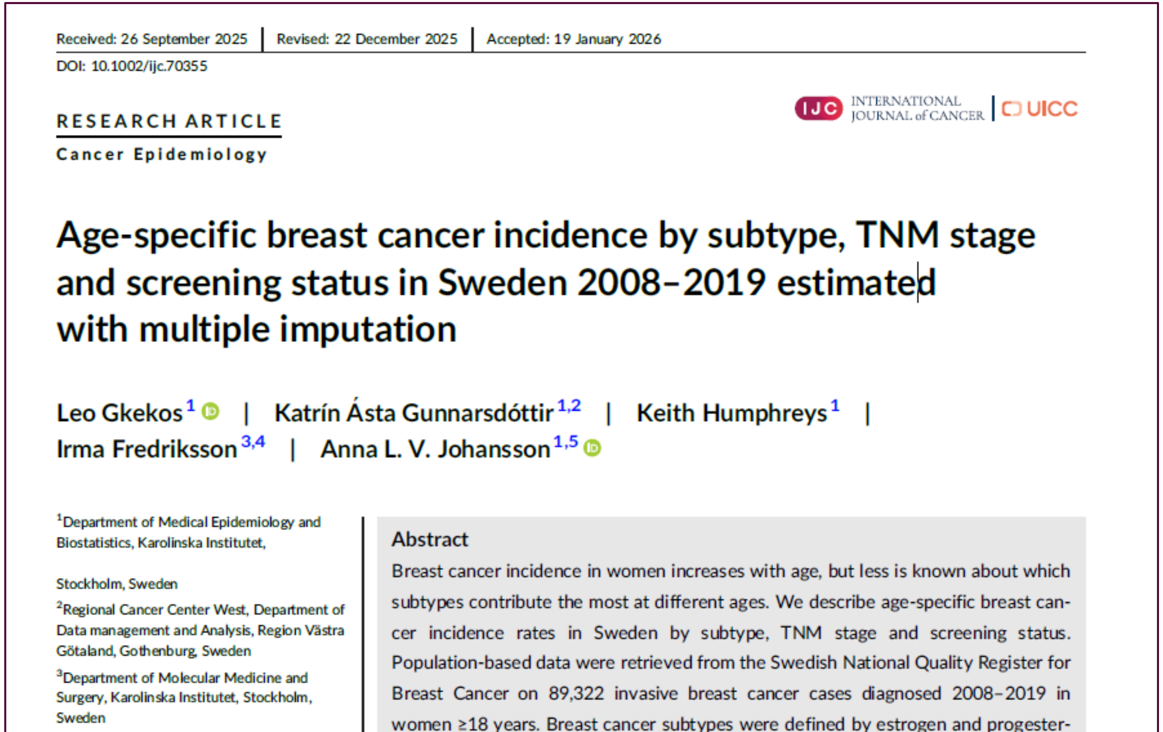
Methods described in Supplemental material.

https://onlinelibrary.wiley.com/doi/full/10.1002/ijc.70355



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RESEARCH ARTICLE

Cancer Epidemiology

Age-specific breast cancer incidence by subtype, TNM stage and screening status in Sweden 2008–2019 estimated with multiple imputation

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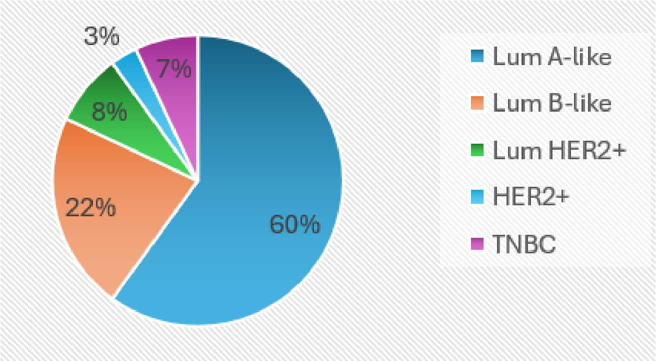
Abstract

Breast cancer incidence in women increases with age, but less is known about which subtypes contribute the most at different ages. We describe age-specific breast cancer incidence rates in Sweden by subtype, TNM stage and screening status. Population-based data were retrieved from the Swedish National Quality Register for Breast Cancer on 89,322 invasive breast cancer cases diagnosed 2008–2019 in women ≥18 years. Breast cancer subtypes were defined by estrogen and progester-

Background

- Breast cancer is not one disease but many **subtypes** with different treatment and survival.
  - Underlying **molecular subtypes** are approximated by clinical subtype ("**surrogate subtype**").
  - **5 "surrogate subtypes**": ER, PR, HER2 receptors, grade and KI67.



