Research Article

Cancer Epidemiology, Biomarkers & Prevention

Molecular Subtypes of Breast Cancer: Long-term Incidence Trends and Prognostic Differences

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Abstract

Background: Secular trends in incidence and prognosis of molecular breast cancer subtypes are poorly described. We studied long-term trends in a population of Norwegian women born 1886–1977.

Methods: A total of 52,949 women were followed for breast cancer incidence, and 1,423 tumors were reclassified into molecular subtypes using IHC and *in situ* hybridization. We compared incidence rates among women born 1886–1928 and 1929–1977, estimated age-specific incidence rate ratios (IRR), and performed multiple imputations to account for unknown subtype. Prognosis was compared for women diagnosed before 1995 and in 1995 or later, estimating cumulative risk of death and HRs.

Results: Between 50 and 69 years of age, incidence rates of Luminal A and Luminal B ($HER2^-$) were higher among women born in 1929 or later, compared with before 1929 [IRRs 50–54 years; after imputations: 3.5; 95% confidence interval (CI), 1.8–6.9 and 2.5; 95% CI, 1.2–5.2, respectively], with no clear differences for other subtypes. Rates of death were lower in women diagnosed in 1995 or later, compared to before 1995, for Luminal A (HR 0.4; 95% CI, 0.3–0.5), Luminal B ($HER2^-$; HR 0.5; 95% CI, 0.3–0.7), and Basal phenotype (HR 0.4; 95% CI, 0.2–0.9).

Conclusions: We found a strong secular incidence increase restricted to Luminal A and Luminal B ($HER2^-$) subtypes, combined with a markedly improved prognosis for these subtypes and for the Basal phenotype.

Impact: This study documents a clear secular increase in incidence and a concomitant improved prognosis for specific molecular breast cancer subtypes. *Cancer Epidemiol Biomarkers Prev; 25(12); 1625–34. ©2016 AACR.*

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Introduction

Breast cancer incidence rates have gradually increased in Norway since the 1950s (1, 2), with a markedly stronger increase starting in the early 1990s. Breast cancer mortality remained stable from the 1950s until around 1995; since then, there has been a clear and consistent decline (1). Similar changes in incidence and mortality have been observed in most developed countries (3–6). However, long-term secular trends in incidence and prognosis of molecular subtypes of breast cancer are poorly documented.

The heterogeneous nature of breast cancer that is observed both clinically and histopathologically, is also apparent in gene expression patterns (7, 8). Using IHC and *in situ* hybridization (ISH) as surrogates for gene expression analysis, archival tumor tissue can be reclassified into molecular subtypes (7–12). We used IHC and ISH to reclassify incident tumors into six subtypes: Luminal A [estrogen receptor (ER) and/or progesterone receptor (PR)+, $HER2^-$, Ki67 <15%], Luminal B ($HER2^-$) (ER and/or PR^+, $HER2^-$, Ki67 $\geq$15%), Luminal B ($HER2^+$) (ER and/or PR^+, $HER2^+$), HER2 type (ER^-, PR^-, $HER2^+$), five negative phenotype [ER^-, PR^-, $HER2^-$, Cytokeratin 5 $(CK5)^-$, and $EGFR^-$], and Basal phenotype [ER^-, PR^-, $HER2^-$, $CK5^+$, and/or $EGFR^+$].

Our main aim was to study long-term trends in incidence of different molecular breast cancer subtypes in a population of Norwegian women born between 1886 and 1977. Our second aim was to study the prognosis of molecular breast cancer subtypes diagnosed among these women.

Materials and Methods

This follow-up study comprises women from two population-based surveys conducted in Nord-Trøndelag County, Norway. Information on incident breast cancer was obtained from the Cancer Registry of Norway, date of death, and/or emigration from Statistics Norway, and causes of death from the Norwegian Cause of Death Registry. Pathology reports and formalin-fixed, paraffin-embedded (FFPE) tissue from the first primary tumor were retrieved from the Department of Pathology and Medical Genetics at St. Olav's Hospital, Trondheim University Hospital, Norway.

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Cohort 1

The first survey was conducted between 1956 and 1959, as part of a larger study that also included two other counties (13). We studied women from Nord-Trøndelag County, comprising a total of 25,727 women born between 1886 and 1928 who were followed for breast cancer occurrence from January 1, 1961, until December 31, 2008. Follow-up was facilitated by the introduction of the unique 11-digit identity number of all Norwegian citizens in 1961. In total, 1,379 incident cases were diagnosed during follow-up, and 909 of these tumors were previously subtyped by our group (11). Some tumors were diagnosed at other hospitals, in particular in the 1960s and 1970s, and tumor tissue from these cases was not available for this study. After diagnosis, all patients were followed until death from breast cancer or death from other causes, or until December 31, 2010.

Cohort 2

The second survey was conducted between 1995 and 1997. In this study, all women in Nord-Trøndelag County aged 20 years or older were invited to participate in the second wave of the HUNT Study in Nord-Trøndelag (14). A total of 34,221 women born between 1897 and 1977 participated. From attendance until December 31, 2009, 728 women were diagnosed with breast cancer. Of these, 157 were already included in Cohort 1. Of the remaining tumors, 57 were unavailable for subtyping, resulting in a total of 514 tumors from Cohort 2 that were subtyped in this study (Fig. 1). After diagnosis, these patients were followed until death from breast cancer or death from other causes, or until December 31, 2013.

