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Trends in breast cancer among elderly women: Development in estrogen and HER2 subtypes in the last ten years

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ABSTRACT

Background: Increasing life expectancy increases breast cancer (BC) rates in elderly, where better health allows for improved tolerance of treatments. We assessed trends in BC incidence of tumor subtypes for women with focus on the elderly.

Methods: Changes in BC incidence in women by age from 2012 to 2021 were assessed using data from the Nordic countries. We calculated the incidence of BC subtypes by age group using data from the Danish Breast Cancer Group (DBCG) database. We used generalized linear models assuming a Poisson distribution.

Results: In the Nordic countries, 205 305 women were diagnosed with BC between 2012 and 2021. In Denmark, 50 858 BC patients were diagnosed between 2012 and 2022, identified with tumor characteristics. Incidence of BC among women aged 80+ increased significantly across the Nordic Countries, with 1.24 % per year (95 % CI: 0.07 %: 2.41 %). In Denmark, in the 80+ group, the ER+/HER2- subtype had the highest increase, with 1.98 % per year (95 % CI: 1.10 %: 2.87 %).

Conclusion: Across the Nordic countries, incidence of BC in women aged 80+ increased. In Denmark, rising incidence of BC is driven by the ER+/HER2- subtype in the 80+ group, which has the best prognosis and gentle treatments. More elderly BC patients will require treatment and follow-up in the future.

1. Introduction

The number of elderly is increasing significantly in the Western world, including the Nordic countries, leading to an expected increase in the number of cancer patients and associated pressure on healthcare systems [1]. In Denmark, the number of people aged 80 or above will more than double from 2020 to 2050 [2]. Breast cancer (BC) is the most common cancer in women [3] and is a complex and heterogeneous disease with treatment and prognosis highly related to tumor subtype and stage. As the health of the aging population improves, the number of elderly BC patients increases as well [4]. Improved health may also result in better tolerance of treatments, making more elderly BC patients eligible for treatment and consequently improving their prognoses.

Subtyping is crucial in the choice of treatment for BC. Divergent trends have been reported with both increasing ER+ (estrogen receptor) and decreasing ER- BC subtypes [5–7], but little is known about trends in the incidence of cancer subtypes characterized by both ER and HER2 (human epidermal growth factor receptor 2).

There is some indication that environmental or external factors may impact the development of different BC subtypes. Most studies have assessed risk factors for the ER subtypes in BC, while knowledge of risk factors for the HER2 subtype is sparse [8]. The ER+/HER2- subtype is known to be more sensitive to known risk factors for BC, like nulliparity, no breastfeeding, early menarche, late menopause, obesity, alcohol consumption, and hormone replacement therapy (HRT) [8]. Lifestyle has not been shown to affect HER2 subtypes, and knowledge of risk factors is less established. However, few studies report that high body mass index (BMI) and oral contraceptives might increase the risk of ER-/HER2- BC [8,9]. Other studies suggest that the risk of ER+/HER2+ and ER-/HER2+ BC increases with later menarche and nulliparity [8, 10]. Thus, different risk-factor profiles within different age or birth cohorts could influence the incidence of specific BC subtypes over time.

Abbreviations: BC, Breast cancer; DBCG, Danish Breast Cancer Group.

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In Denmark, HER2 assessment was introduced in 2005, primarily to younger patients, and was implemented as a standard procedure in all BC patients since 2010 [11]. So far, no comprehensive assessment of the development of subtypes in the different age groups has been conducted. Changes in classification and criteria for ER+ and procedures for HER2 assessment in the last 15 years could disturb the description of such trends. However, all pathology departments in Denmark are regulated by national guidelines from the Danish Breast Cancer Group (DBCG) to ensure comparability in ER and HER2 assessment. Furthermore, the departments undergo regular external assessments of procedures and essays and report immunohistochemistry (IHC) and fluorescence in situ hybridizing (FISH) scores directly to the DBCG registry to ensure transparency. Knowledge of the development of BC subtypes according to age could provide crucial information related to planning future BC treatment among specific age groups. We sought to investigate the development of BC in age groups with a focus on the elderly population in the Nordic countries and assess trends in BC subtypes related to ER and HER2 in Denmark.

2. Methods

2.1. Study design and population

2.1.1. NORDCAN

Data on incident female (sex assigned at birth) BC cases in Denmark, Finland, Norway, and Sweden was captured from the Association of the Nordic Cancer Registries database (NORDCAN) [12,13], developed and analyzed in collaboration with the International Agency for Research on Cancer (IARC), which also developed and hosted the publicly available database. NORDCAN includes high-quality, anonymous data on cancer incidence, mortality, survival, and prevalence in groups of patients from the Nordic countries over six decades and is updated annually. Population statistics on the background population are implemented in NORDCAN. The database does not include data on BC subtypes.