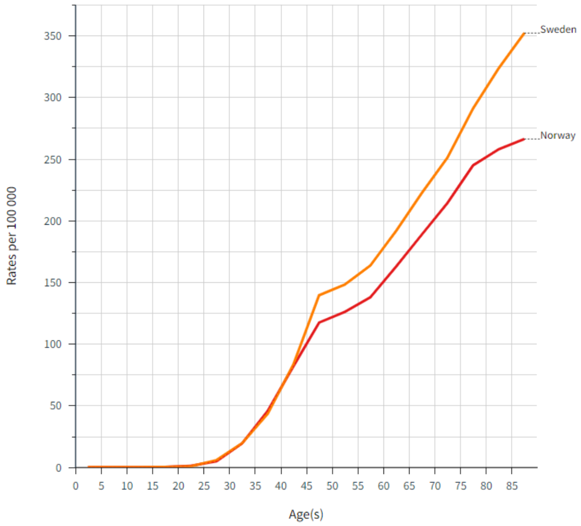
- Breast cancer subtypes have (partly) different underlying **risk factors** and **age-specific risk**.
- Also, **screening** is more likely to detect luminal tumours, while interval cancers are more often TNBC.

Screening has changed the age-specific incidence pattern of breast cancer

- Data from NORDCAN.

Rates per 100 000, Incidence, Females, [1975-1984]
Breast
Norway - Sweden

Before screening



NORDCAN | **IARC** - https://gco.iarc.who.int
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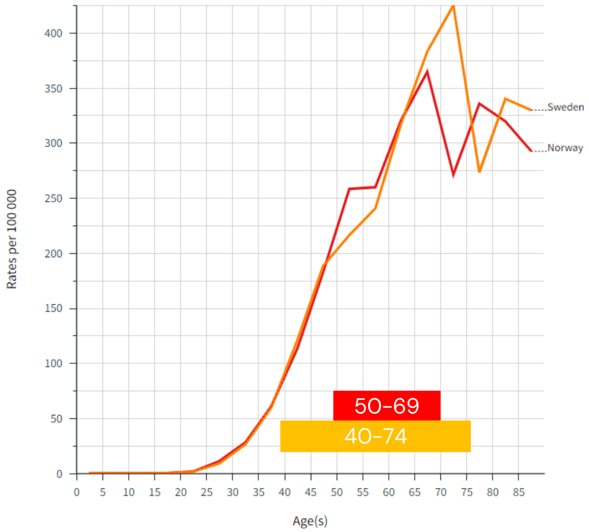
Rates per 100 000, Incidence, Females, [2013-2022]
Breast
Norway - Sweden

After screening



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Data version: 9.4 - 07.2024
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Our aim: Incidence rates of BC subtypes across age

- **Our aim** was to estimate and describe **subtype-specific BC incidence across age**.

- This will be correlated with screening, as well as shifts in underlying risk factors.
  - E.g. reproductive risk factors, obesity, alcohol, MHT (menopausal hormone therapy), genetics, etc.

- These results are important as basis for studies on clinical outcomes, e.g. understanding case-mix over time and ages, and studies on screening, e.g. extended screening ages.

What data did we have

- Swedish National Quality Register of Breast Cancer (NKBC) was established in 2008.
  - Nationwide (population-based) cancer register.
  - Collects detailed **routine clinical** information on **all new** breast cancer cases diagnosed in women and men.
    - Patient and **tumour characteristics**, diagnostic work-up, planned/given treatment, follow-up.
  - One recorded tumour per side (max 2 per person) for Swedish residents only.

- We had data for women diagnosed with **invasive** BC 2008-2019, aged ≥20 at diagnosis. N=89,322

- Information on
  - **Date and age of diagnosis**
  - **Subtype: ER, PR, HER2, grade**
  - Stage: tumour size (T), lymph node metastasis (N), distant metastasis (M)
  - Screen-detected or symptomatically detected

What data did we have

- 5 surrogate subtypes were based on: ER, PR, HER2, grade.

Surrogate subtype	ER	PR	HER2	Grade
Luminal A-like	+ + –	+ – +	– – –	Grade 1,2 Grade 1 Grade 1,2
Luminal B-like	+ + –	+ – +	– – –	Grade 3 Grade 2,3 Grade 3
Luminal HER2	+	+/-	+	Grade 1-3
HER2 positive	–	–	+	Grade 1-3
Triple-negative (TNBC)	–	–	–	Grade 1-3
% missing	4.1%	4.2%	7.9%	16.4%