In this study, we merged data from the two cohorts (Fig. 1). In accordance with the requirements and conditions of the ethical approval of the study, patient identity was known to us for breast cancer cases but not for the underlying populations. Because there was some overlap in birth year between Cohort 1 and 2, we restricted Cohort 2 to women born after 1928 ($n = 27{,}222$) to avoid duplicate observations in the incidence analyses. In the restricted cohort, there were 529 incident breast cancers, including 480 of the 514 cases that could be subtyped. In the analysis of incidence rates, we therefore used data from a total of 1,908 incident breast cancers that occurred among 52,949 women; 1,379 (909 subtyped cases) from Cohort 1 and 529 (480 subtyped cases) from Cohort 2.

In the analyses of prognosis for different breast cancer subtypes, we included all 514 cases from Cohort 2 and the 909 cases from Cohort 1, yielding a total of 1,423 subtyped cases.

Specimen characteristics

New 4-μm-thick sections from representative paraffin blocks were stained with hematoxylin–erythrosine–saffron (HES), reviewed by two pathologists independently, and classified into histopathologic type and grade (15, 16). Any discrepancies were discussed, and consensus reached. Tumor size was measured on the glass slide, and correlated to information in the pathology report. In cases with multifocal tumors, the largest tumor was selected.

Tissue microarrays (TMA) were constructed using the Tissue Arrayer MiniCore 3 with TMA Designer2 software (Alphelys). Three tissue cores (1 mm in diameter) from the tumor periphery were inserted into TMA recipient blocks, and 4-μm-thick sections were cut and mounted on Superfrost+ glass slides, dried at 37°C overnight, and stored in the freezer at −20°C. For IHC, slides were heated to 60°C for 2 hours, and pretreated in a PT Link, Pre-Treatment Module for Tissue Specimens (Dako Denmark A/S, 2600 Glostrup, DK) with buffer (Low pH Target Retrieval Solution K8005 for Ki67, High pH Target Retrieval Solution K8004 for all other markers) at 97°C for 20 minutes.

Slides were stained with HES, and immunostaining for ER (Clone SP1, concentration 33 mg/mL, dilution 1:100; Cell Marque), PR (Clone 16, concentration 360 mg/L, dilution 1:400; NovoCastra Laboratories), HER2 (Clone CB11, concentration 3.9 g/L, dilution 1:640; Novocastra), the proliferation marker Ki67 (Clone MIB1, concentration 35 mg/L, dilution 1:100; Dako Denmark A/S), and Basal markers CK5 (Clone XM26, concentration 50 mg/L, dilution 1:100; Novocastra) and EGFR (Clone 2-18C9, concentration ready to use, no dilution; Dako) was done in a DakoCytomationAutostainer Plus (Dako). Dako REAL EnVision Detection System with Peroxidase/DAB+, Rabbit/Mouse, code K5007, was used for visualization for all markers except EGFR. EGFR was immunostained and visualized with EGFR pharmDX

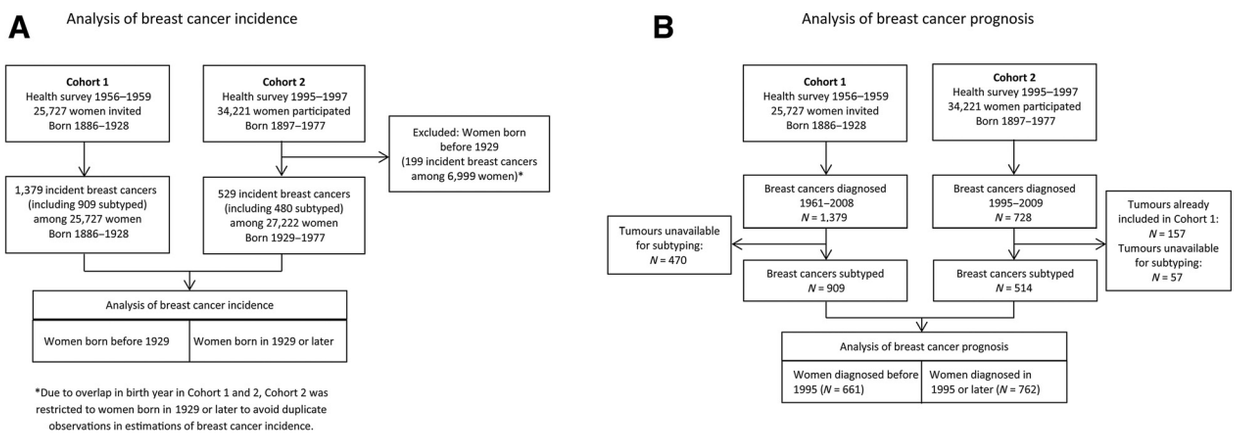

Figure 1.
Overview of study population. **A,** Analysis of breast cancer incidence. **B,** Analysis of breast cancer prognosis.

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Kit, code K1494 (Dako). Negative controls were included in all staining runs.

