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Article

Aprepitant use during chemotherapy and association with survival in women with early breast cancer

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Abstract

Background: Preclinical studies have shown that aprepitant, an antiemetic used to prevent chemotherapy-induced nausea and vomiting, slows mammary tumor growth and progression. Here, we evaluated the association between aprepitant and survival in a large cohort of women with early breast cancer.

Methods: Using linked nationwide registry data, we identified 13 811 women diagnosed with early breast cancer between 2008 and 2020 in Norway, who received chemotherapy and antiemetics. Women were followed for metastasis and death from 1 year after diagnosis until the end of 2021. To evaluate the association between aprepitant use and distant disease-free survival (DDFS) and breast cancer-specific survival (BCSS), we used Cox regression models, controlling for tumor and patient characteristics, chemotherapy regimens, and use of other antiemetics.

Results: During chemotherapy, 7047 (51%) women were supplied with aprepitant. Overall, aprepitant use was associated with better DDFS ($HR_{DDFS} = 0.89$; 95% CI = 0.79 to 1.00) and BCSS ($HR_{BCSS} = 0.83$; 95% CI = 0.71 to 0.97). The survival advantage was specific to women with non-luminal breast cancer ($HR_{DDFS} = 0.69$; 95% CI = 0.56 to 0.83; $HR_{BCSS} = 0.64$; 95% CI = 0.51 to 0.81) and was strongest in women with triple negative breast cancer (TNBC) ($HR_{DDFS} = 0.66$; 95% CI = 0.53 to 0.83; $HR_{BCSS} = 0.61$; 95% CI = 0.47 to 0.80). In women with non-luminal breast cancer, longer durations of aprepitant use were associated with increasingly favorable survival outcomes (DDFS: $P_{trend} = .002$; BCSS: $P_{trend} = .016$). Supply of other antiemetics of different drug classes was not associated with survival.

Conclusions: Aprepitant use during chemotherapy treatment was associated with better prognosis for women with non-luminal early breast cancer, in particular TNBC. Long-term clinical trials are required to confirm these findings.

Introduction

Breast cancer is the most common cancer in women.[1] Routine mammography screening has profoundly increased the incidence of breast cancer diagnosed at an early stage.[2] For women with early breast cancer, a multimodal treatment approach that includes systemic chemotherapy is commonly used to prevent cancer recurrence.[3,4] Despite these efforts, many women still die from cancer recurrence, with the highest recurrence rates among those with human epidermal growth factor receptor 2 (HER2) positive or triple negative breast cancer (TNBC).[5] Therefore, there are ongoing efforts to improve treatment approaches for early breast cancer. Repurposing of drugs with well-characterized safety profiles is an attractive path for rapid translation to improve cancer treatment.

Chemotherapy-induced nausea and vomiting (CINV) is a prevalent side effect of systemic chemotherapy in early breast cancer patients, affecting up to 60% of patients.[6] Aprepitant, a neurokinin 1 receptor (NK1R) antagonist, was first included in the antiemetic guidelines in the early 2000s due to its proven efficacy in preventing CINV in clinical trials.[7,8] Aprepitant prevents nausea by acting

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in the brainstem to prevent endogenous ligand substance P from binding NK1R.[9] NK1R expression has been observed in human breast cancer and may be upregulated in breast cancer cells compared to normal epithelial cells.[10,11] Recent preclinical studies found that NK1R antagonism using aprepitant reduced tumor and metastatic growth,[12] likely by inhibiting substance P-mediated tumor cell proliferation and invasion.[11-13]

Little is known about how aprepitant use could impact long-term survival outcomes in women with breast cancer. Here, we examine whether aprepitant use as an antiemetic at the time of systemic chemotherapy treatment is associated with survival outcomes in a large population-based cohort of women with early breast cancer.

Methods

Selection of the population

In this retrospective cohort study, we identified all women who received a diagnosis of invasive breast carcinoma from 2008 to 2020 in Norway ($n = 42\,915$; Figure 1). We excluded, sequentially, women with a previous invasive cancer ($n = 4033$), stage IV or unknown stage breast cancer ($n = 4969$), and women not receiving chemotherapy ($n = 19\,288$) and not receiving antiemetics ($n = 250$). Since we used data from the first year after diagnosis to determine cancer treatment and antiemetic use, we additionally excluded women with a follow-up period of less than 1 year ($n = 113$). Finally, to avoid the breast cancer treatment being influenced by treatment for a second cancer, we further excluded women who were diagnosed with a second cancer within the first year after diagnosis ($n = 451$). This led to a final study population of 13 811 women with breast cancer. For the analysis of risk of metastasis, 436 patients who received a diagnosis of metastasis in the first year after diagnosis were further excluded.

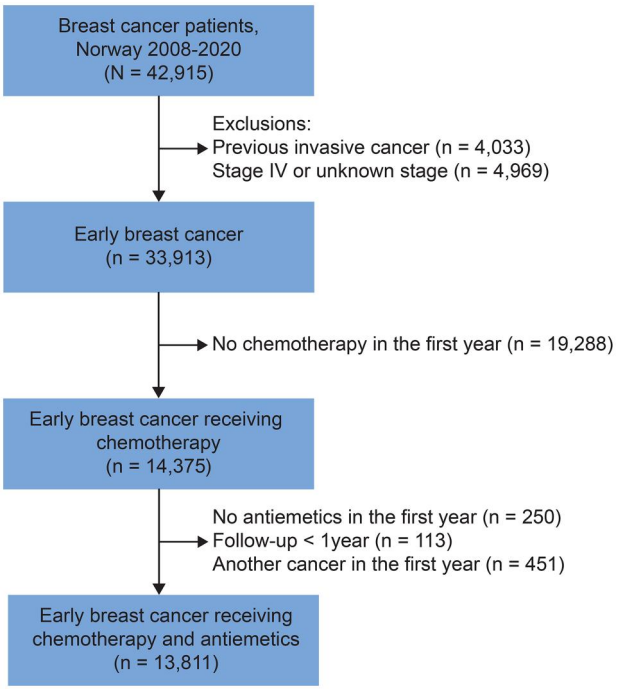

Figure 1. Selection of study population. Final study population was selected from all women diagnosed with breast cancer in Norway in 2008-2020.