2.1.2. DBCG

In Denmark, the Danish Breast Cancer Group (DBCG) database has gathered extensive data on tumor characteristics of incident BC, including ER status [14,15], since 1977. HER2 status was introduced in the database in 2007. The database is known to have a high level of completeness and validity and is described more thoroughly elsewhere [11].

We obtained data on incident invasive BC cases and tumor characteristics in Danish women (sex assigned at birth) diagnosed between 2012 and 2022 from the DBCG database. We included data on the year of diagnosis, age, tumor size, lymph node status, tumor grade, and receptor status divided into ER and HER2. Data on the Danish background population from 2012 to 2022 were accessed from the Statistics Denmark website and compiled into age groups (<40, 40–49, 50–59, 60–69, 70–79, and 80+). Data from Statistics Denmark are publicly available [16].

2.2. Subtyping

In Denmark, pathology examinations take place exclusively in the public health system, organized under five regions and 14 departments that all perform the pathology examinations adhering to the national guidelines of DBCG [17]. Therefore, all immunohistochemistry (IHC) and fluorescence in situ hybridizing (FISH) done on breast biopsies and surgical specimens are examined with a high level of comparability.

The quality of subtyping and use of essays in the regional departments are checked semiannually as part of an external quality assurance program by NordiQC [18] to ensure comparability in essays, and these did not change for most of the pathology departments in the study period, as reported by Nielsen et al. [19]. The tumor molecular subtype was evaluated by ER and HER2. Regarding ER expression, data was reported as percentages by the specialized pathology departments dealing with breast pathology to the DBCG. Positive ER status was defined as ≥10 % of the tumor cells stained and negative if <10 % stained. HER2 expression was reported as IHC score, 0 and 1+ were defined as negative, 3+ as positive, and 2+ was further assessed by FISH, and if the HER2-to-centromere 17 copy number ratio was >2.0, it was counted as positive. No gene amplification was counted as negative. HER2 gene amplification was defined according to the ASCO/CAP recommendations at that time [20,21]. In the case of borderline (equivocal) HER2 score, the specimen was retested with IHC or FISH [17]. The IHC divided the tumors into four subgroups: ER+/HER2-, ER+/HER2+, ER-/HER2+, and ER-/HER-. If either ER or HER2 status were unknown, the combined receptor type was assumed to be unknown. Lymph nodes (LN) were considered positive if they contained more than ten tumor cells, while patients with only isolated tumor cells were considered LN-negative. Due to entry errors, we introduced a maximum tumor size set to 150 mm, otherwise coded as unknown.

2.3. Statistical analyses

We modulated incidences in age groups using the descriptive epidemiology tools in NORDCAN. Furthermore, we used the NORDCAN tools to obtain the estimated annual percentage change (EAPC) in BC in women in the four biggest Nordic countries. The EAPC describes the magnitude of the change in trend. It is the average annual rate of change in the age-standardized rate (ASR) for Nordic countries over the period selected. It is calculated by fitting a regression line to the natural logarithm of the ASR (Nordic) using the calendar year as a regressor variable [13].

Calculations based on data from the DBCG database and population data were conducted using a generalized linear model and a log-linear regression assuming an underlying Poisson distribution to assess incidence rate ratios (IRR) between years in the receptor subtypes in each age group in Denmark. The IRR is based on the calendar year as the regression variable. The EAPC from NORDCAN can be interpreted similarly to the IRR [22], and we will address the IRR as EAPC in the results. We used the chi-square and the Kruskal-Wallis test to compare heterogeneity between the age groups' baseline characteristics and the chi-square test to compare heterogeneity in the trend in incidence in the subgroups. A p-value of <0.05 was considered statistically significant. Data was analyzed using R Studio version 2023.06.0 + 421.

We chose to allocate the unknown receptor cases to ER±/HER2± based on the observed proportions of receptor cases for each age group and year of diagnosis. Analyses made before the unknown receptor cases were allocated, including unknown receptor cases, are shown in the supplementary material. To assess possible registration bias caused by changes in laboratory methods and positivity criteria, we performed explanatory analyses on ER and HER2 separately, as shown in the supplementary material.

3. Results

3.1. NORDCAN

A total of 205 305 women were diagnosed with BC in the Nordic countries between 2012 and 2021, with 27 651 women in the oldest age group 80+ (13.5 %) (Table 1). The distribution of BC cases between the Nordic countries was as follows: Denmark 47 996 (23.4 %), Finland 48 832 (23,8 %), Norway 34 628 (16.9 %), and Sweden 73 849 (36.0 %) (Table 1).