15.5% missing subtype

Incidence rate estimation

- Incidence rate: $\lambda(\text{age, year}) = N_{\text{cases}} / N_{\text{poprisk}}$
- N_{cases} : From NKBC : **case population (individual level)**
- N_{poprisk} : From Statistics Sweden: **population at risk (counts** by 1-year age, 1-year calendar time)
- Estimated rates separately for each of the 5 subtypes.
  - Lum A: $\lambda_1(\text{age, year}) = N_{\text{cases, subtype 1}} / N_{\text{poprisk}}$
  - Lum B: $\lambda_2(\text{age, year}) = N_{\text{cases , subtype 2}} / N_{\text{poprisk}}$
  - Lum HER2: $\lambda_3(\text{age, year}) = N_{\text{cases , subtype 3}} / N_{\text{poprisk}}$
  - HER2 pos: $\lambda_4(\text{age, year}) = N_{\text{cases , subtype 4}} / N_{\text{poprisk}}$
  - TNBC: $\lambda_5(\text{age, year}) = N_{\text{cases , subtype 5}} / N_{\text{poprisk}}$

Note: Same N_{poprisk} for all incidence rates.
Only the numerator differs.

- **Incidence rates** can be estimated with Poisson regression for rates:
  - $\ln(\lambda_i(\text{age, year})) = \alpha * X_{\text{age}} + \beta * X_{\text{year}}$
  - $\ln(d_i(\text{age, year})) = \alpha * X_{\text{age}} + \beta * X_{\text{year}} + \ln(N_{\text{poprisk}})$
  - We ignored the calendar time effect (as only 2008-2019): $\ln(d_i(\text{age})) = \alpha * X_{\text{age}} + \ln(N_{\text{poprisk}})$
  - For stability, we estimated rates per 2-year age groups, i.e. <30, 30-31, 32-33, ..., 90-91, 92-93, 94+.

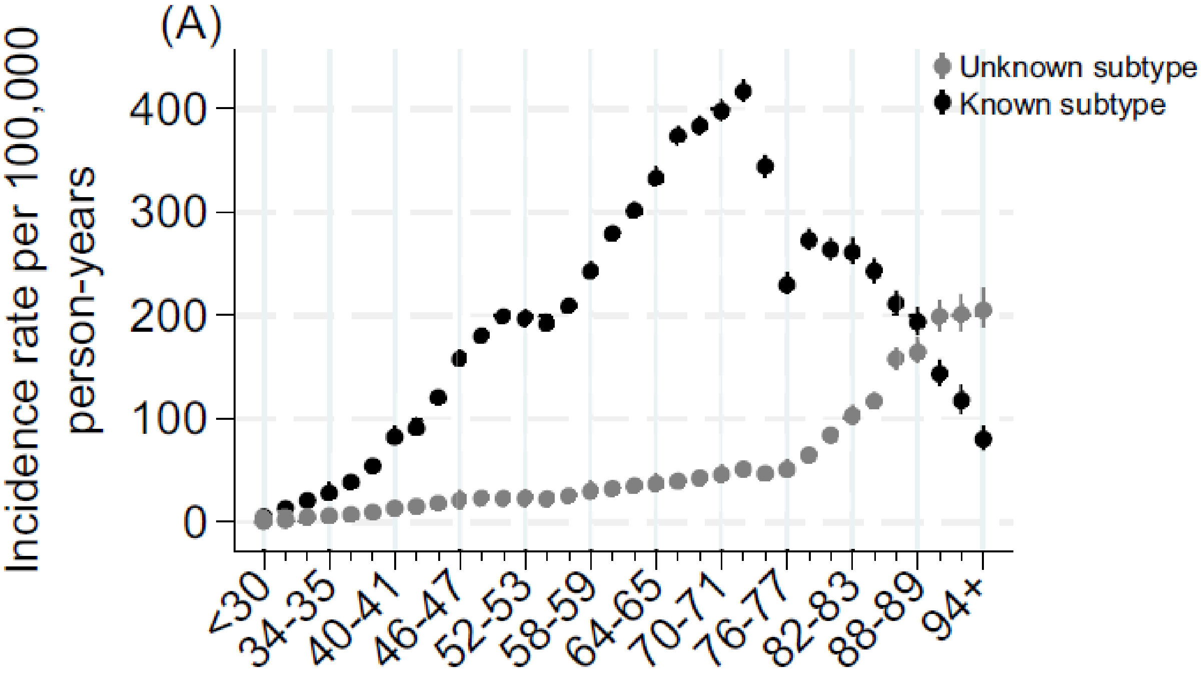
Missing data – on subtype

- Missing subtype: 15.5%; components had varying missing %
  - ER 4.1%, PR 4.2%, HER2 7.9%, grade 16.4%
  - **Leads to underestimation of the incidence rates with 15.5% - severe bias!**

- Reasons for missing
  - **Administrative missing** – not recorded in the earlier years, or in some regions/hospitals >> likely MCAR
  - Missing for **known reasons** – frail older women who are not eligible for certain treatments will not be investigated in detail, and thus will not be subtyped >> likely MAR (depending on known factors (age, treatment, comorbidity), which we can adjust for)
  - Missing for **unknown reasons** >> still likely MAR (depending on known factors)? Could also be MCAR/MNAR?