Data sources

Norwegian residents are assigned a unique personal identification number, which allows univocal linkage between national registries. For the present study, we linked data from the Cancer Registry of Norway (CRN[14]), the National Patient Registry (NPR[15]), the Norwegian Prescription Database (NorPD[16]), Statistics Norway,[17] and Cause of Death Registry.[18]

Data on cancer characteristics were retrieved from different sources at the CRN: the incidence database, the breast cancer registry,[19] the radiation database, and the systemic anticancer treatment (SACT) database.[20] Tumor grade was based on the sixth digit in the ICD-O-3 morphology code. Data on estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2), and Ki-67 are retrieved from pathology reports. We categorized breast cancers into 5 molecular subtypes: luminal A (ER+ and/or PgR+, HER2-, Ki-67 $\leq$ 14), luminal B HER2- (ER+ and/or PgR+, HER2-, Ki-67 > 14), luminal B HER2+ (ER+ and/or PgR+, HER2+), HER2+ (ER-, PgR-, HER2+), and TNBC (ER-, PgR-, HER2-). For luminal HER2- cancers, where Ki-67 status was missing, we assigned tumor grade I as luminal A and tumor grade II-III as luminal B HER2-.[21]

Data on systemic cancer treatments were obtained from the SACT database, which collects information automatically and electronically from hospital systems.[20] To address gaps in treatment data for the earliest years and from the Northern Norway Regional Health Authority, we supplemented with additional information from the NPR, which includes cancer therapies administered in hospitals, and the NorPD, which includes cancer therapies dispensed by pharmacies. Data on radiotherapy and surgery were retrieved from the radiation database and incidence database, respectively.

To assess comorbidities, we reviewed patients' medical history prior to their breast cancer diagnosis. We utilized predefined ICD-10 codes from the NPR and ATC codes from the NorPD to identify cases of diabetes, cardiovascular disease, and chronic obstructive pulmonary disease.[22]

To determine exposure to antiemetics, we used date dispensed, ATC code, drug strength, and number of defined daily doses provided by NorPD. Women were defined as users of aprepitant (ATC code A04AD12) if they filled 1 or more prescriptions for aprepitant within the year following their diagnosis. Aprepitant was mostly prescribed as a 3-day treatment pack containing one 125 mg capsule and two 80 mg capsules. For other antiemetics, women were defined as users of netupitant/palonosetron (Akynzeo; ATC code A04AA55), ondansetron (A04AA01), dexamethasone (H02AB02), or metoclopramide (A03FA01) if they filled 1 or more prescriptions for those drugs within the year following their diagnosis. Netupitant/palonosetron is prescribed as a 1-day treatment pack and combines netupitant, a selective NK1 receptor antagonist in the same drug class as aprepitant, and palonosetron, a 5-HT3 antagonist in the same drug class as ondansetron. The observed combinations of antiemetics are reported in Table S1.

Statistics Norway provided data on education, CRN provided data on distant relapse, and the Cause of Death Registry provided data on cause of death.

Statistical analysis

We summarized continuous variables as medians with interquartile ranges, and categorical variables as frequencies with proportions. We compared the distribution of both continuous and categorical variables between aprepitant users and nonusers using the standardized mean difference (SMD). For

variables with more than 2 categories, we used the binary recoding approach, which compares each category to the combined other categories. SMD ≤ 0.1 indicated negligible imbalance, SMD > 0.1 and ≤0.2 moderate imbalance, and SMD > 0.2 notable imbalance.[23,24]

Follow-up started 1 year after the date of diagnosis, since cancer treatment type and use of antiemetics were defined using data from the first year following diagnosis. Distant disease-free survival (DDFS) was defined as time from start of follow-up to date of distant metastasis, death, emigration, or December 31, 2021, whichever occurred first. The event of interest was distant metastasis or death from any cause in case of no metastasis.[25] Breast cancer-specific survival (BCSS) was defined as time from start of follow-up to date of death, emigration, or December 31, 2021, whichever occurred first. The event of interest was breast cancer-specific death. When calculating the cumulative incidence of breast cancer-specific deaths, deaths from causes other than breast cancer were treated as competing events, using the method described by Fine and Gray.[26]

We used Cox proportional hazard regression models and reported hazard ratios (HR) with corresponding 95% confidence intervals (CI). We used time from 1 year after diagnosis as the time scale. Models were adjusted *a priori* for the following variables: age at diagnosis in years, year of diagnosis, stage (I, II, III), tumor grade (I, II, III, missing), molecular subtype (luminal A, luminal B HER2-, luminal B HER2+, HER2+, TNBC, missing), use of netupitant/palonosetron, ondansetron, dexamethasone and metoclopramide, presence of cardiovascular disease, chronic obstructive pulmonary disease, and diabetes. We further adjusted the models for chemotherapy type using 4 categories (anthracycline-based, anthracycline- and taxane-based, taxane-based, other) and total number of chemotherapy cycles received in the first year after diagnosis (continuous), as both variables showed an association with aprepitant use and prognosis. As duration of chemotherapy and total number of regimens show collinearity with chemotherapy types and number of chemotherapy cycle, these parameters were not included in the models. When analyzing the association between duration of aprepitant use and survival, we classified exposure into no use, <12 days, 12 days and >12 days. Twelve days was selected as the cutoff because most commonly used chemotherapy regimens are administered over 4 cycles and aprepitant is typically administered over 3 days for each cycle.[27,28] To test the linear trend between days of aprepitant use and survival, the duration of use was used as a continuous variable with 4 values. The number of chemotherapy cycles was divided according to tertiles. The homogeneity of hazard ratios (HRs) across the strata of a specific variable was tested by including an interaction term between that variable and aprepitant use in the model.