3.2. DBCG

A total of 50 858 Danish women were diagnosed with invasive BC and registered in the DBCG database between 2012 and 2022; 6432 were in the age group 80+ (12.6 %) (Table 1).

Table 1
Descriptive statistics for breast cancer patients in The Nordic countries from the NORDCAN database between 2012 and 2021 and tumor characteristics of Danish women with breast cancer in the DBCG database diagnosed between 2012 and 2022, divided into age groups.

Age group (years)	Total	<40	40–49	50–59	60–69	70–79	80+	
NORDCAN¤ 2012–2021 No. of patients (%)								
Denmark	47 996 (23.4)	1930	5947	10 360	13 413	9916	6430	
Finland	48 832 (23.8)	1529	4966	10 436	15 202	9978	6721	
Norway	34 628 (16.9)	1684	5190	8302	9575	5746	4131	
Sweden	73 849 (36.0)	2961	9888	13 941	20 220	16 470	10 369	
All countries	205 305 (100)	8104 (3.9)	25 991 (12.7)	43 039 (21.0)	58 410 (28.5)	42 110 (20.5)	27 651 (13.5)	
DBCG 2012–2022 No. of patients (%)	50 858 (100)	2049 (4.0)	6327 (12.4)	11 200 (22.0)	14 340 (28.2)	10 510 (20.1)	6432 (12.6)	p^a
Tumor size (mm)								
Median [IQR]	17 [11-26]	21 [14-31]	20 [13-30]	15 [10-23]	14 [9-21]	20 [14-28]	23 [16-32]	
Missing (%)	2106 (4.1 %)	82 (4.0 %)	204 (3.2 %)	255 (2.3 %)	308 (2.1 %)	438 (4.2 %)	819 (12.7 %)	<0.0001
Tumor grade								
I	12 488 (24.6 %)	157 (7.7 %)	1141 (18.0 %)	3053 (27.3 %)	4201 (29.3 %)	2451 (23.3 %)	1485 (23.1 %)	
II + III	34 445 (67.7 %)	1714 (83.7 %)	4748 (75.0 %)	7414 (66.2 %)	9194 (64.1 %)	7255 (69.0 %)	4120 (64.1 %)	
Unclassified	3925 (7.7 %)	178 (8.7 %)	438 (6.9 %)	733 (6.5 %)	945 (6.6 %)	804 (7.6 %)	827 (12.9 %)	<0.0001
Receptor status								
ER+/HER2-	38415 (75.5 %)	937 (45.7 %)	4243 (67.1 %)	8419 (75.2 %)	11502 (80.2 %)	8246 (78.5 %)	5068 (78.8 %)	
ER+/HER2+	4683 (9.2 %)	313 (15.3 %)	804 (12.7 %)	1138 (10.2 %)	1129 (7.9 %)	802 (7.6 %)	497 (7.7 %)	
ER-/HER2+	2283 (4.5 %)	185 (9.0 %)	379 (6.0 %)	577 (5.2 %)	486 (3.4 %)	416 (4.0 %)	240 (3.7 %)	
ER-/HER2-	5477 (10.8 %)	614 (30.0 %)	901 (14.2 %)	1066 (9.5 %)	1223 (8.5 %)	1046 (10.0 %)	627 (9.7 %)	<0.0001
Lymph nodes								
Negative	28 821 (56.7 %)	1085 (53.0 %)	3372 (53.3 %)	6934 (61.9 %)	9599 (66.9 %)	5719 (54.4 %)	2112 (32.8 %)	
Positive	17 372 (34.2 %)	895 (43.7 %)	2780 (43.9 %)	3969 (35.4 %)	4196 (29.3 %)	3701 (35.2 %)	1831 (28.5 %)	
Missing	4665 (9.2 %)	69 (3.4 %)	175 (2.8 %)	297 (2.7 %)	545 (3.8 %)	1090 (10.4 %)	2489 (38.7 %)	<0.0001

¤ = Absolute numbers for breast cancer cases. SD = standard deviation, IQR = interquartile range. Data on the background population is not shown for NORDCAN or the Danish population.
[a] = P-value for heterogeneity.

The youngest age groups <40 and 40–49 had a higher portion of ER-/HER2- (30.0 % and 14.2 %), respectively, compared to the older patients (8.5%–10.0 %). The ER+/HER2- subtype was dominant in all age groups but more pronounced in those over 59, with 78.5 %–80.2 % (Table 1).