- Solution >> **Multiple Imputation with Chained Equations (MICE).**
  - Model-based method to impute missing data based on information in known variables (MAR).

Missing information depends on age



Multiple Imputation with Chained Equations (MICE)

- We have applied **multiple imputation with chained equations** (MICE).
- This involves a 2-step procedure
  - ✓ Step 1: Imputation model to generate *m* imputed (completed) datasets.
  - ✓ Step 2: Analysis (substantive) model (i.e. Poisson) to estimate incidence rates and pooling parameters across imputed datasets using Rubin’s rules #1 (mean) and #2 (variance).
- Key points:
  - Imputation model must capture the underlying reasons (patterns) for missing, e.g. age.
  - Imputation model must also reflect the analysis model, e.g. rates vary by age.
  - We added many clinical variables as auxiliary variables, and interactions with age (not trivial!). This will make the MAR assumption more likely.
- Implemented in Stata **mi package**:
  - Step 1: **mi impute**
  - Step 2: **mi estimate**

Building the imputation model

Variable	Missing of N=89,322 N (%)	Type in imputation	Imputation model (logistic, ordinal)	Analytical model (Poisson)
Age of diagnosis	Complete	Complete	X	X
Year of diagnosis	Complete	Auxiliary	X	
Region	Complete	Auxiliary	X	
Country of birth	Complete	Auxiliary	X	
Educational level	1,055 (1.18%)	Auxiliary / imputed	X	
Screening status	386 (0.43%)	Auxiliary / imputed	X	
T	251 (0.28%)	Auxiliary / imputed	X	
N	606 (0.68%)	Auxiliary / imputed	X	
M	Complete[a]	Auxiliary	X	
Stage (TNM)	465 (0.52%)		Not included (composite)	
Grade	14,610 (16.35%)	Imputed	X	
ER	3,657 (4.09%)	Imputed	X	
PR	3,778 (4.23%)	Imputed	X	
HER2	7,049 (7.89%)	Imputed	X	
Subtype	13,857 (15.51%)		Not included (composite)	X
Surgery	7,046 (7.89%)	Auxiliary / imputed	X	
Chemotherapy	17,818 (19.95%)	Auxiliary / imputed	X	
Radiotherapy	17,941 (20.08%)	Auxiliary / imputed	X	
Endocrine therapy	17,535 (19.63%)	Auxiliary / imputed	X	
Targeted therapy	17,992 (20.14%)	Auxiliary / imputed	X	
Survival indicators, CumHaz.(BC, OS)	Complete	Auxiliary	X	

Nelson-Aalen estimator of cumlative hazard of BC death and Overall death (OS)

[a]=deterministic prediction before imputation.

Step 1: Imputation model

- We used command **mi impute**.
- A total of *m*=30 imputed datasets, with 20 iterations, were generated.
  - *m* was chosen to be larger than the highest percentage of missing values among the variables (Targeted therapy=20.14%), according to the rule of thumb by White et al (2011).
- In the chained equations, each variable was regressed on all other variables
  - logistic regression models were applied to binary outcome variables (ER, PR, HER2, chemotherapy, radiotherapy, endocrine therapy, targeted therapy, screening status), while
  - ordinal regression was used for categorical outcome variables (grade, nodal involvement N, surgery type, T stage, educational level).
- The imputation models were **stratified by age at diagnosis** (using the ***by* option** in **mi estimate**)
  - thus corresponding to including **all pairwise interactions of age at diagnosis** (<40, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, ≥80) with **each** covariate in the model.
  - Important to include age-interactions! As our analysis model were modelling age-varying incidence rates.

Step 2: Analysis model and pooling

- We combined the (imputed) variables ER, PR, HER2 and grade into the **surrogate subtype variable** using the **mi passive:** command.
  - Using mi passive: we can create a new variable from the imputed variables.
  - Such a new variable can be used in mi commands.

- To each of the *m* imputed datasets, we fitted the **analytical Poisson model** with 2-year age groups as covariates; and saved the estimated parameters and standard errors.
  - This generated *m* sets of parameter estimates (and standard errors).