We ran 4 sensitivity analyses. First, to increase the stringency of the definition of antiemetic use, we defined a drug user as a woman with at least 2 prescriptions in the first year after diagnosis instead of 1 prescription. Second, to minimize the potential interference of netupitant/palonosetron, we restricted the analysis to women diagnosed with breast cancer through 2016 (Figure S1). Third, to compare antiemetic regimens that differed only in aprepitant use (Table S1), we restricted the analysis to women receiving 1 of 4 specific antiemetic combinations: (1) metoclopramide + ondansetron with or without aprepitant; (2) metoclopramide + ondansetron + dexamethasone with or without aprepitant; (3) metoclopramide + dexamethasone with or without aprepitant; or (4) metoclopramide alone with or without aprepitant. We then fit a single multivariable Cox regression model, stratified by these 4 groups, to estimate the overall effect of aprepitant use. Finally, as both aprepitant and netupitant are NK1R antagonists, we analyzed aprepitant and netupitant/palonosetron as 1 single drug class.

The statistical analysis was run independently by 2 statisticians, E.B. and S.H. Analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA), R software, version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria), and Stata, version 18.5 (StataCorp LP, College Station, TX, USA). Results with *P*-value < .05 were considered statistically significant.

Results

The study included 13 811 women who were diagnosed with early breast cancer in Norway between 2008 and 2020 and were treated with chemotherapy (Figure 1). Among them, 7047 (51.0%) women were supplied aprepitant during chemotherapy, and 6764 (49.0%) were not (Table 1). Patient and cancer characteristics were evenly distributed between aprepitant users and non-users. Compared to non-users, aprepitant users were treated with more chemotherapy regimens and cycles and more likely to receive anthracycline-taxane chemotherapy regimens. Aprepitant use rose steadily from 2008 to 2015 and then declined concurrently with the introduction of netupitant/palonosetron (Figure S1). Among aprepitant non-users, approximately one-third of the person-years were accounted for by individuals who used netupitant/palonosetron.

Women were followed for a median of 5.2 years. Overall, the use of aprepitant was associated with better DDFS and BCSS (HR_{DDFS} = 0.89; 95% CI = 0.79 to 1.00; HR_{BCSS} = 0.83; 95% CI = 0.71 to 0.97; Figure 2, A and B). Stratified analyses show a significant association between aprepitant use and improved survival in women with non-luminal breast cancers (HR_{DDFS} = 0.69; 95% CI = 0.56 to 0.83; HR_{BCSS} = 0.64; 95% CI = 0.51 to 0.81; Figures 2, C and D and 3), but not with luminal breast cancers (HR_{DDFS} = 0.98; 95% CI = 0.85 to 1.13; HR_{BCSS} = 1.03; 95% CI = 0.85 to 1.25; Figures 2, E and F and 3). The survival advantage was strongest in women with TNBC (HR_{DDFS} = 0.66; 95% CI = 0.53 to 0.83; HR_{BCSS} = 0.61; 95% CI = 0.47 to 0.80; Figure 3; Figures S2 and S3). The association between use of aprepitant and improved survival was more pronounced in women aged 55 and older compared to younger women (Figure 3). In women with non-luminal breast cancers, chemotherapy use was similar in aprepitant users and non-users (Table S2), and the association between aprepitant use and survival did not differ significantly according to chemotherapy type (Table S3).

Women were supplied aprepitant typically for 12 days (<12 days *n* = 1331, 12 days *n* = 3799, >12 days *n* = 1917). In women with non-luminal breast cancer, HRs for DDFS for <12 days, 12 days, and >12 days of aprepitant use, compared to no use, were 0.84 (95% CI = 0.63 to 1.11), 0.68 (95% CI = 0.54 to 0.85), and 0.54 (95% CI = 0.39 to 0.75), respectively (P_{trend} = .002; Figure 4). The same figures for BCSS were 0.68 (95% CI = 0.48 to 0.96), 0.63 (95% CI = 0.49 to 0.83), and 0.61 (95% CI = 0.42 to 0.88; P_{trend} = .016). No trend was observed among women with luminal breast cancer. The association between length of aprepitant use and survival was significantly different between luminal and non-luminal cancers ($P_{interaction}$ = .006 for DDFS and $P_{interaction}$ = .004 for BCSS). Supply of other antiemetics was not associated with survival (Table S4).

Table 1. Characteristics and treatments of the study population, overall and by use of aprepitant.