3.3. Trends in the incidence of breast cancer

3.3.1. NORDCAN

From 2012 to 2021, the EAPC in incidence for women aged 80+ increased significantly across the Nordic countries, with 1.24 % (95 % CI: 0.07 %: 2.41 %) (Table 2, Fig. 1 A), whereas no significant trends were seen in the younger age groups. Substantial increases in the age group 80+ were also seen within countries, i.e., in Denmark and Finland, with 1.14 % (95 % CI: 0.08 %: 2.21 %) and 2.20 % (95 % CI: 1.04 %: 3.38 %), respectively. However, Norway and Sweden showed no significant increase in EAPC for women aged 80+. (Table 2). An increase of 2.52 % (95 % CI: 1.22 %: 3.82 %) was found for women aged 70–79 in Norway (Table 2).

3.3.2. DBCG

From 2012 to 2022, the EAPC in incidence for women aged 80+ years increased significantly in Denmark, with 1.24 % (95 % CI: 0.47 %: 2.03 %) (Table 3, Fig. 1 B). Among women aged 80+, a marked increase in the ER+/HER2- subtype was found with an EAPC of 1.98 % (95 % CI: 1.10 %: 2.87 %) (Table 3, Fig. 2 C). The increase was steeper before allocating the unknown receptor cases (Supplementary Table S2). Among women aged 80+, we also saw a decrease in the ER+/HER2+ subtype of -3.40 % (95 % CI: -6.10 %: -0.62 %) (Table 3, Fig. 2 C). The decrease was not significant before allocating the unknown receptor cases (Supplementary Table S2 and Fig. 3 C). Among women aged 70–79, we saw a slight increase in the ER+/HER2- subtype with an EAPC of 0.87 % (95 % CI: 0.17 %: 1:57 %) (Table 3, Fig. 2 D). However, the test for heterogeneity between subtypes in the 70–79 age group was not significant ($p = 0.12$).

The age groups 60–69 and 50–59 showed decreasing EAPCs in incidence of -1.17 % (95 % CI: −1.68 %: -0.66 %) and -0.66 % (95 % CI: -1.25 %: -0.08 %) (Table 3, Fig. 1 B). In both age groups, the dominant subtype was ER+/HER2-, with decreases in EAPC of −1.06 % (95 % CI: -1.63 %: -0.49 %) and -0.94 % (95 % CI: -1.61 %: -0.27 %), respectively (Table 3, Fig. 2 E and F). However, they were not significant.

Furthermore, in the 60–69 age group, the ER-/HER2- subtype had a decreasing trend: -1.87 % (95 % CI: -3.59 %: -0.11 %) but was not significant either (Table 3.).

Table 2
Descriptive statistics for female breast cancer patients in the Nordic countries in the NORDCAN database between 2012 and 2021, including EAPCs with 95 % CI of incidence for Denmark, Finland, Norway, and Sweden and total for the Nordic countries using an ASR pr. 100.000 person-years (Nordic). EAPC = estimated annual percentage change, ASR = age-standardized rate, CI = confidence interval. NORDCAN = database on Cancer in the Nordic countries.

EAPCs NORDCAN (2012–2021)					
Age groups	Total	Denmark	Finland	Norway	Sweden
<40	1.22 % [-4.52 %: 7.31 %]	1.29 % [-4.09 %: 6.98 %]	1.57 % [-4.43: 7.96]	1.50 % [-4.26 %: 7.60 %]	0.93 % [-4.90 %: 7.11 %]
40–49	0.40 % [-1.36 %: 2.18 %]	-0.26 % [-1.99 %: 1.50 %]	-0.11 % [-1.86 %: 1.67 %]	1.21 % [-0.59 %: 3.04 %]	0.70 % [-1.04 %: 2.48 %]
50–59	0.21 % [-1.55 %: 1.15 %]	-1.09 % [-2.38 %: 0.22 %]	-0.28 % [-1.55 %: 1.01 %]	1.24 % [-0.13 %: 2.62 %]	-0.21 % [-1.63 %: 1.23 %]
60–69	-0.78 % [-1.89 %: 0.34 %]	-1.47 % [-2.54 %: -0.38 %]	-0.22 % [-1.29 %: 0.85 %]	0.80 % [-0.39 %: 1.99 %]	-1.37 % [-2.50 %: -0.23 %]
70–79	0.72 % [-0.43 %: 1.89 %]	0.54 % [-0.57 %: 1.66 %]	1.84 % [0.70 %: 2.99 %]	2.52 % [1.22 %: 3.82 %]	-0.32 % [-1.46 %: 0.83 %]
80+	1.24 % [0.07 %: 2.41 %]	1.14 % [0.08 %: 2.21 %]	2.20 % [1.04 %: 3.38 %]	0.91 % [-0.35 %: 2.18 %]	0.61 % [-0.57 %: 1.81 %]