Chromogenic ISH (Cohort 1) and fluorescence ISH (Cohort 2) were used to demonstrate the *HER2* gene and chromosome 17 centromere. The Dual-Colour Probe Kit HER2 CISH pharmDx Kit, code 109 (Dako) was used for CISH (11), and HER2 IQFISH DAKO pharmDX Kit K 5731 (Dako) was used for FISH. Pretreatment was done with pepsin solution at 37○C for 25 minutes for both CISH and FISH.

Scoring and reporting

Slides were scanned using Ariol SL-50 3.3 Scan system (Genetix Europe Ltd.). IHC markers were assessed by two researchers independently. Discrepant results were discussed and consensus reached.

HER2 status was assessed with a bright-field microscope (Nikon Eclipse 80*i*; Cohort 1) and a fluorescence microscope (Nikon Eclipse 90*i*) with Cytovision software version 3.7 (Applied Imaging International Ltd.; Cohort 2).

Classification of markers

ER and PR were positive when $\geq$1% of tumor nuclei showed positive staining, irrespective of staining intensity (17). Ki67 was counted in 500 tumor cells (hotspots), and considered high when $\geq$15% of nuclei were positive, irrespective of staining intensity (10, 18–20). Membranous staining for HER2 was scored from 0 to +3, (0/+1 negative; +2 borderline/equivocal; +3 positive; ref. 21). *HER2* amplification was defined as a gene to chromosome ratio $\geq$2. At least 20 nonoverlapping, well-preserved tumor cell nuclei with signals for both *HER2* and chromosome 17 centromere were assessed. Tumors with unsuccessful ISH, but IHC +3, were considered positive.

For CK5 and EGFR, a staining index was calculated by multiplying the proportion of positive staining cells [1 (<10 %); 2 (10%–50%); 3 (>50 %)] by staining pattern/intensity. Staining intensity for CK5 was defined as 0 (no staining); 1 (weak); 2 (moderate), and 3 (strong). For EGFR, membranous staining was 0 (no staining); 1 (faint, incomplete staining); 2 (moderate intensity, circumferential staining); 3 (strong intensity, circumferential staining), according to Dako PharmDX Kit guidelines. A staining index of 0–1 was classified as negative, 2–9 as positive. The REMARK recommendations for reporting tumor marker studies were followed (22).

Classification of tumors

Tumors were classified into the following six molecular subtypes: Luminal A, Luminal B ($HER2^-$), Luminal B (HER2+), HER2 type, 5 negative phenotype, and Basal phenotype, based on IHC and ISH results, as previously described (11).

To allow comparison with previous studies (23–25), tumors were also classified into four subtypes according to hormone $receptor^-$ and HER2 status: ER^+ and/or PR^+, $HER2^-$; ER^+ and/or PR^+, $HER2^+$; ER^- and PR^-, $HER2^+$; and ER^- and PR^-, $HER2^-$. The results are presented as supplementary material.

Statistical analyses

During follow-up for breast cancer occurrence, censoring was done at time of death or emigration. Incidence rates were estimated separately for women born before 1929 and women born in 1929 or later. Age-specific rates were calculated to account for differences in age at baseline, and variations in age at diagnosis between subtypes. Estimates of incidence rates were plotted according to birth year and age for all incident cancers combined, and for each subtype separately. Poisson regression was used to compare incidence rates between women born before 1929 and women born in 1929 or later. The data allowed comparison of incidence rates in the age range 50–69 years. In the comparisons of Luminal A and Luminal B ($HER2^-$), we had sufficient statistical power to use 5-year categories of age within that age-range, estimated as incidence rate ratios (IRR) with 95% confidence intervals (CI). For the remaining subtypes, statistical power was limited and we used 10-year categories in the incidence comparisons.

For some cases, tumor tissue was unavailable, or the tumors could not be subtyped for other reasons. Thus, tumors from 34% of cases born before 1929, and 9% of cases born in 1929 or later could not be subtyped. Consequently, the observed subtype-specific incidence rates would underestimate the true rates, and underestimation would be greater for women born before 1929, because their tumor subtype was more likely to be unknown. To compensate for this, we performed multiple imputations to predict the molecular subtype of these tumors (24, 26), assuming samples were missing at random (27). The imputation model included all information available: age (5-year categories) and calendar year at diagnosis (continuous), stage (I, II, III, IV, unknown), and extent of disease (disease localized to the breast, local invasion, regional lymph nodes, distant lymph nodes or organ metastases, unknown) as reported by the Cancer Registry of Norway, year of birth (5-year categories), observation time after diagnosis (log-transformed, continuous), and survival status (alive, death from breast cancer, death from other causes). Excluding each of the following variables in turn—stage, extent of disease or survival time—had no major influence on the imputed rates, nor did changing the categorization of continuous variables. Descriptive statistics for the information used in the imputation models are available in Supplementary Table S1. Incidence rates with 95% CIs were calculated based on 50 imputed data sets according to birth year and 5-year age categories.

In analyses of prognosis, we distinguished between women diagnosed before 1995 and women diagnosed in 1995 or later, to approximate the gradual implementation of adjuvant treatment (including effective chemotherapy, antihormonal treatment and trastuzumab) in Norway (28). For each subtype, we calculated cumulative incidence of death from breast cancer at 5 and 15 years after diagnosis, treating deaths from other causes as competing events. Gray's test was used to test equality between cumulative incidence curves.