Variable	Categories	All patients $n = 13\,811$	Aprepitant $n = 7047$	No aprepitant $n = 6764$	SMD
Age (years)	Median (IQR)	54 (46-63)	53 (46-62)	54 (47-64)	0.13
Year of diagnosis	2008-2012	3699 (26.8)	2268 (32.2)	1431 (21.2)	**0.94**
	2013-2016	5682 (41.1)	4602 (65.3)	1080 (16.0)	
	2017-2020	4430 (32.1)	177 (2.5)	4253 (62.9)	
Stage	I	4944 (35.8)	2658 (37.7)	2286 (33.8)	0.06
	II	6211 (45.0)	3109 (44.1)	3102 (45.9)	
	III	2656 (19.2)	1280 (18.2)	1376 (20.3)	
ER/PgR	At least one positive	10209 (73.9)	5314 (75.4)	4895 (72.4)	0.04
	Both negative	3026 (21.9)	1497 (21.2)	1529 (22.6)	
	Missing	576 (4.2)	236 (3.3)	340 (5.0)	
HER2	Not overexpressed	9909 (71.7)	4897 (72.4)	5012 (71.1)	0.05
	Overexpressed	3135 (22.7)	1447 (21.4)	1688 (24)	
	Missing	767 (5.6)	420 (6.2)	347 (4.9)	
Tumor grade	I	491 (3.6)	287 (4.1)	204 (3.0)	0.05
	II	6037 (43.7)	3181 (45.1)	2856 (42.2)	
	III	6467 (46.8)	3233 (45.9)	3234 (47.8)	
	Missing	816 (5.9)	346 (4.9)	470 (6.9)	
Molecular subtype	Luminal A	481 (3.5)	233 (3.3)	248 (3.7)	0.03
	Luminal B HER2-	7200 (52.1)	3715 (52.7)	3485 (51.5)	
	Luminal B HER2+	2112 (15.3)	1146 (16.3)	966 (14.3)	
	HER2	1014 (7.3)	536 (7.6)	478 (7.1)	
	Triple negative	2011 (14.6)	961 (13.6)	1050 (15.5)	
	Missing	993 (7.2)	456 (6.5)	537 (7.9)	
Comorbidities at diagnosis	CVD	1870 (13.5)	866 (12.3)	1004 (14.8)	0.07
	COPD	430 (3.1)	167 (2.4)	263 (3.9)	0.09
	Diabetes	736 (5.3)	340 (4.8)	396 (5.9)	0.05
Education	Compulsory	2417 (17.5)	1205 (17.1)	1212 (17.9)	0.02
	Intermediate	5442 (39.4)	2775 (39.4)	2667 (39.4)	
	University or higher	5821 (42.1)	3007 (42.7)	2814 (41.6)	
	Missing	131 (0.9)	60 (0.9)	71 (1.0)	
Surgery	Conservative	7737 (56.0)	3653 (51.8)	4084 (60.4)	0.17
	Mastectomy	5971 (43.2)	3349 (47.5)	2622 (38.8)	
	No surgery	103 (0.7)	45 (0.6)	58 (0.9)	
Radiotherapy	Yes	11378 (82.4)	5697 (80.8)	5681 (84.0)	0.08
Hormone therapy	Yes	10432 (75.5)	5389 (76.5)	5043 (74.6)	0.04
Anti-HER2 therapy	Yes	3532 (25.6)	1942 (27.6)	1590 (23.5)	0.09
CT type	Anthracycline-based	4161 (30.1)	2010 (28.5)	2151 (31.8)	**0.22**
	Anthracycline-taxanes	8928 (64.6)	4960 (70.4)	3968 (58.7)	
	Taxane-based	668 (4.8)	70 (1.0)	598 (8.8)	
	Other	54 (0.4)	7 (0.1)	47 (0.7)	
Total CT duration (months)	Median (IQR)	4.9 (3.5-5.3)	4.9 (3.5-5.3)	4.6 (2.5-5.3)	**0.30**
Total CT cycles	Median (IQR)	10 (6-15)	10 (6-16)	9 (6-15)	0.16
Number of CT regimens	1	4588 (33.2)	1983 (28.1)	2605 (38.5)	**0.22**
	2	9036 (65.4)	4979 (70.7)	4057 (60.0)	
	≥ 3	187 (1.4)	85 (1.2)	102 (1.5)	
Other antiemetics	Netupitant/palonosetron	4279 (31.0)	104 (1.5)	4175 (61.7)	**1.70**
	Dexamethasone	6740 (48.8)	2290 (32.5)	4450 (65.8)	**0.71**
	Metoclopramide	12635 (91.5)	6433 (91.3)	6202 (91.7)	0.01
	Ondansetron	9372 (67.9)	5998 (85.1)	3374 (49.9)	**0.81**

Abbreviations: ER = estrogen receptor; PgR = progesterone receptor; CVD = cardiovascular disease; COPD = chronic obstructive pulmonary disease; CT = chemotherapy; IQR = interquartile range; SMD = standardized mean difference; SMD ≤ 0.1 = negligible imbalance; SMD > 0.1 and ≤ 0.2 = moderate imbalance; SMD > 0.2 = notable imbalance (bold font).