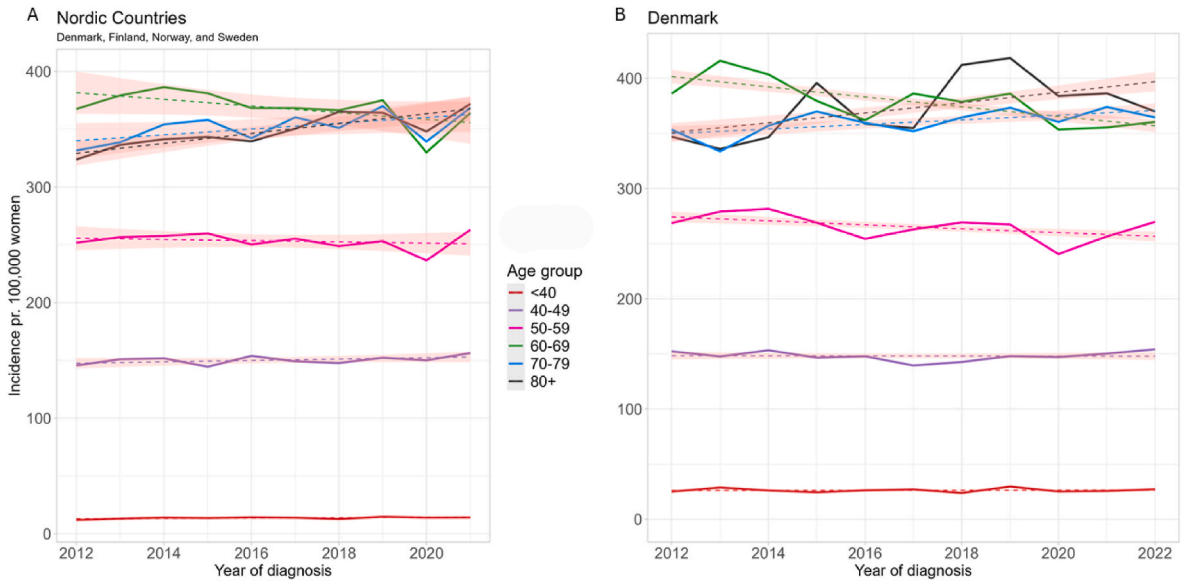

Fig. 1. A: Incidence of breast cancer in women in the Nordic countries, including Denmark, Finland, Norway, and Sweden, from 2012 to 2021 per 100 000 ASR (Nordic), including a fitted linear trend. Made with data from the NORDCAN database.
B: The incidence of breast cancer per 100 000 Danish women from 2012 to 2022 in age groups and the predicted incidence with 95 % confidence intervals (CI). Data is from the Danish Breast Cancer Group (DBCG) database. ASR = age-standardized rate.

Table 3
EAPCs with 95 % CI of incidence for Danish women with breast cancer in the DBCG database diagnosed between 2012 and 2022, of age groups and of subtypes in age groups. EAPC = estimated annual percentage change, CI = confidence interval, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, * = P-value for heterogeneity.

EAPCs DBCG (2012–2022)						
Age groups	Total	Receptor subtypes				*p**
		ER+/ HER2-	ER+/ HER2+	ER-/ HER2+	ER-/ HER2-	
<40	0.12 % [-1.24 %: 1.50 %]	-0,32 % [-2.31 %: 1.72 %]	-1.73 % [-5.10 %: 1.77 %]	1.08 % [-3.44 %: 5.81 %]	1.47 % [-1.04 %: 4.05 %]	0.47
40–49	-0.02 % [-0.80 %: 0.76 %]	-0.87 % [-1.81 %: 0.08 %]	0.73 % [-1.45 %: 2.95 %]	3.60 % [0.33 %: 6.98 %]	1.86 % [-0.23 %: 4.00 %]	0.01
50–59	-0.66 % [-1.25 %: -0.08 %]	-0.94 % [-1.61 %: -0.27 %]	0.39 % [-1.45 %: 2.27 %]	-0.98 % [-3.49 %: 1.60 %]	0.61 % [-1.29 %: 2.54 %]	0.30
60–69	-1.17 % [-1.68 %: -0.66 %]	-1.06 % [-1.63 %: -0.49 %]	-1.61 % [-3.41 %: 0.22 %]	-0.98 % [-3.72 %: 1.83 %]	-1.87 % [-3.59 %: -0.11 %]	0.81
70–79	0.59 % [-0.03 %: 1.21 %]	0.87 % [0.17 %: 1.57 %]	-1.00 % [-3.15 %: 1.20 %]	-2.15 % [-5.10 %: 0.89 %]	0.76 % [-1.19 %: 2.74 %]	0.12
80+	1.24 % [0.47 %: 2.03 %]	1.98 % [1.10 %: 2.87 %]	-3.40 % [-6.10 %: -0.62 %]	0.25 % [-3.62 %: 4.27 %]	-0.66 % [-3.07 %: 1.82 %]	0.001
	*p <0.001**					