- To estimate **pooled parameters**, we manually applied Rubin's rules to the *m* parameters:
  - Rubin's rule #1: **Pooled parameter** is the mean of the estimated parameters for the imputed data sets (i.e. taking average of *m* parameters).
  - Rubin's rule #2: **Standard error of the pooled parameter**; incl. both within-between imputations variances.
- This is typically done by **mi estimate. I will come back to why we did not use mi estimate.**

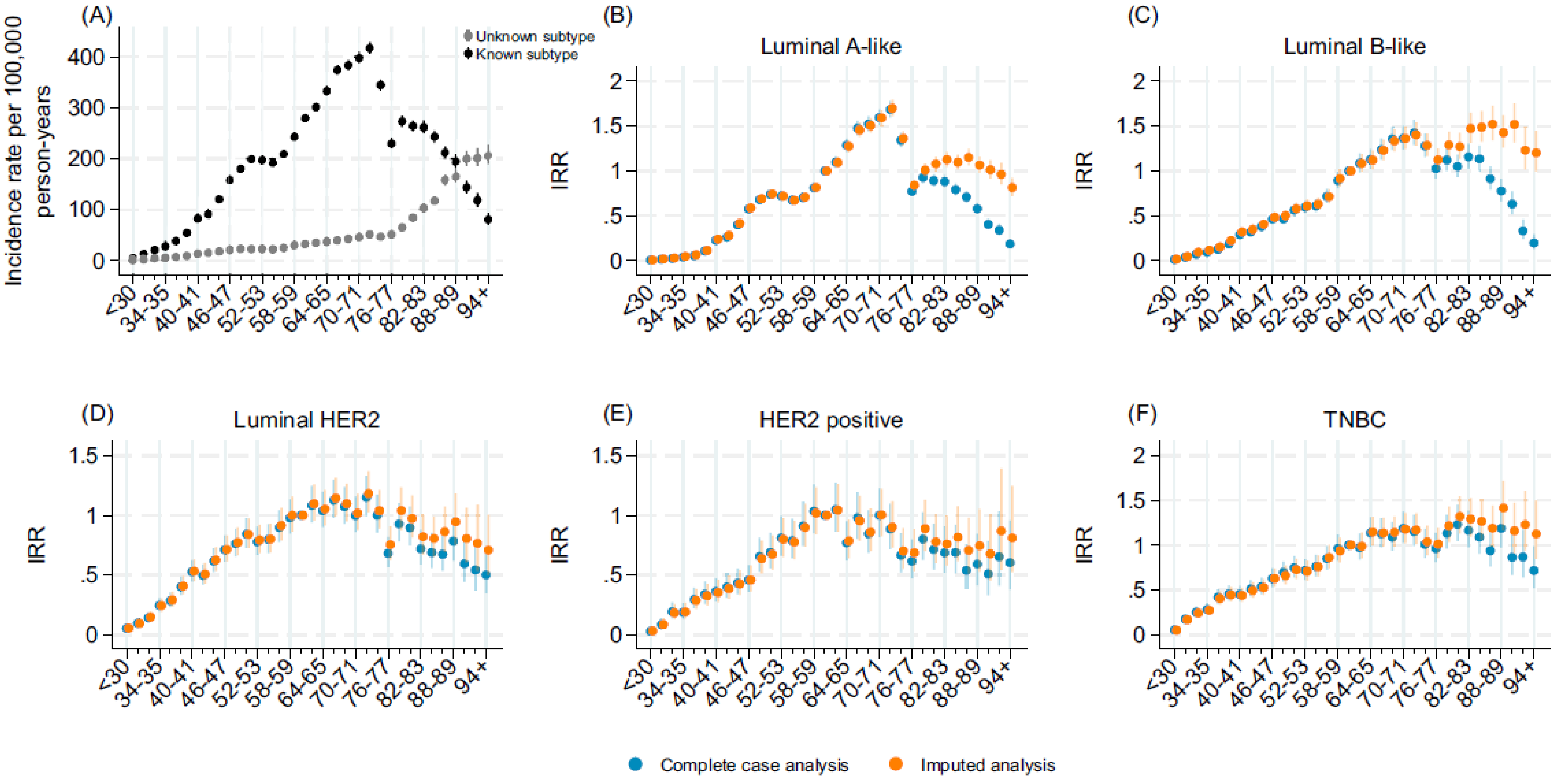


FIGURE 2 Breast cancer incidence rates of known and unknown subtype by age at diagnosis (A) and comparison of incidence rate ratios