Sensitivity analyses

First, when we used 2 prescriptions to define aprepitant users instead of one prescription, the results did not vary substantially: $HR_{DDFS} = 0.87$ (95% CI = 0.78 to 0.98) and $HR_{BCSS} = 0.82$ (95% CI = 0.71 to 0.95). Notably, use of netupitant/palonosetron, defined by 2 prescriptions instead of 1, was associated with BCSS (but not with DDFS) when the analysis was limited to women diagnosed between 2016 and 2020—$HR_{DDFS} = 0.90$ (95% CI = 0.63 to 1.28); $HR_{BCSS} = 0.69$ (95% CI = 0.48 to 0.99). Second, when we limited the analysis to women diagnosed in 2008-2016, aprepitant estimates did not change substantially: $HR_{DDFS} = 0.88$ (95% CI = 0.79 to 1.00; *P*-value = .045) and $HR_{BCSS} = 0.86$ (95% CI = 0.74 to 1.02). Third, when we limited the analysis to regimens differing only by aprepitant use, the results did not vary substantially: $HR_{DDFS} = 0.88$ (95% CI = 0.77 to 0.99) and $HR_{BCSS} = 0.85$ (95% CI = 0.73 to 1.01). Fourth, when we evaluated aprepitant and netupitant/palonosetron as a single NK1R antagonist-containing drug class, its use was associated with improved survival: $HR_{DDFS} = 0.88$ (95% CI = 0.78 to 0.99) and $HR_{BCSS} = 0.84$ (95% CI = 0.71 to 0.98).

Discussion

Using linkage of nationwide population-based registries, our analyses provide the first evidence that aprepitant supply during chemotherapy is associated with improved survival in women diagnosed with early breast cancer. We found that a survival

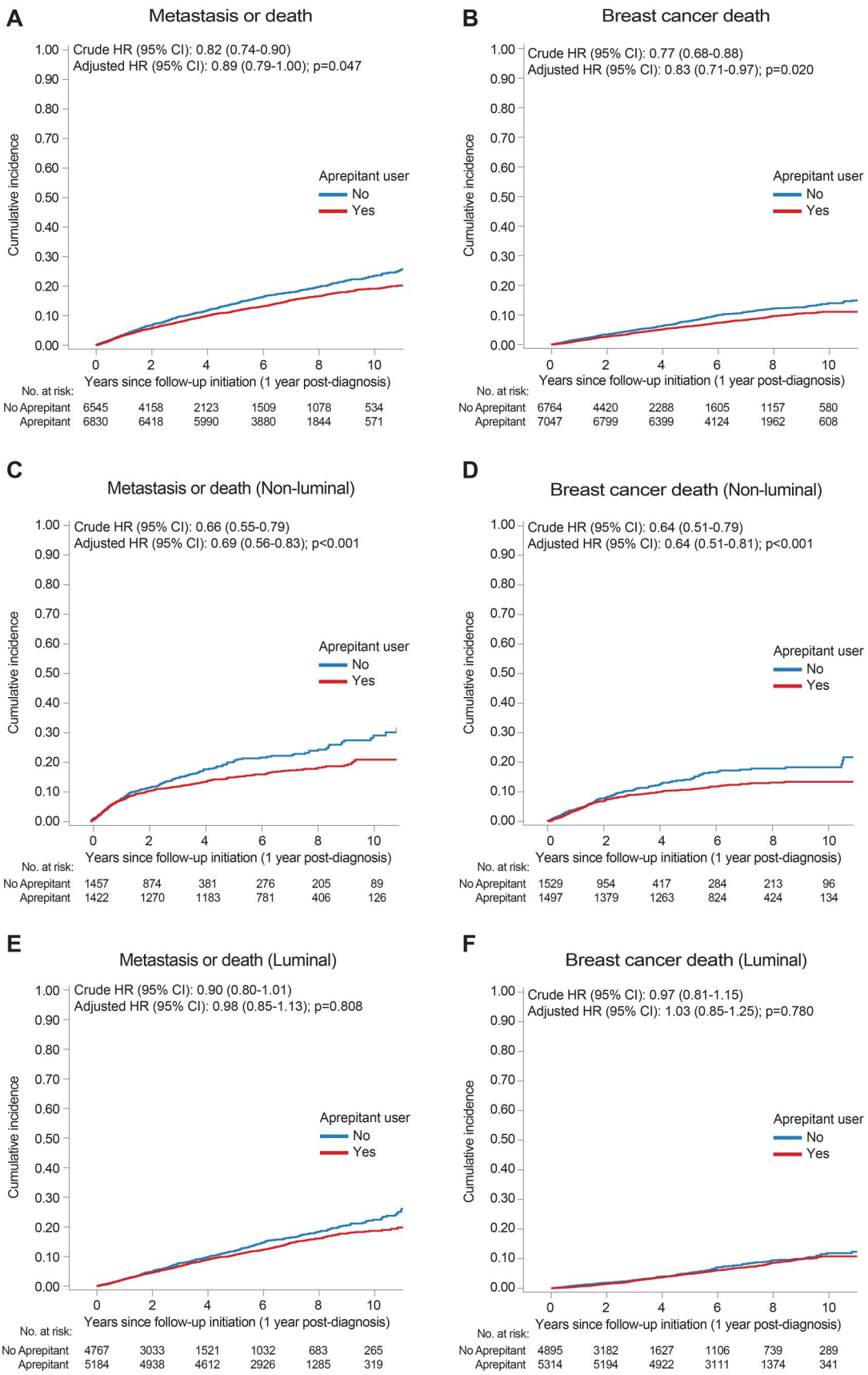

Figure 2. Distant disease-free survival and breast cancer-specific survival according to aprepitant use. Cumulative incidence of metastasis or death as first event in all women (**A**), women with non-luminal (**C**) and luminal breast cancer (**E**) stratified by aprepitant use. Cumulative incidence of breast cancer-specific death in all women (**B**), women with non-luminal (**D**) and luminal breast cancer (**F**) stratified by aprepitant use. Abbreviations: HR = hazard ratio; CI = confidence interval; DDFS = distant disease-free survival (event of interest: metastasis or death as first event); BCCS = breast cancer-specific survival (event of interest: breast cancer death).

