Breast Cancer in Younger Women: A Multicentre Study of Clinical and Pathological Features

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Background

Breast cancer (BC) in women <50 years is rising faster than in older age groups and carries distinct challenges.[1] Younger patients often have more aggressive clinico-pathological features (higher grade, higher Ki-67, triple-negative subtypes, greater nodal burden). There are a number of baseline risk factors in this population: reproductive exposures (hormonal contraception), lifestyle factors (obesity, alcohol, smoking), and germline predisposition (e.g., BRCA1/2), which collectively may shape tumour biology at diagnosis[2]

Despite therapeutic advances, survival outcomes remain poorer in younger patients, and their under-representation in trials limits age-specific evidence.[3] These gaps motivate our evaluation of risk factors, clinico-pathological characteristics, and outcomes in women <50.

Methods

We conducted a multicentre retrospective study of women under 50 years (n=376) diagnosed with invasive BC. All cases were discussed at the University College London Hospitals (UCLH) or Whittington Health (WH) Breast Multidisciplinary Team meetings from May 2019 to February 2025. Patients were stratified into five age groups: ≤30, 31–35, 36–40, 41–45, 46–49. Variables collected included age at diagnosis, risk factors, tumour characteristics, recurrence and treatment data.

Group comparisons for categorical variables were performed using the χ^2 test. Continuous variables were compared using the Mann-Whitney U test for two-group comparisons and the Kruskal-Wallis test for comparisons across multiple groups. Multivariable logistic regression models were constructed to identify independent predictors of high-grade (grade 3) tumours. Covariates were selected based on clinical relevance and univariate significance.

Results & Discussion

A total of 376 women aged 15–49 years (median 43 years, IQR 39–46.25) were included. The majority of patients were premenopausal (93.6%).

Tumour characteristics at diagnosis

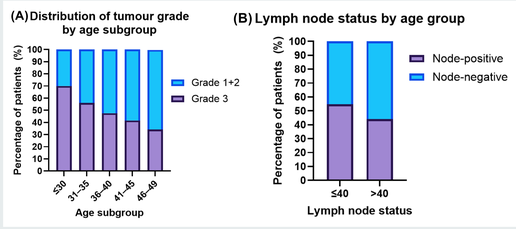
At diagnosis, 47.1% of patients were lymph node-positive and 6.9% presented with metastatic disease. Multifocal or multicentric tumours occurred in 29.3% of patients. The median tumour size was 25 mm (IQR 17–36).

Invasive ductal carcinoma predominated (89.4%). The most common molecular subtype was ER+/HER2− (62.9%). 43.1% of tumours were grade 3, with a median Ki-67 index of 20% (IQR 9.75–40.0).

Age-stratified differences in tumour characteristics

Women aged ≤40 had more aggressive disease features than those >40, including higher rates of grade 3 tumours (p=0.003), greater lymph node positivity (p=0.049), larger tumours (p=0.005), and higher Ki-67 indices (p=0.032). The proportion of grade 3 tumours declined progressively across the five age subgroups (p=0.009) (Figure 1).

Figure 1. Distribution of tumour grade (A) and lymph node status (B) by age subgroup. Grade 3 tumours and node positivity declined with increasing age (p=0.009 and p=0.0493, χ^2 tests).



Patients aged ≤30 years had a lower proportion of ER+HER2− tumours than those >30 years (40.0% vs 67.4%, p=0.0118).

BMI Links

Median BMI was higher in TNBC cases than in non-TNBC cases (27.39 vs 24.30 kg/m². Higher BMI was also associated with a greater odds of ER-negative disease (OR 1.05 per kg/m², 95% CI 1.01–1.10, p=0.028).

Genetics

172 (45.7%) had genetic data available for review; 38 (10.1%) had a pathogenic variant, including BRCA1/2 in 32 (8.5%). Pathogenic variants were more prevalent in ≤35 years than >35 years (p=0.0498). Notably, 50% of mutation carriers reported no family history of breast or ovarian cancer.

Multivariable Analysis

Two logistic regression models were performed to identify predictors of grade 3 tumours (vs grade 1–2) (Figure 2).

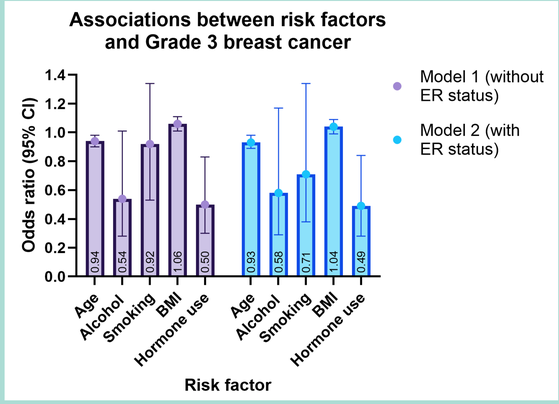
Model 1 (without ER adjustment):

- Younger age, higher BMI, and non-use of hormonal contraception were independently associated with grade 3 disease.
  - Age: OR 0.94 (95% CI 0.90–0.98, p=0.006)
  - BMI: OR 1.06 (1.01–1.11, p=0.017)
  - Hormonal contraception use: OR 0.50 (0.30–0.83, p=0.008)
- Alcohol use showed a borderline inverse association: OR 0.54 (0.28–1.01, p=0.052); smoking was not significant.

Model 2 (adjusted for ER status):

- Younger age and hormonal contraception use remained independent predictors of grade 3 tumours, but the associations of BMI and alcohol use were no longer significant. This suggests that the BMI-grade and alcohol-grade relationships may be partly mediated through tumour ER phenotype.

Figure 2. Forest plot showing odds ratios (95% CI) for grade 3 vs grade 1–2 tumours. Model 1 adjusted for age, alcohol use, smoking, BMI, and hormone use (oral contraceptive pills and hormonal IUDs); Model 2 additionally adjusted for ER status.



Treatment Outcomes

Neoadjuvant systemic therapy was administered to 34.0% of patients. In this subgroup, 66.7% of TNBC and 64.3% of HER2-positive tumours achieved a pathological complete response. At the time of analysis, 21 patients (5.8%) had documented recurrence and 10 (2.7%) had died.

Conclusions

BC in women under 50, particularly those ≤40 years, is characterised by higher grade, elevated Ki-67, and more frequent nodal positivity. These patterns underscore the need for prompt referral and multidisciplinary input in this group. Clinicians must maintain a high index of suspicion when evaluating breast symptoms in young women and perform careful nodal assessment. The association between higher BMI and grade 3 tumours suggests that inflammatory pathways may contribute to tumour aggressiveness, highlighting the importance of addressing adiposity and other modifiable lifestyle factors early in survivorship and prevention strategies. As half of mutation carriers reported no family history of BC, relying on family history alone for genetic testing may miss patients with pathogenic variants, suggesting the current UK testing criteria may be expanded to a wider patient cohort.

Future work must prioritise survivorship, addressing fertility, premature menopause, and psychological wellbeing in young women with BC. The main limitation of this study is its small, retrospective design. A prospective registry capturing clinical, pathological, and survivorship data would strengthen the evidence base and improve risk stratification in this population.

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