We used Cox proportional hazards models to compare the rate of death within each diagnostic period according to molecular subtype, and to compare the rate of death for each subtype between diagnostic periods. In the latter analysis, estimations were made for the first 5 and 15 years after diagnosis, and for the entire follow-up period. We estimated hazard ratios (HR) with 95% CIs from the month of diagnosis until death, with censoring at time of death from other causes, and with adjustments for age, stage and histopathologic grade at diagnosis. No clear violations of proportionality were found in log-minus-log plots. Stata version 13.1 (Stata Corp.) was used for statistical analyses.

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Table 1. Incidence rates and incidence rate ratios of breast cancer molecular subtypes according to age at diagnosis and year of birth

		Observed				Imputed[a]			
		Incidence rate (cases/100,000 person-years)				Incidence rate (cases/100,000 person-years)			
Molecular subtype	Age	Women born 1886–1928	Women born 1929–1977	IRR	(95% CI)	Women born 1886–1928	Women born 1929–1977	IRR	(95% CI)
Total[b]	50–54	97.3	195.7	2.1	(1.5–2.8)				
	55–59	122.6	213.2	1.7	(1.3–2.3)				
	60–64	149.5	309.4	2.1	(1.6–2.7)				
	65–69	179.7	235.5	1.3	(1.0–1.7)				
Luminal A	50–54	9.9	76.1	7.7	(3.4–17.4)	24.3	84.7	3.5	(1.8–6.9)
	55–59	17.7	118.4	6.7	(3.8–11.9)	34.9	132.3	3.8	(2.3–6.4)
	60–64	35.5	158.9	4.5	(2.9–6.8)	54.9	177.3	3.2	(2.2–4.8)
	65–69	60.9	142.0	2.3	(1.6–3.5)	86.4	154.3	1.8	(1.2–2.6)
Luminal B ($HER2^-$)	50–54	8.5	50.0	5.9	(2.4–14.5)	23.1	57.6	2.5	(1.2–5.2)
	55–59	25.9	37.9	1.5	(0.8–2.8)	45.3	44.7	1.0	(0.5–1.9)
	60–64	19.9	66.9	3.4	(1.8–6.2)	37.5	71.9	1.9	(1.1–3.4)
	65–69	32.4	38.1	1.2	(0.6–2.3)	49.5	41.6	0.8	(0.4–1.6)
Luminal B ($HER2^+$)	50–59	9.6	10.2	1.1	(0.5–2.4)	17.6	13.8	0.8	(0.4–1.7)
	60–69	8.1	21.6	2.7	(1.3–5.5)	14.0	23.1	1.7	(0.8–3.5)
HER2 type	50–59	8.3	11.3	1.4	(0.6–3.1)	18.2	13.9	0.8	(0.4–1.6)
	60–69	9.1	7.7	0.8	(0.3–2.3)	15.1	9.4	0.6	(0.2–1.6)
Five negative phenotype	50–59[c]	—	—	—	—	—	—	—	—
	60–69	5.6	7.7	1.4	(0.5–4.0)	10.1	9.1	0.9	(0.3–2.6)
Basal phenotype	50–59	4.5	13.6	3.0	(1.2–7.8)	8.9	16.2	1.8	(0.8–4.3)
	60–69	7.1	7.7	1.1	(0.4–3.0)	11.1	9.0	0.8	(0.3–2.6)

[a]Based on 50 imputed datasets using age (5-year categories) and calendar year at diagnosis (continuous), stage (I, II, III, IV, unknown), and extent of disease (disease localized to the breast, local invasion, regional lymph nodes, distant lymph nodes or organ metastases, unknown) as reported by the Cancer Registry of Norway, year of birth (5-year categories), observation time after diagnosis (log-transformed, continuous) and survival status (alive, death from breast cancer, death from other causes).
[b]Total breast cancer incidence from the Cancer Registry of Norway, including cases with unknown subtype.
[c]Too few observations.

Ethical approval

The study was approved by the Regional Committee for Medical and Health Sciences Research Ethics (REK; ref. no.: 836/2009).

Results

Age-specific incidence rates according to year of birth

Mean age at baseline was 51.0 years for women born before 1929, and 43.4 years for women born in 1929 or later. Mean follow-up times in the two groups of women were 29.7 and 13.1 years, respectively.

Between 50 and 69 years of age, total breast cancer incidence was higher for women born in 1929 or later, compared to women born before 1929 (Table 1 and Supplementary Fig. S1). In subtype-specific analyses, incidence rates of Luminal A and Luminal B ($HER2^-$) were consistently higher in women born in 1929 or later (Table 1 and Fig. 2). The higher incidence was particularly evident in the age group 50–54 years (IRR 7.7; 95% CI, 3.4–17.4 and IRR 5.9; 95% CI, 2.4–14.5, respectively) and weaker in the 65–69 year age group [IRR 2.3; 95% CI, 1.6–3.5 for Luminal A and IRR 1.2; 95% CI, 0.6–2.3 for Luminal B ($HER2^-$)]. Although the incidence rates for Luminal B ($HER2^+$) and nonluminal subtypes were also higher for women born in 1929 or later, the differences were much less pronounced and varied considerably between age groups.