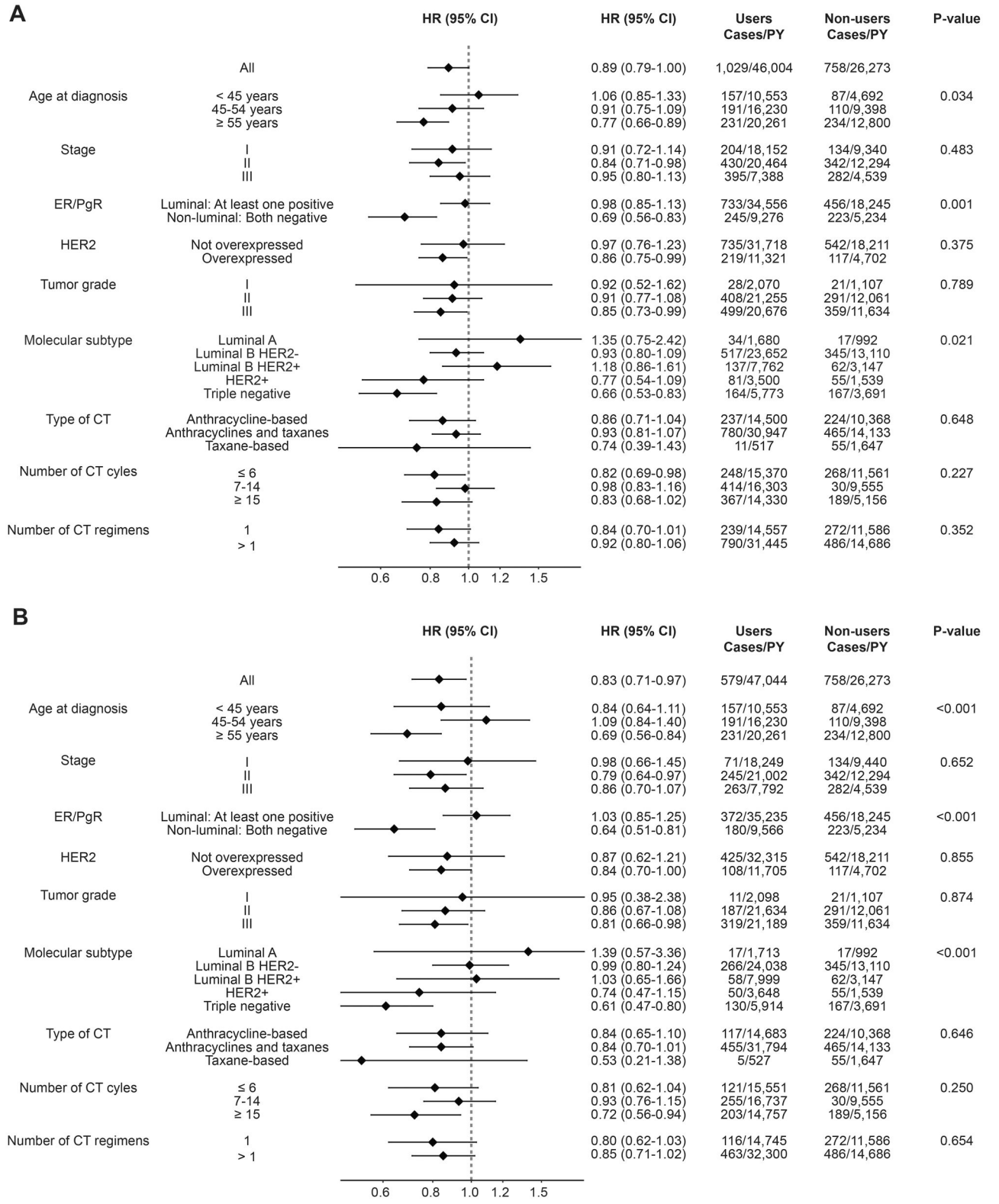

Figure 3. Association between aprepitant use and survival stratified by clinical parameters. Hazard ratios (HR) and 95% confidence interval (CI) for the association between use of aprepitant and distant disease-free survival (**A**) and breast cancer-specific survival (**B**), overall and stratified by age at diagnosis, stage, hormone receptor and HER2 receptor status, tumor grade, molecular subtype, type of chemotherapy (CT), number of chemotherapy cycles and regimens. Abbreviations: HR = hazard ratio; CI = confidence interval; ER = estrogen receptor; PgR = progesterone receptor; HER2 = human epidermal growth factor receptor 2; CT = chemotherapy; PY = personal years.