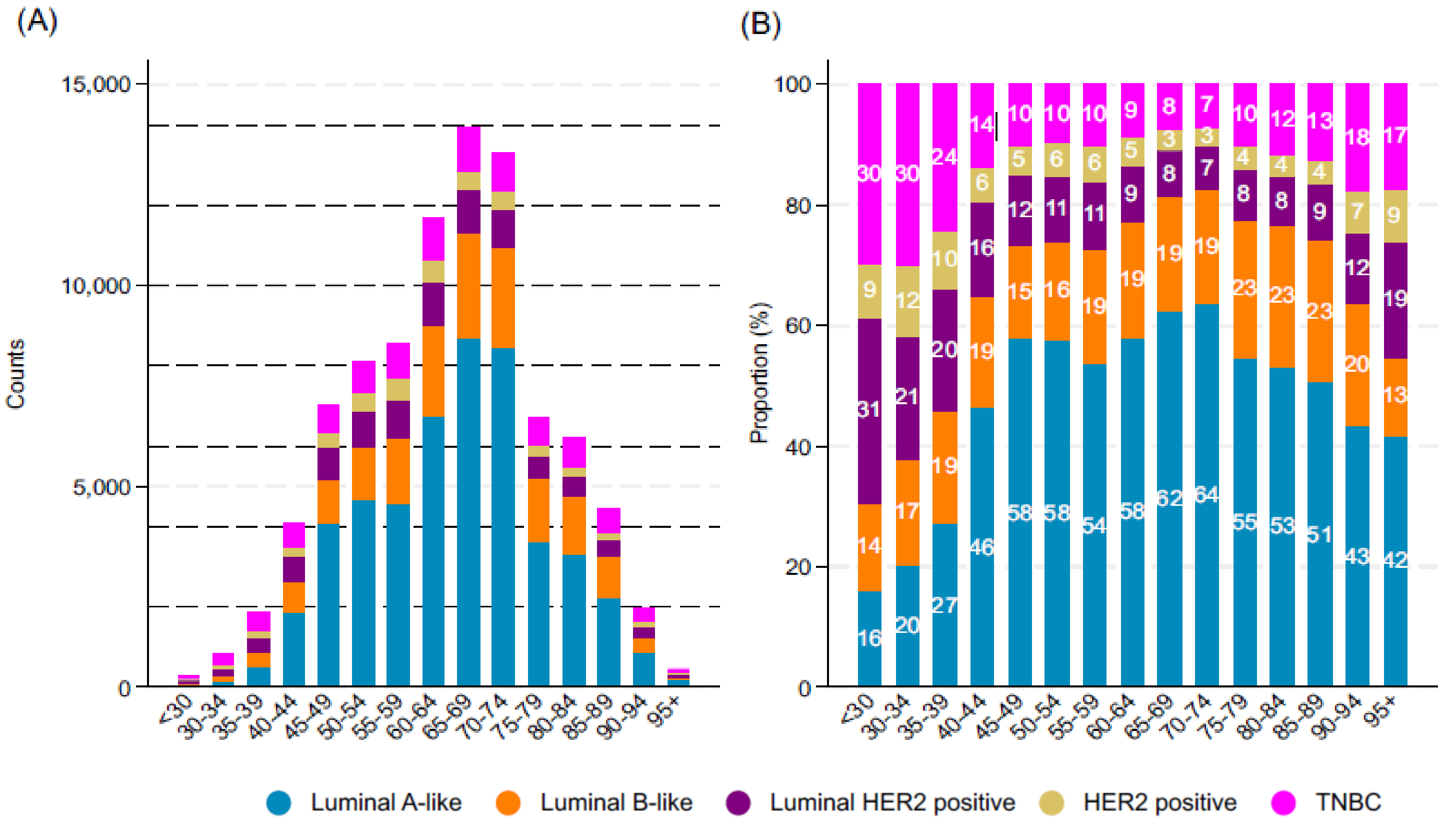
Appropriately estimating cancer incidence – without loss of cases

- A key strength of this analysis is that we included all women with missing subtype.
- Important as we were interested in the **absolute incidence rate** (not just relative rates):
  - If women with missing subtype are excluded - subtype-incidence rates will be underestimated.
- Relative effects are likely less impacted – at least in younger ages.