After imputation for unknown subtype, the observed relative rates (IRR) for Luminal A and Luminal B (HER^-) were strongly attenuated (Table 1). Thus, the IRR for Luminal A breast cancer in the age group 50–54 years was reduced from 7.7 to 3.5 (95% CI, 1.8–6.9), and for Luminal B ($HER2^-$), there was a corresponding reduction in IRR from 5.9 to 2.5 (95% CI, 1.2–5.2) after imputation. The IRRs for Luminal B (HER2+) and the nonluminal subtypes were almost fully attenuated after imputation (Table 1).

Incidence analysis based on observed data for the four subtypes determined by ER, PR, and HER2 status showed a marked incidence increase for the ER^+, PR^+, $HER2^-$ subtype, with an IRR of 6.9 (95% CI, 3.8–12.6) for the age group 50–54 years. After imputation, the IRR was attenuated to 3.1 (95% CI, 1.9–5.1). The results of these analyses are reported in detail in Supplementary Table S2 and Supplementary Fig. S2.

Prognosis according to molecular subtype and year of diagnosis

Mean follow-up after diagnosis was 9.8 years for patients diagnosed before 1995, and 7.9 years for patients diagnosed in 1995 or later. Women diagnosed in 1995 or later were on average younger, and their tumors were more often Luminal A and of lower grade. Furthermore, tumors diagnosed in 1995 or later were generally smaller compared to those diagnosed before 1995 (Table 2). However, information on tumor size was frequently missing or insufficiently described in the pathology reports from the first diagnostic period.

In both diagnostic periods, Luminal A had the best prognosis, and HER2 type had the poorest (Table 3 and Fig. 3). Although the absolute risks of death for each subtype differed between diagnostic periods, the patterns of risk between subtypes remained roughly similar.

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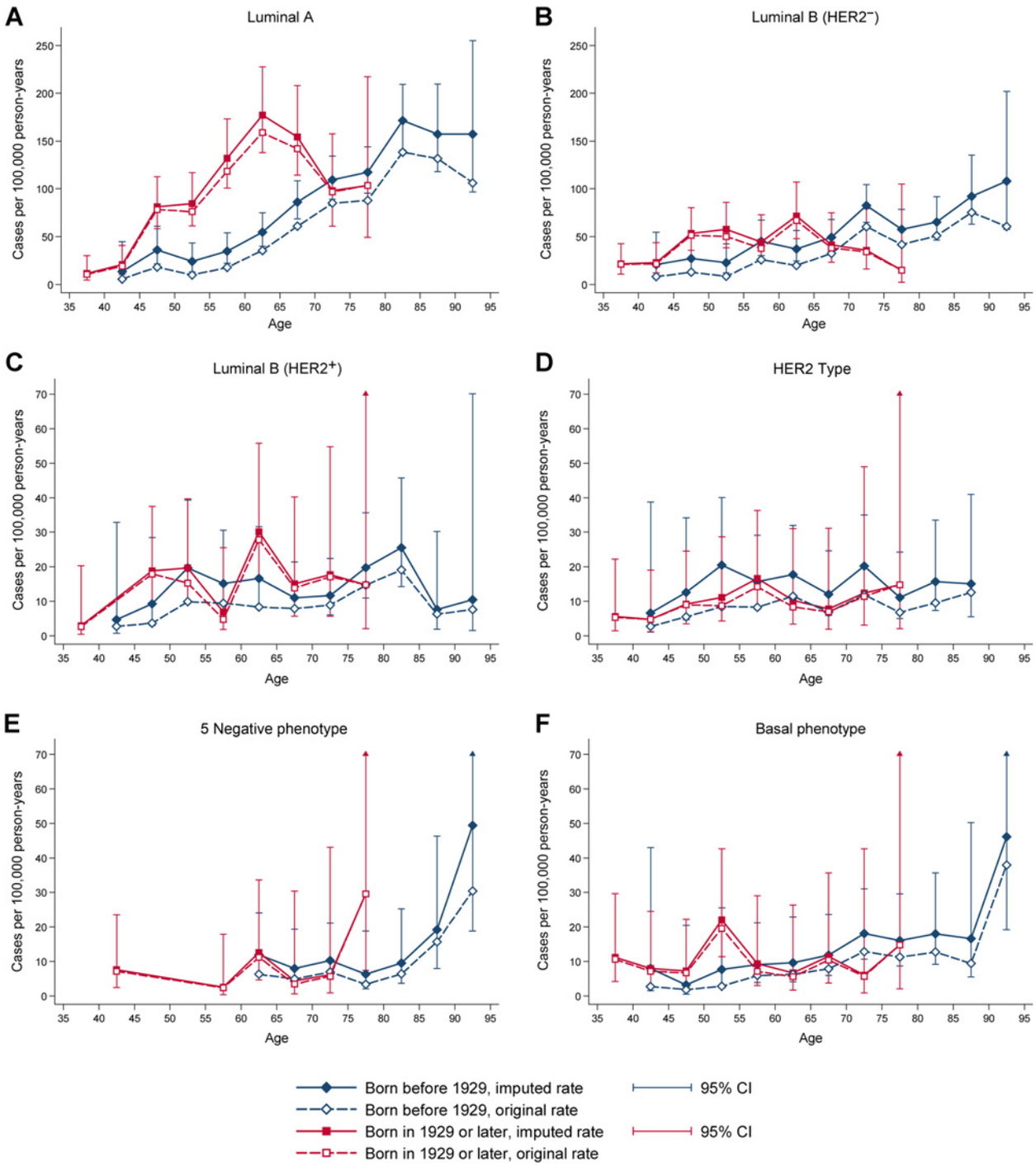

Figure 2.