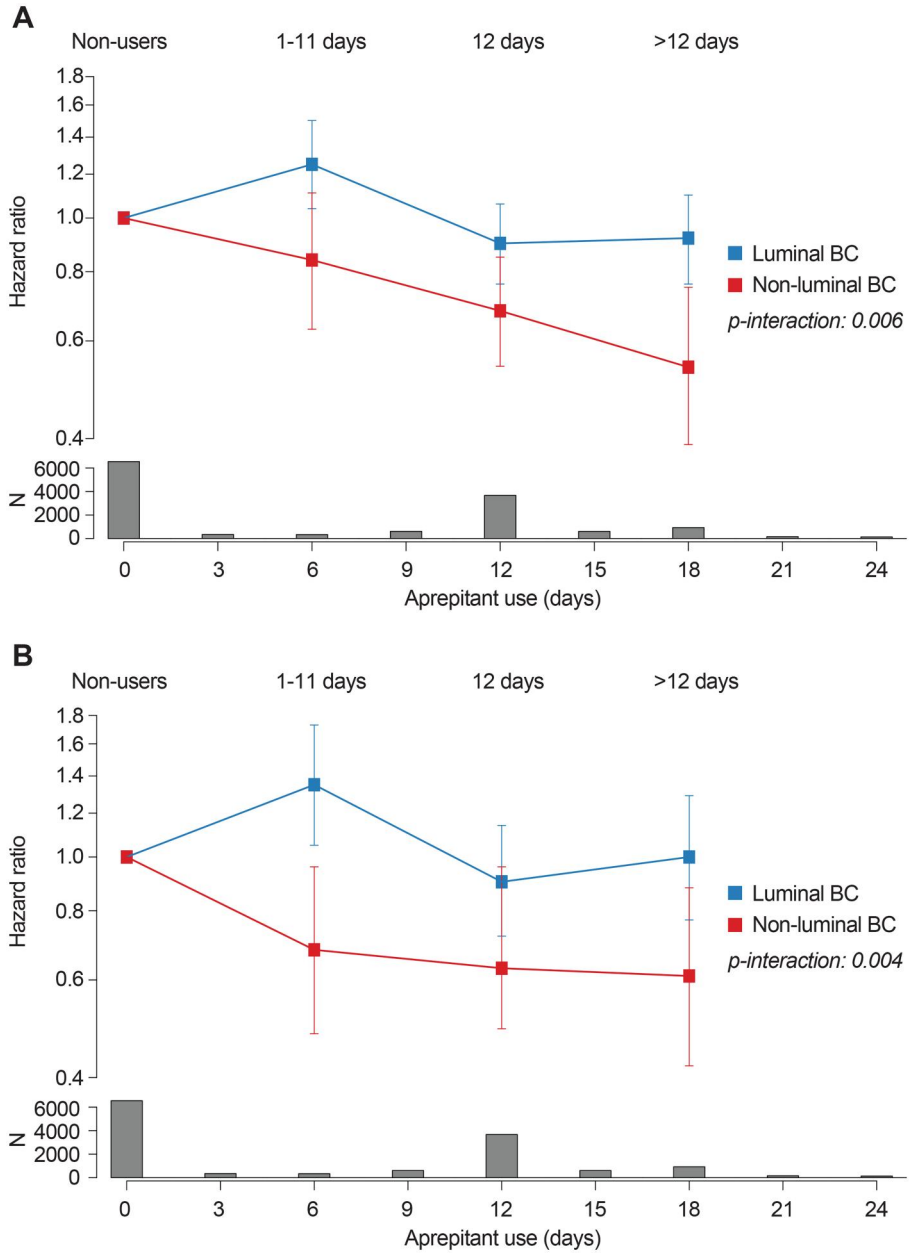

Figure 4. Association between duration of aprepitant use and survival. Hazard ratios (HR) and 95% confidence interval (CI) for the association between days of aprepitant use and distant disease-free survival (**A**) and breast cancer-specific survival (**B**) in women with luminal and non-luminal breast cancer. Abbreviations: BC = breast cancer; N = number of aprepitant users.

advantage of aprepitant was most pronounced in women with non-luminal breast cancer, specifically TNBC. Furthermore, in women with non-luminal breast cancer, longer durations of aprepitant use were associated with increasingly favorable survival.

Choice of antiemetic drugs used to prevent CINV is guided by the emetogenicity of the chemotherapy regimen.[28] Recent guidelines recommended the use of aprepitant, an NK1R antagonist, only in patients treated with highly emetogenic and platinum-based chemotherapy regimens.[27,28] The findings of the current study might suggest that expanding the use of aprepitant as a routine antiemetic regimen during chemotherapy treatment may provide potential long-term benefits for cancer outcomes. Akynzeo, a combination of the NK1R antagonist netupitant and 5-HT3 receptor antagonist palonosetron,[29] offers a convenient single-dose treatment option compared to the multi-drug, multi-day aprepitant-based regimen. Our analyses revealed an association of Akynzeo with improved BCSS but not DDFS, and only in women who receive 2 or more prescriptions. The fact that we did not observe a clear association between Akynzeo and survival may be due to the short follow-up in Akynzeo users. The use of Akynzeo in Norway has increased significantly in recent years (Figure S1), likely due to its ease of single dosing regimen and non-inferior efficacy as the 3-day aprepitant regimen in preventing CINV.[30] However, if current findings are confirmed, there is substantial reason to prefer the multi-day aprepitant regimen, which is still recommended under current antiemetic guidelines.[27,28] Notably, the other antiemetics—dexamethasone, metoclopramide, and ondansetron—were not associated with any impact on survival. Collectively, the current findings suggest that survival benefits may be specific to NK1R antagonists.

We found the greatest survival benefits associated with aprepitant use in women with non-luminal breast cancer, specifically TNBC. Notably, in women with non-luminal breast cancer chemotherapy use was similar in aprepitant users and non-users, and the association between aprepitant use and survival did not differ significantly according to chemotherapy type, suggesting that survival benefits associated with aprepitant use are unlikely to be due to the amount or type of chemotherapy used. As aprepitant inhibits the binding of substance P to NK1R, variation in NK1R expression by tumor cells or substance P concentration in tumors across different molecular subtypes may contribute to this finding. A high density of sensory nerves that release substance P in tumors was reported in human TNBC,[31] and future studies are warranted to determine whether there are biological differences across breast cancer molecular subtypes and if they predict response to aprepitant use.