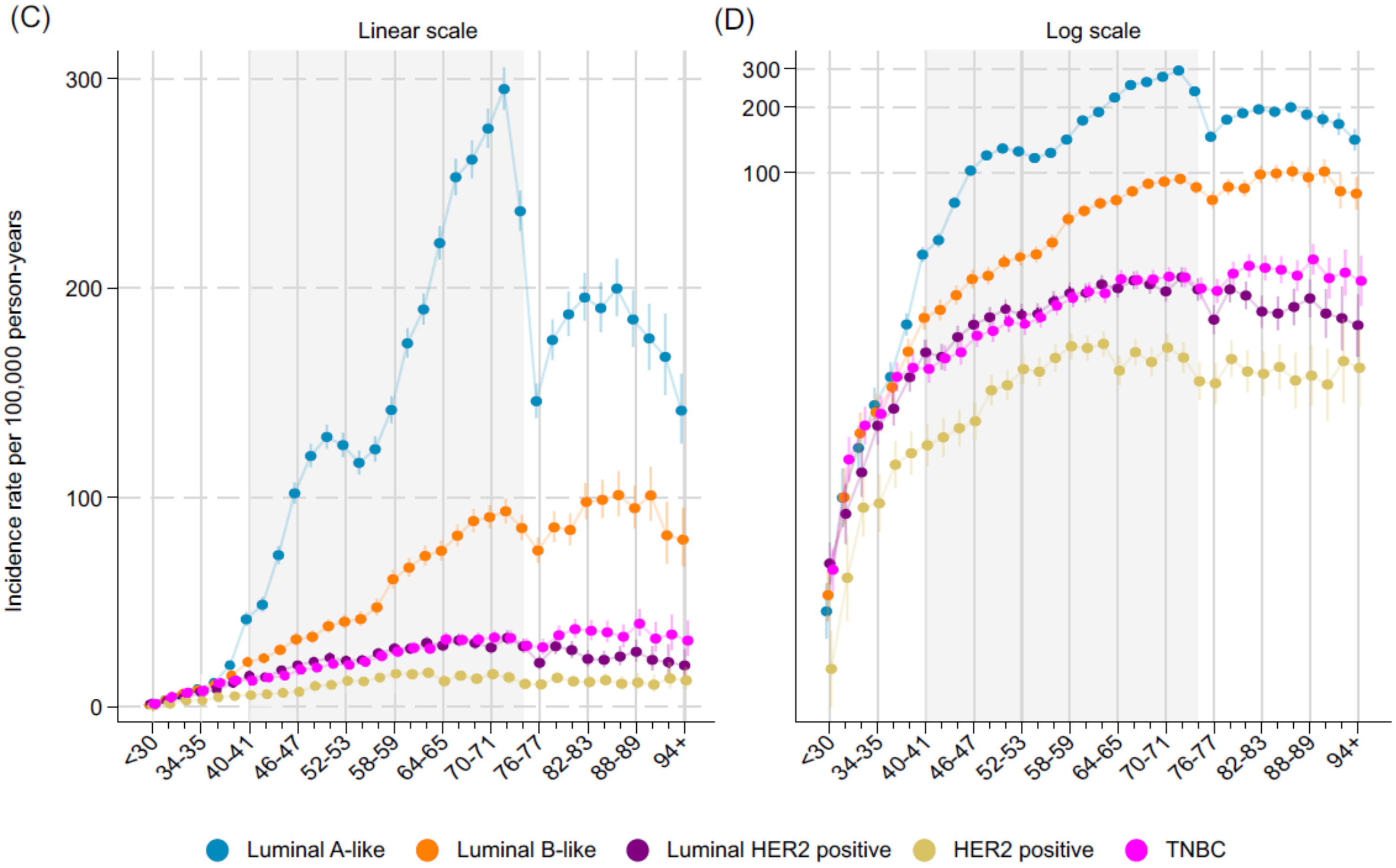
- The parameter estimates from the Poisson model represent
  - **Intercept**: rate in reference age
  - **Coefficients for covariates** (age effect): rate ratios (vs. the reference age)

- From these parameter estimates from the Poisson model, we can obtain at different ages
  - **Incidence rates** – directly from the parameters in the model.
  - **Proportions, counts** – by multiplying rate fractions of total rate (%) with the known N.
  - "pool-last-principle": to obtain **pooled** incidence rates & proportions:
    - transform rates/proportions from params in each imputed dataset >> then pooled them.

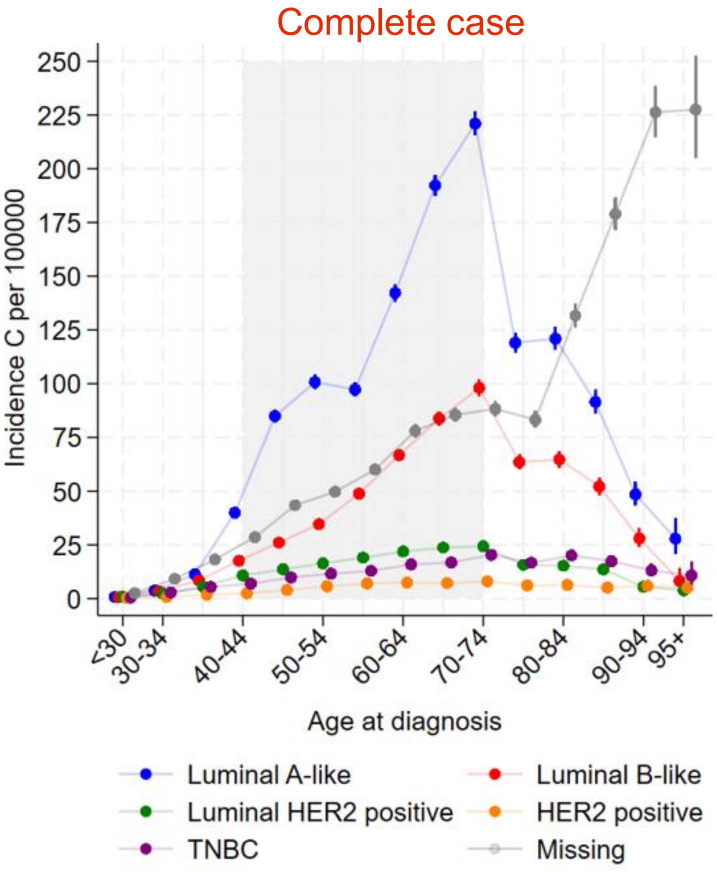
Results: Pooled counts and proportions post-estimated from parameters in Poisson model.