Subtype-specific breast cancer incidence rates according to age and year of birth. Blue lines: women born before 1929. Red lines: women born in 1929 or later. Dotted lines (red and blue) represent incidence rates of subtyped cases. Solid lines (red and blue) represent average incidence rates from 50 imputed datasets with corresponding 95% CIs.

The cumulative risk of death from Luminal A breast cancer was 37 % (95% CI, 32%–44%) after 15 years of follow-up for women diagnosed before 1995 (Table 3; Fig. 3), and 13% (95% CI, 9%–17 %) in women diagnosed in 1995 or later, indicating a strong decline in case fatality from the first to the second diagnostic period. The corresponding cumulative risk of death for women

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Table 2. Characteristics of breast cancer cases with successfully subtyped tumors

Women with incident breast cancer	Diagnosis before 1995		Diagnosis in 1995 or later	
Number of women	661		762	
Mean age at diagnosis (SD)	69.5	(10.4)	65.5	(14.3)
Mean follow-up after diagnosis (SD)	9.8	(8.7)	7.9	(4.4)
Deaths from breast cancer (%)	293	(44)	131	(17)
Deaths from other causes (%)	316	(48)	145	(19)
Molecular subtype (%)				
Luminal A	291	(44)	414	(54)
Luminal B ($HER2^-$)	194	(29)	183	(24)
Luminal B ($HER2^+$)	55	(8)	57	(7)
HER2 type	53	(8)	36	(5)
Five negative phenotype	23	(3)	25	(3)
Basal phenotype	45	(7)	47	(6)
Histopathologic grade (%)				
1	78	(12)	145	(19)
2	346	(52)	397	(52)
3	237	(36)	220	(29)
Unknown	—		—	
Regional lymph node metastasis (%)				
Yes	234	(35)	239	(31)
No	238	(35)	418	(55)
Unknown histopathology[a]	189	(29)	105	(14)
Tumor size (%)				
≤2 cm	268	(41)	466	(61)
>2–5 cm	27	(4)	236	(31)
>5 cm	9	(1)	29	(4)
Uncertain, but >2 cm	141	(21)	4	(1)
Uncertain	216	(33)	27	(4)
Stage (%)[b]				
I	338	(51)	390	(51)
II	239	(36)	314	(41)
III	43	(7)	35	(5)
IV	35	(5)	23	(3)
Unknown	6	(1)	—	
Extent of disease (%)[b]				
Disease localized to the breast	225	(34)	369	(48)
Local invasion	23	(3)	14	(2)
Regional lymph nodes	155	(23)	234	(31)
Distant lymph node or organ metastases	25	(4)	22	(3)
Unknown	233	(35)	123	(16)

[a]Includes cases where histopathologic examination was done, but reports were not available, and cases where no axillary lymph nodes were removed.
[b]As recorded by the Cancer Registry of Norway. Information is based on histopathologic and/or clinical examination.

diagnosed with HER2 type was 57% (95% CI, 44%–71%) and 42% (95% CI, 28%–60%).

We used Cox regression analysis to compare rates of death between subtypes in each diagnostic period, and found that among women diagnosed before 1995, the rate of death from HER2 type was more than twice as high (age-adjusted HR 2.3; 95% CI, 1.5–3.5) as for Luminal A. The corresponding HR for women diagnosed with HER2 type in 1995 or later was much higher (age-adjusted HR 5.1; 95% CI, 2.8–9.3). Adjusting for histopathologic grade or stage of disease at diagnosis did not substantially influence these results.

We also used Cox regression analysis to compare rates of death for each subtype between diagnostic periods (Table 3). Generally, rates of death were lower for women diagnosed in 1995 or later, although precision was low for the less common subtypes. Thus, for the entire follow-up period, the rate of death was 60% lower for Luminal A (age-adjusted HR 0.4; 95% CI, 0.3–0.5), 50% lower for Luminal B ($HER2^-$; age-adjusted HR 0.5; 95% CI, 0.3–0.7), and 60% lower for Basal phenotype (age-adjusted HR 0.4; 95% CI, 0.2–0.9). Changes between diagnostic periods for the other subtypes were less apparent (Table 3). The results remained similar when analyses were restricted to the first 5 and 15 years after diagnosis, with clear improvements in survival between diagnostic periods for Luminal A, Luminal B, ($HER2^-$) and Basal phenotype (Supplementary Table S3). Analyses based on the four subtypes determined by ER, PR, and HER2 status showed that both before and after 1995, the ER^+, PR^+, $HER2^-$ subtype had the best prognosis (Supplementary Table S4 and Supplementary Fig. S3). Comparing prognosis between diagnostic periods, clear improvements were seen for the ER^+, PR^+, $HER2^-$ subtype (HR 0.4; 95% CI, 0.3–0.5), and for the triple negative (ER^-, PR^-, $HER2^-$) subtype (HR 0.5; 95% CI, 0.3–0.9; Supplementary Tables S4 and S5).