In the 40–49 age group, we saw a significant increase in the ER-/HER2+ subtype of 3.60 % (95 % CI: 0.33 %: 6.98 %) (Table 3, Fig. 2 G).

The EAPC varied by subtype in the youngest age group, <40, with the smallest sample size (2,049, Table 1), and none of the trends were significant (Table 3, Fig. 1 B and 2 H). The unknown receptor cases decreased significantly in the age groups over 59 years, with −13.36 % to −16.85 % (Supplementary Table S2). The separate analyses on ER and HER2 showed no significant rise in ER + or HER2+ during the period (Supplementary Table S3 and Figs. 4 and 5).

4. Discussion

Comparing rates of BC across the four biggest Nordic countries, we found an increasing trend in the incidence of BC in the oldest age group, 80+ in all countries, from 2012 to 2021. We found this increase driven by the ER+/HER2- subtype in Denmark. In contrast, the age groups 50–59 and 60–69, invited for the population screening, had steadily decreasing trends, also driven by the ER+/HER2- subtype.

To our knowledge, this is the most extensive study describing the development in BC incidence among the elderly in Nordic countries throughout the last ten years, combined with information on development in subtypes, including ER and HER2 status information. Consistent with our findings, other Western countries report increasing EAPC in the oldest age groups included in the Global Cancer Observatory (GLOBOCAN) [23].

Earlier studies on the ER subtype report increasing ER+ and decreasing ER- subtypes in Denmark [5], U.S [6]. and Ireland [7]. The study from Ireland also reported data on the incidence of HER2 status in patients diagnosed between 2004 and 2014 and found a significant increase per year of 2.87 % in the ER+/HER2- subtype and decreases per year of 4.58 % and 3 % in the ER-/HER+ and ER-/HER2- subtypes, respectively [7]. However, these analyses did not include stratification by age groups.

We found similar trends in the ER+/HER2- subtype, as reported by Mullooly et al. [7], however, as they found a decrease in the incidence of the ER-/HER2+ and ER-/HER2- subgroups, our results did not support that in any age group. Denmark is somewhat comparable to Ireland in race, lifestyle, and risk factors for BC [24,25]. The number of patients with unknown receptor cases could add to the differences in results between our study and Mullooly et al., as they reported 15.6 % unknown receptor cases in roughly 25 000 patients [7], whereas our study had only 2.4 % unknown receptor cases in more than 50 000 patients and a decreasing trend in the oldest age groups, which had the most unknown receptor cases.