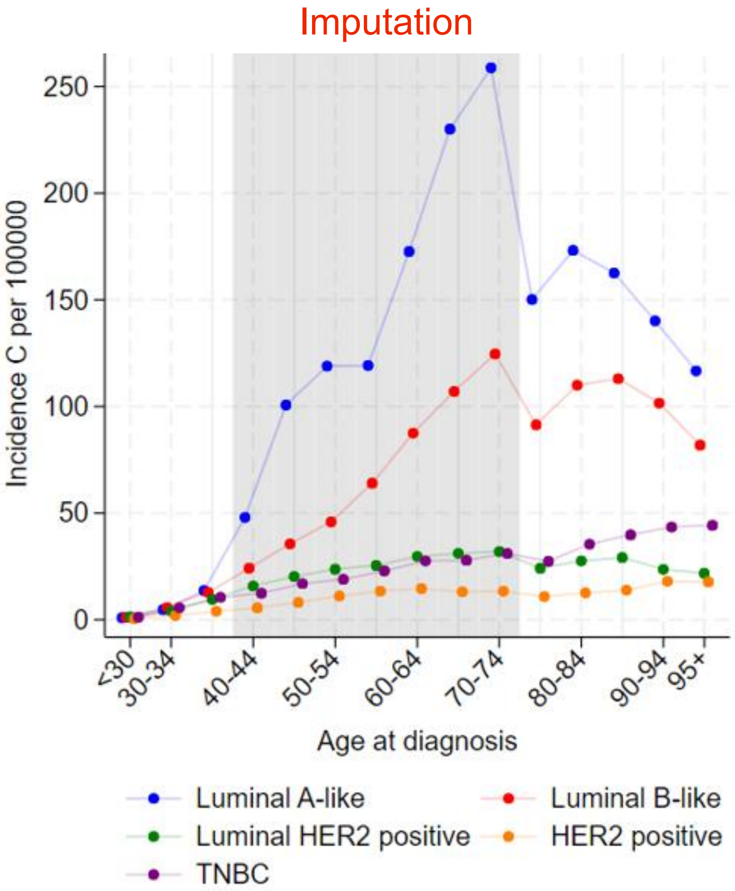


Results: Pooled incidence rates from parameters in Poisson model



Results not in the published paper! Absolute rates are higher in imputed analysis, esp. older ages.





Why we could not use **mi estimate** to obtain the pooled estimates

- MICE only works on individual-level data: We applied Poisson regression to individual level data.
- We only imputed the case dataset.
  - We then added the counts of "population-at-risk" for each individual, as an offset (in "pop_at_risk" variable).
  - E.g. **. poisson d_subtype1 i.age, exposure(pop_at_risk)**

- For each subtype: We restricted the case dataset to those with that subtype.
  - E.g. For the estimation of subtype 1 incidence – we only included the women with subtype 1.
- However, since we imputed the "outcome" (subtype):
  - Number of outcomes will differ for different *m* datasets.
    - Imputation m=1: 45000 Lum A
    - Imputation m=2: 44000 Lum A. etc.
  - This created **imputed datasets of different sizes for each subtype-specific model**.
  - As far as we could work out, **mi estimate** requires imputed datasets of the same size (same number of obs).
- In many applications of MICE, the interest is in imputing a covariate (exposure/treatment, confounder, etc.) – this will not change the size of the imputed datasets.

In conclusion

- This is one of the first studies to estimate subtype-specific BC incidence using MICE.
- MICE was important to avoid underestimation of incidence rates – up to 15.5% in our data.

- Essential to include a broad imputation model that captures the underlying missing data mechanism.
  - We had access to a wide range of clinical variables.
- Also important to include the correlation structures from the analysis model in the imputation model.

- **mi package** was a very powerful tool – it enabled us to estimate rates and impute the data.
  - Yet we faced challenges when using **mi estimate** for imputed datasets of different sizes.
- This is an example of **imputing the outcome** – while most examples in literature focus on imputing covariates (exposure/treatment, confounder) in regression models.

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