Discussion

This large population-based study of women born between 1886 and 1977 shows that for women aged 50–69 years, the incidence of breast cancer was higher among those born in 1929 or later, compared to women born before 1929. This was primarily due to a much higher incidence of the low-proliferative Luminal A tumors, but also to some extent for Luminal B ($HER2^-$) tumors. The prognosis was generally better for women diagnosed in 1995 or later, compared to before 1995, but clear improvements in

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Table 3. Absolute and relative risk of death from breast cancer according to molecular subtype and diagnostic period

		Cumulative incidence of death from breast cancer				Age-adjusted hazard ratio of death from breast cancer[a]		
		First 5 years after diagnosis		First 15 years after diagnosis		Total follow-up time after diagnosis		
Molecular subtype	Patients (*n*)	Deaths (*n*)	Cum. inc. %, (95% CI)	Deaths (*n*)	Cum. inc. %, (95% CI)	Deaths (*n*)	Within period HR (95% CI)	Between periods HR (95% CI)[b]
Women diagnosed before 1995								
Luminal A	291	54	19 (15–24)	103	37 (32–44)	112	1.0	1
Luminal B (HER2$^-$)	194	45	23 (18–30)	79	42 (35–49)	87	1.3 (1.0–1.7)	1
Luminal B (HER2$^+$)	55	20	36 (25–51)	25	46 (34–60)	28	1.3 (0.9–2.0)	1
HER2 type	53	27	51 (38–65)	30	57 (44–71)	31	2.3 (1.5–3.5)	1
Five negative phenotype	23	10	43 (26–66)	13	57 (38–77)	13	1.7 (1.0–3.1)	1
Basal phenotype	45	18	40 (27–56)	22	50 (36–65)	22	1.6 (1.0–2.5)	1
Women diagnosed in 1995 or later								
Luminal A	414	30	7 (5–10)	44	13 (9–17)	44	1.0	0.4 (0.3–0.5)
Luminal B (HER2$^-$)	183	25	14 (10–20)	34	23 (16–32)	34	2.0 (1.2–3.1)	0.5 (0.3–0.7)
Luminal B (HER2$^+$)	57	11	20 (11–32)	18	42 (27–63)	18	3.6 (2.1–6.3)	0.7 (0.4–1.3)
HER2 type	36	13	36 (23–54)	15	42 (28–60)	15	5.1 (2.8–9.3)	0.6 (0.3–1.1)
Five negative phenotype	25	8	32 (17–54)	9	36 (21–58)	9	4.2 (2.0–8.6)	0.6 (0.3–1.6)
Basal phenotype	47	9	20 (11–34)	11	26 (15–42)	11	2.7 (1.4–5.2)	0.4 (0.2–0.9)

Abbreviation: Cum. inc., cumulative incidence.

[a]HR from Cox regression, adjusted for age (≤49, 50–59, 60–64, 65–69, 70–74, 75+ years). Adjustments for grade or stage of disease did not substantially influence the results.

[b]Diagnosis before 1995 was used as the reference.

prognosis were seen for Luminal A, Luminal B (HER2$^-$), and the Basal phenotype. Luminal A had the best prognosis and HER2 type had the poorest in both diagnostic periods.

The participants came from a single county in Norway, which is predominantly rural and ethnically homogeneous, with little migration (14). This increases the comparability over time within the study population. Incident tumors were reclassified into molecular subtypes and included in analyses of incidence and long-term prognosis, using reliable end-point data from national registries.

Molecular subtyping was performed in the same laboratory, using the same antibodies for IHC in all tumors. This ensured that the observed incidence differences were not caused by different antibody sensitivities or cut-off levels. Subtyping of tumors was done according to the same algorithm. Tumor tissue covered a diagnostic time span of several decades, and although preanalytical conditions may have varied, valuable information can be drawn from archival tissue blocks (29).

Most breast cancers are hormone receptor positive (luminal) and HER2 negative. Our results are in agreement with previous studies showing that HER2 negative luminal tumors are more common among older, postmenopausal women (30, 31), and that nonluminal subtypes are more common in younger women (30, 31).

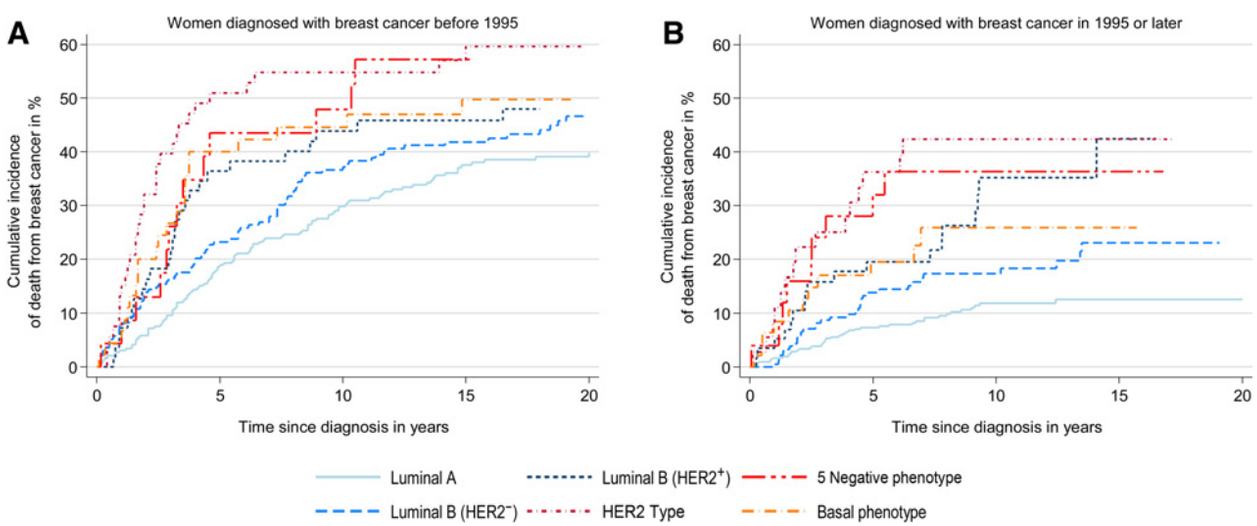

Figure 3.