Known risk factors for the ER+/HER2- subtype are primarily related

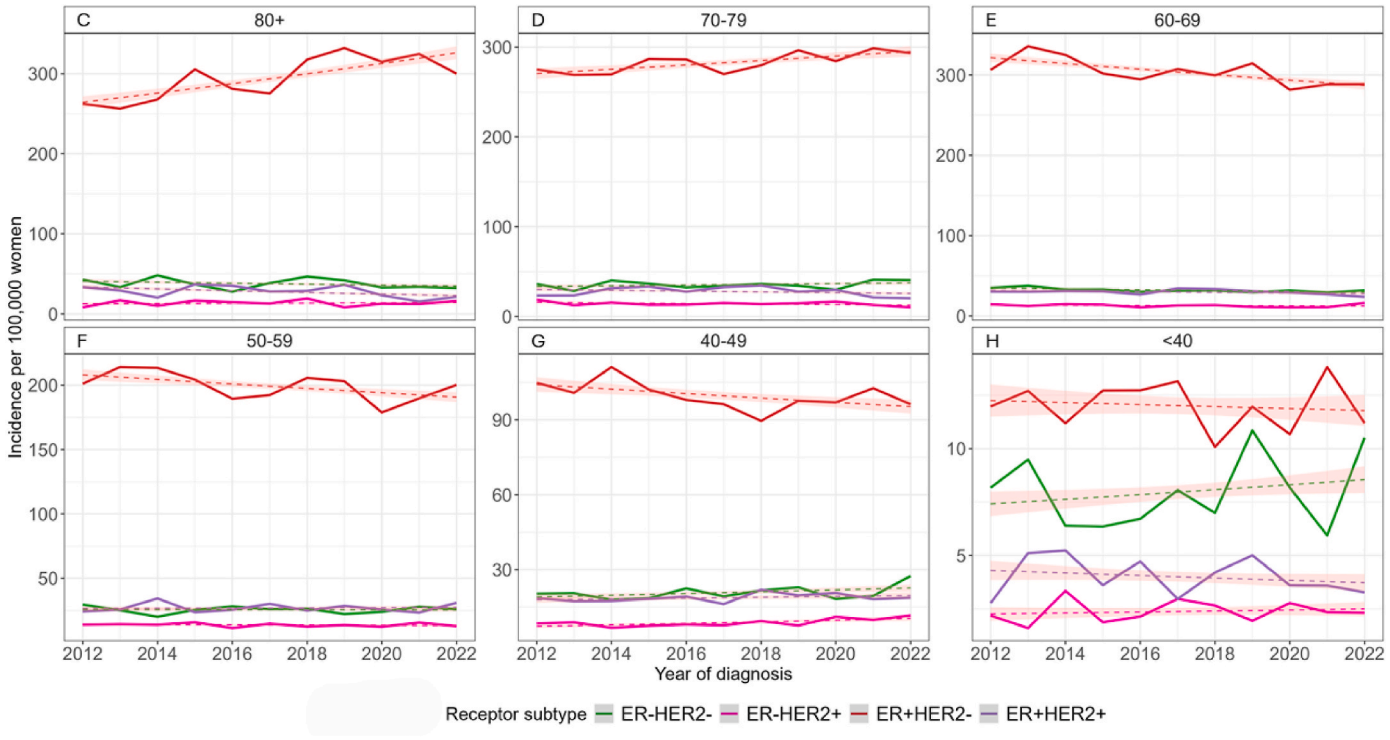

Fig. 2. The incidence of breast cancer per 100 000 Danish women in age groups from 2012 to 2022, grouped by receptor subtype and with the predicted incidence with 95 % CI. Data is from the Danish Breast Cancer Group (DBCG) database. ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, CI = confidence interval.

to lifestyle, parity, and HRT. In Denmark, BMI has increased during the last 25 years and is expected to continue rising [26]. Higher BMI is known to increase the risk of BC in postmenopausal women [27]. Meanwhile, birth rates are decreasing in Denmark, and this combination could increase the incidence of the ER+/HER2- subtype. However, the current decrease in parity would not be relevant to our findings in women older than 80.

The age-standardized incidence of BC in the oldest age group is increasing in the Nordic countries, and considering the growing number of individuals in the age group, this will imply an increasing burden on the healthcare system. With the national ongoing screening programs in age groups 50–69 in Denmark, Norway, and Finland and 40–74 in Sweden and with relatively high compliance (over 73 % in all countries) [28], one would have hoped the incidence in older women would have leveled off, which is not the case. Reasons for the increase in cancer cases in the elderly could be due to older women being increasingly healthy and with more awareness of early cancer signs, hence, more often being diagnosed compared to the years before screening was introduced. Also, accelerated surgery, more breast-conserving surgery, and less invasive surgery in the axilla, together with milder anesthetics, have caused clinicians to consider surgery in increasingly older patients [29].

Another point is that only a small proportion of the women we study have been screened since population-based screening was introduced late in the 1990s in Denmark. Hence, any screening effect on the elderly should only be assessed by a proper cohort analysis of the invited population.

In contrast to recent studies, we found significantly decreasing trends in BC incidence in the 50–59 and 60–69 age groups dominated by the ER+/HER2- subtype. These age groups have been invited to the national screening program in Denmark since 2008 [28]. We shortened the study period to avoid the program's impact on the detection of BC. The screening program includes mammography, which can detect BCs earlier, e.g., carcinoma in situ. Therefore, after an initial phase of more BC diagnoses, it can cause a decrease in incident invasive cancers and an increase in non-invasive BC. In Denmark, the incidence of ductal carcinoma in situ (DCIS) has increased to 13–16 % in the age groups 50–59 and 60–69 [30,31], in the period from 2010 to 2024. Furthermore, our study found the ER-/HER2- subtype not to be increasing in any age group, which is an essential negative finding since this subtype has the worst short-term prognosis.

