Molecular Subtype-Specific Risk of Subsequent Acute Myeloid Leukemia Following Breast Cancer: A Population-Based SEER Analysis

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BACKGROUND & QUESTION

Breast cancer (BC) survivors are at risk for therapy-related acute myeloid leukemia (**t-AML**).

Whether this risk **varies by BC molecular subtype** and latency period is **not well defined.**

What is the subtype-specific risk and latency pattern of subsequent AML following BC?

METHODS

- **Data Source:** SEER 18 registries (2000–2022)
- **Population:** Women with first primary invasive BC (n = 1,103,491)
- **Follow-up:** From BC diagnosis to AML, death, or last follow-up
- **Analysis:** Standardized Incidence Ratios (SIRs) by subtype and latency; Poisson regression
- **Latency Intervals:** <1 year, 1–5 years, 5–10 years, ≥10 years

COHORT OVERVIEW

Breast Cancer Cohort	Subsequent AML Cases	Median Follow-up	Total Person-Years
1,103,491 women	1,412 cases	7.2 years (IQR 3.1–11.4)	3,921,020 PY

SIR = Observed AML cases / Expected AML cases (vs. general population)
SIR > 1 indicates higher risk than **expected.**

RESULTS

OVERALL RISK BY MOLECULAR SUBTYPE

BC Molecular Subtype	Observed AML Cases	Expected Cases	SIR (95% CI)
Triple-Negative (TNBC)	428	124.0	3.45 (3.13–3.80)
HER2-Enriched	281	96.1	2.92 (2.59–3.26)
Luminal B	478	236.4	2.02 (1.83–2.23)
Luminal A	225	129.3	1.74 (1.53–1.98)

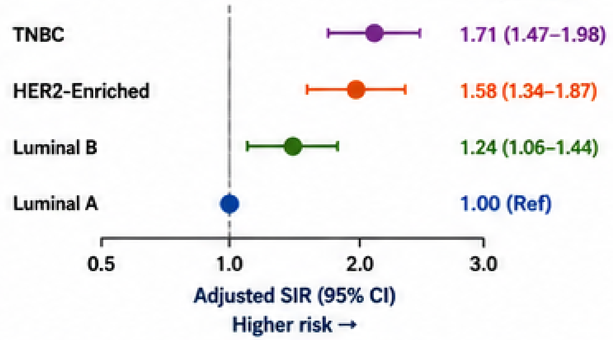
Highest overall risk: TNBC (SIR 3.45, 95% CI 3.13–3.80)

SIR BY LATENCY INTERVAL AND SUBTYPE

Latency from BC Diagnosis	TNBC	HER2-Enriched	Luminal B	Luminal A
<1 year	2.07	1.69	1.30	1.05
1–5 years	4.93	3.91	2.54	2.00
5–10 years	3.18	2.78	1.80	1.52
≥10 years	2.10	2.15	1.48	1.32

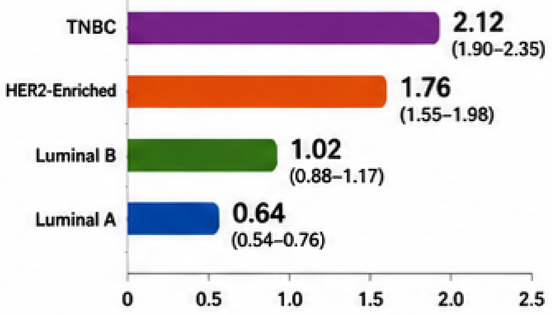
Peak risk at 1–5 years for all subtypes; highest in TNBC (SIR 4.93)

MULTIVARIABLE ANALYSIS (POISSON REGRESSION)



TNBC remains independently associated with highest AML risk

ABSOLUTE EXCESS RISK PER 10,000 PY



Greatest absolute excess risk in TNBC

INTERPRETATION

- BC survivors have a higher-than-expected risk of AML, varying by molecular subtype.
- Risk peaks at 1–5 years post-BC diagnosis, especially for TNBC.
- Even after adjustment, TNBC shows the highest independent risk and greatest absolute excess.

LIMITATIONS

- SEER lacks data on chemotherapy, radiotherapy, and endocrine therapy.
- **Potential misclassification** of molecular subtypes.
- **Residual confounding** possible.

CLINICAL IMPLICATION

- TNBC survivors may benefit from closer hematologic monitoring, particularly within the first 5 years.
- Risk stratification by subtype can inform survivorship counseling and long-term follow-up strategies.

KEY TAKEAWAYS

1. AML risk differs by BC molecular subtype.
2. Highest risk: TNBC, especially 1–5 years.
3. Elevated risk persists even after adjustment.

TAKE-HOME MESSAGE: Subsequent AML risk is subtype- and latency-dependent, with the strongest signal in TNBC at 1–5 years.