Cumulative incidence of death from breast cancer according to molecular subtypes. **A,** Women diagnosed before 1995 (Gray test: $P = 0.0004$). **B,** Women diagnosed in 1995 or later (Gray test: $P = <0.0001$).

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Increased incidence of breast cancer over time has been reported by others (3, 4, 32), and ER positive tumors may account for most of this increase (3, 32, 33). It has been suggested that mammography screening favors detection of HER2 negative luminal tumors (34–37) and that menopausal hormone use may increase the risk for hormone receptor positive tumors (38–40).

The Norwegian Breast Cancer Screening Program was implemented in Nord-Trøndelag County in 2001. It entails biennial screening of women aged 50–69 years. Women in this study who were born before 1929 were not eligible for the screening program, and some of the higher incidence of HER2 negative luminal tumors that we found in women born after 1929 could be due to a combination of increased unsystematic use of mammography for screening purposes during the 1990s (41, 42), and later implementation of organized mammography screening.

Between 1987 and 2001, use of menopausal hormone therapy increased greatly in Norway, after which an increase in hormone receptor positive tumors (ER and/or PR > 10%) was observed (41). The use of hormone therapy declined after 2001 (43, 44).

The observed increase in use of menopausal hormone therapy concurred with increased use of mammography for screening purposes. Therefore, some of the higher incidence of Luminal A and Luminal B ($HER2^-$) tumors observed for women born between 1929 and 1977 may be attributed to mammography screening and menopausal hormone therapy (3, 41, 45), both of which were negligible exposures in women born before 1929.

The impact of risk factors seems to differ between molecular subtypes, and it is possible that the higher incidence of HER2 negative luminal tumors among women born in 1929 or later may also be explained by differences in reproductive and lifestyle factors, such as age at menarche, age at first birth, parity, age at menopause, and body mass index (39, 40, 46, 47).

Some tumors were unavailable for subtyping (34% of cases born before 1929, and 9% of cases born in 1929 or later), mainly because patients were diagnosed at other hospitals. We therefore used multiple imputations to compensate for the resulting underestimation of subtype-specific incidence rates. Even when all clinical information available is included in the imputation models, it is difficult to assess how well the imputed rates reflect the true rates for each subtype. This uncertainty is also reflected in the relatively wide confidence intervals for the imputed rates. Although weaker after imputation, the differences in incidence rates persisted for the HER2 negative luminal subtypes, whereas the observed differences for Luminal B (HER^+) and nonluminal subtypes disappeared after imputation for unknown subtype. Imputations had stronger effects on the subtype-specific rates for women born before 1929, due to a higher frequency of unknown subtype among these women.

Breast cancer mortality in Norway has declined since the mid-1990s, and this has been attributed to earlier detection (48, 49), and improved treatment (50–52). We found that the prognosis was generally better for women diagnosed with breast cancer in 1995 or later, compared to before 1995, confirming the findings of others (6, 23, 53).

Differences in prognosis (9, 54) and treatment response (55, 56) between subtypes have been demonstrated, and in accordance with others, we found clear reductions in case fatality for $HER2^-$ luminal subtypes from the first to the second diagnostic period (6, 53). We also found clear reductions in case fatality for the Basal phenotype.

The HER2 type had the worst prognosis irrespective of diagnostic period, and compared to Luminal A, the relative rate of death from HER2 type increased dramatically from the first to the second diagnostic period. This increase could probably be attributed to longer survival among Luminal A patients diagnosed in 1995 or later. Because Luminal tumors are more likely to be detected by screening (34–36), it is plausible that the longer survival among many Luminal A cases diagnosed after 1995 may be due to earlier detection by mammography (lead-time bias). Aggressive subtypes, such as the Basal phenotype or the HER2 type, are more likely to present clinically, and lead-time bias may be a negligible issue for these subtypes (34–37).

Contrary to others (23), we could not demonstrate clear improvements in survival for the HER2 type between diagnostic periods. One possible explanation could be that targeted treatment with trastuzumab was not implemented until the last years of the observation period.

In conclusion, there has been a dramatic secular increase in the incidence rates of Luminal A and Luminal B ($HER2^-$) breast cancer, whereas the incidence of Luminal B ($HER2^+$) and nonluminal subtypes have remained relatively stable. The prognoses for Luminal A, Luminal B ($HER2^-$), and Basal phenotype have clearly improved after 1995.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Valla, L.J. Vatten, M.J. Engstrøm, O.A. Haugen, L.A. Akslen, J.H. Bjørngaard, A.M. Bofin, S. Opdahl
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