4.1. *Strengths and limitations*

We consider the size of the included population and the completeness of the DBCG register to be clear strengths of our study, as they provide high-quality data on the development of BC subtypes in Denmark in the last ten years. The criteria for positivity regarding ER status and laboratory methods for HER2 status have changed in the period, and we believe the tight national regulation, external control, and thorough reporting of the use of assays in the pathology departments in Denmark have made the possibilities for bias caused by these changes, very low.

We also restricted our analyses to 2012 to 2022 to eliminate the residual effects on disease incidence of the implementation of the national screening program for BC in Denmark in 2008.

To lower the possibility of registration bias, mainly due to missing HER2 status, we allocated the unknown ER and HER2 receptor cases to either positive or negative based on the observed proportions of receptor cases for each age group and year of diagnosis.

Data on incident cancers in NORDCAN are harmonized to fit multiple countries using a uniform coding system [13]. The DBCG data are based on incident cancers registered in the Danish Pathology Registry and are not likewise filtered. Thus, the databases differ in their definition of BC cases, but the differences are minor and do not impact the conclusions.

Elderly patients have more comorbidities. Since they are often not included in clinical trials, clinicians lack solid evidence regarding elderly patients and the effects of various treatments, thus leading clinicians to occasionally deviating from treatment guidelines.

Accordingly, treatment and follow-up are more likely to vary in the elderly [4,32]. With an expected increase in the elderly population and more elderly with BC who can tolerate more intensive treatment, more elderly BC patients will require adequate follow-up and rehabilitation. Thus, geriatric assessment, including residual life expectancy, performance status, and patient preferences, should guide the decision-making process [33]. Our analyses include data from the Nordic countries, but they highlight trends that might apply to other Western countries with analogous risk profiles for BC.

In conclusion, we found an increasing incidence of BC in women 80+ in the four biggest Nordic countries. Further analyses of Danish data suggested that the ER+/HER2- subtype was driving the increase in incidence in the oldest age group (80+) in Denmark. As life expectancy increases, more elderly BC patients must be expected. With the ER+/HER2- subtype driving the change, and since it is known for gentle treatments and the best prognosis, we must expect that more elderly cancer patients can tolerate treatment and require it in the future.

CRediT authorship contribution statement

Frederik K. Palshof: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Lina S. Mørch:** Writing – review & editing, Validation, Supervision, Conceptualization. **Maj-Britt R. Jensen:** Writing – review & editing, Validation, Supervision, Conceptualization. **Hans H. Storm:** Writing – review & editing, Validation, Supervision. **Niels Kroman:** Writing – review & editing, Validation, Supervision, Conceptualization. **Tove H.F. Tvedskov:** Writing – review & editing, Validation, Supervision, Conceptualization.

Ethics approval and consent to participate

The Danish Clinical Quality Program—National Clinical Registries (RKKP) approved and provided the data. According to Danish legislation, register-based research does not require ethics approval or informed consent. The study was performed following the Declaration of Helsinki. In agreement with the General Data Protection Regulation, the project isregistered in the Danish Cancer Society's internal list of projects that are dealing withpersonalized data.

Availability of data and materials

Data from NORDCAN is publicly available at www.nordcan.iarc.fr/en.

The datasets generated and analyzed during the current study are not publicly available due to the restriction on personal data from the Danish Clinical Quality Program—National Clinical Registries (RKKP), but they can be made available by application from the RKKP.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, Frederik K Palshof used Grammarly from Grammarly Inc. to improve the readability and language of the manuscript. After using this tool, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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Declaration of competing interest

Maj-Britt R. Jensen is on the advisory board for Novartis, which is outside the submitted work, and Tove H. F. Tvedskov is on the advisory board for MSD, which is also outside the submitted work. The rest of the manuscript's authors declare no financial or non-financial competing interests.

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Glossary

ASR	Age-standardized rate
BC	Breast cancer
BMI	Body Mass Index
CI	Confidence interval
ER	Estrogen receptor
EAPC	Estimated annual percentage change
DBCG	Danish Breast Cancer Group
DCIS	Ductal carcinoma in situ
FISH	Fluorescence in situ hybridizing
GLOBOCAN	Global Cancer Observatory
HER2	Human epidermal growth factor receptor 2
HRT	Hormone-replacement therapy
IARC	Internation Agency for Research on Cancer
IHC	Immunohistochemistry
IRR	Incidence rate-ratio
IQR	Interquartile range
LN	Lymph node
NORDCAN	Database on cancer in the Nordic countries
RKKP	The Danish Clinical Quality Program - National Clinical Registries
SD	Standard deviation

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2024.103860.

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