Our analyses reveal an association between aprepitant length of use and progressively increasing survival benefits in women with non-luminal breast cancer, indicating that duration of exposure to aprepitant may be important for its impact on survival. As aprepitant is commonly prescribed during the first 3 days of chemotherapy treatment,[27,32] one can wonder whether greater survival would be observed if additional aprepitant was supplied in addition to the standard dosing schedule. Two independent case studies have reported aprepitant supply to patients with cancer in a non-standard dosing schedule.[33,34] In 1 case study, sustained (7 months) daily use of aprepitant (80 mg/day) reduced a cancer biomarker in a woman with metastatic breast cancer.[33] The second case study reported that daily high dose of aprepitant (1140 mg/day) for 45 days during radiotherapy treatment was well tolerated by a male patient with lung cancer, and that no tumor mass was detected in the lung 6 months after radiotherapy and aprepitant treatment.[34] These observations suggest the feasibility of long-term treatment with aprepitant and support the hypothesis that aprepitant may help control cancer progression.

We observed pronounced survival benefit of aprepitant in women older than 55 years. While the reason is unknown, clinical studies in healthy older adults and preclinical studies in aged rodents found elevated circulating substance P compared to in their younger counterparts,[35,36] suggesting greater NK1R activity in older adults. Future studies are needed to determine if aprepitant may provide a greater survival advantage in the older population.

There is a growing interest in repurposing NK1R antagonists as anti-cancer treatment.[9] As aprepitant is commonly prescribed alongside chemotherapy treatment,[28] the survival benefits associated with aprepitant observed here may be due to its impact on chemotherapy efficacy. Supporting this hypothesis, several preclinical studies have shown that concomitant treatment of cancer cells with aprepitant and chemotherapy further reduced cell viability compared to chemotherapy alone.[37-39] Future mechanistic studies should explore how aprepitant interacts with commonly used chemotherapy drugs.

Our study has some strengths. It utilizes comprehensive high-quality nationwide data from patients treated in the Norwegian clinical practice. This is the first study to demonstrate an association between aprepitant use and survival in cancer patients. The findings on aprepitant are adjusted for numerous patient and cancer characteristics as well as cancer treatments and use of other antiemetics. Additionally, various sensitivity analyses confirm the robustness of our results.

Our study also has some limitations. First, some non-aprepitant users used netupitant, found in Akynzeo. As netupitant is of the same drug class as aprepitant, our primary analysis may underestimate the impact of aprepitant on survival. To address this, we ran 2 different sensitivity analyses to exclude the potential influence of Akynzeo on analysis and confirmed the significant survival benefits associated with aprepitant use, especially in non-luminal breast cancer. Second, aprepitant users and non-users differed in the use of chemotherapy in the overall population. To address this, the Cox proportional hazard regression models were adjusted for the type of chemotherapy used and the number of treatment cycles. Furthermore, the stratified analysis revealed no significant heterogeneity in the HRs based on the type of chemotherapy. Moreover, we observed significant survival advantage with aprepitant use in the women with non-luminal breast cancer, where chemotherapy use was similar between aprepitant users and non-users. Nevertheless, the potential residual confounding by the use of chemotherapy and the interaction between aprepitant and chemotherapy type warrants thorough investigation in future studies. Third, non-adherence to prescribed antiemetic drugs is prevalent,[40] which may underestimate the impact of aprepitant use on survival in our current study. Fourth, the survival analysis began 1 year after diagnosis, limiting the applicability of our findings to women surviving at least a year. However, this restriction is likely to have minimal impact on the findings as most patients with early breast cancer survive beyond 1 year. Fifth, since all women in our analysis received at least 1 antiemetic, we could not compare aprepitant use with no antiemetic use.

Conclusions

Our finding that aprepitant supply during chemotherapy treatment is associated with survival benefits in women with early non-luminal breast cancer, particularly TNBC, might have important clinical implications. Further studies are urgently needed to evaluate the effect of aprepitant in preventing cancer relapse.

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Author contributions

Edoardo Botteri (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Validation; Visualization; Writing—original draft; Writing—review & editing), Sarah Hjorth (Data curation; Formal analysis; Investigation; Methodology; Resources), Fabio Conforti (Conceptualization; Writing—review & editing), Vincenzo Bagnardi (Visualization; Writing—review & editing), Bettina K. Andreassen (Data curation; Funding acquisition; Resources), Nathalie C. Støer (Data curation; Investigation; Resources), Sameer Bhargava (Writing—review & editing), Giske Ursin (Writing—review & editing), Sara Gandini (Writing—review & editing), Erica K. Sloan (Conceptualization; Funding acquisition; Writing—original draft), and Aeson Chang (Conceptualization; Funding acquisition; Writing—original draft).

Supplementary material

Supplementary material is available at *JNCI: Journal of the National Cancer Institute* online.

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Conflicts of interest

Sameer Bhargava has received personal fees from Gilead for work that is unrelated to this project. Other authors indicated no potential conflicts of interest.

Data availability

Norwegian law precludes the data used in this study being made publicly available. However, the data used in this study may be requested by application to helsedata.no following ethical approval by the Regional Committee for Medical and Health Research Ethics. Further information is available from the corresponding author upon request.

Data access, responsibility, and analysis

Edoardo Botteri and Sarah Hjorth had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical approval

The use and reporting of de-identified data from the CRN complied with its regulations for the collection and handling of health information. The use, linkage, and reporting of de-identified data from other registries were approved by the regional ethics committee (2018/775/REK sør-øst B) and all involved registries. The use of patient registry data in this study is legally authorized under the General Data Protection Regulation (GDPR), based on Articles 6(1)(e) and 9(2)(j), which allow data processing for research purposes in the public interest. In addition, the study is supported by a legal exemption from confidentiality obligations, as granted under the Health Register Act §19e.

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