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Non-steroidal anti-inflammatory medication use and endometrial cancer survival: A population-based Norwegian cohort study

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[Correction added on 28 April 2025, after first online publication: The copyright line was changed.]

Abstract

While nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to improve survival in certain cancers, data in patients with endometrial cancer (EC) is conflicting. This study investigated use of aspirin and nonaspirin NSAIDs (NA-NSAIDs) and EC-specific—and all-cause death. This nationwide cohort study linked data from the Cancer Registry of Norway with The Norwegian Prescription database. Patients diagnosed with EC from 2004 to 2018 were included. Post-diagnosis exposure to aspirin and NA-NSAIDs was defined as ≥3 consecutive prescriptions ≥30 days after EC diagnosis, with pre-diagnosis use as ≥2 filled prescriptions <6 months prior to diagnosis. Follow-up started 10 months after diagnosis. Hazard ratios for the risk of death were calculated with multivariable Cox-regression models. Our study population included 7751 individuals with EC, 685 (9%) were aspirin users and 620 (8%) were NA-NSAIDs users. The median follow-up time was 5.0 years, with 1518 (20%) deaths observed ($n = 728$ (9%) EC-specific). In multivariable analysis, aspirin use was significantly associated with a 19% higher risk of all-cause death compared to non-users (HR = 1.19, 95% CI [1.01–1.41]). The association was stronger among combined pre- and postdiagnosis use (HR = 1.35 [1.12–1.64]). NA-NSAIDs use increased risk of cancer-related death (HR = 1.25 [0.99–1.58]) and there was a dose–response association with significantly higher risk of cancer-specific death with higher cumulative doses (HR = 1.33 [1.02–1.75]). We found a higher risk of cancer-specific—and all-cause death among patients that used aspirin and NA-NSAIDs after a diagnosis of EC. Further studies on the biological mechanisms underlying these associations are needed.

KEYWORDS

aspirin, endometrial cancer, NSAIDS, survival, tertiary prevention

What's New?

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) may improve survival in certain types of cancer, but evidence has been inconclusive so far regarding their effect on endometrial

Renée Turzanski Fortner and Kristina Lindemann have contributed equally to this study.

cancer survival. Here, the authors present data from a large population-based cohort study in Norway, including 7751 individuals with endometrial cancer. Among the study participants, 9% used aspirin and 8% used non-aspirin NSAIDs. They found that use of either aspirin or other NSAIDs after endometrial cancer diagnosis increased patients' risk of death. These results highlight the need for more data regarding the effects of NSAIDs on the immune system and endometrial cancer progression.

1 | INTRODUCTION

Endometrial cancer (EC) is the most common gynecological cancer in the developed world.[1,2] The incidence rates worldwide have been increasing in recent years,[3–5] in part due to a rising incidence of obesity, a major risk factor for EC.[6] Most women present with early-stage disease amendable to surgery and with a favorable prognosis.[7,8] Patients diagnosed at advanced stages or with relapsed disease have poorer outcomes, with 5-year survival rates often not exceeding 20%.[1,9] Due to the rising incidence rates in EC and the variation in oncological outcome there is a need for improved knowledge on tertiary preventative strategies for EC.[10] Non-steroidal anti-inflammatory drugs (NSAIDs) have been explored in this context for their potential for drug repurposing.

NSAIDs belong to a drug class comprised of several medications with antipyretic, anti-inflammatory, analgesic effects and anti-platelet activity.[11] Aspirin is one of those drugs and low doses of aspirin are commonly used for primary and secondary prevention of cardiovascular disease.[12] Aspirin use has been shown to improve survival in colorectal cancer,[13] a cancer sharing similarities with specific EC-subtypes through certain genetic mutations such as microsatellite instability events and defects in DNA mismatch repair genes.[14,15] Other studies have shown a beneficial effect of aspirin use on survival of ovarian cancer, one of the most lethal gynecological cancers.[16,17]

Few studies have examined the association between NSAID use and risk of death from EC. Two studies utilizing data on NSAID use recorded in the medical records at the time of primary diagnosis showed improved EC-survival in aspirin users.[18,19] This contrasts to one study examining self-reported pre-diagnosis use of aspirin and non-aspirin NSAIDs (NA-NSAIDs) where an increased risk of cancer-specific death in patients with endometroid EC was reported.[20] However, two registry-based studies did not find any association between aspirin use and EC mortality.[21,22] When examining the association with use of NA-NSAIDs, poorer survival with higher doses of NA-NSAID use has been reported.[23] Given the methodological differences and the contradictory results of previous studies more data on NSAID use and EC survival is needed.

The aim of this study was to investigate the association between the use of aspirin and NA-NSAIDs and endometrial cancer-specific— and all-cause death.

2 | METHODS AND MATERIAL

This population-based nationwide cohort study linked patients diagnosed with EC with information on their use of aspirin and NA-NSAIDs. The assignment of a unique personal identification number to all Norwegian residents allows the linkage of multiple registries for research purposes. We identified the study population by linking the Cancer Registry of Norway (CRN) data to the Norwegian Prescription Database (NorPD). These registries cover more than 99% of the Norwegian population and include individuals in an unselected and consecutive manner.[24,25] Further linkage was made to the Cause of Death Registry[26] and socioeconomic data were available from Statistics Norway.[27] The CRN records patients with endometrial cancers based on the International Classification of Diseases, 10th revision (ICD-10), with further classification of malignant lesions based on the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3).[28] The CRN includes detailed information on each cancer diagnosis such as stage, age at diagnosis and tumor morphology. NorPD includes information about all prescription medications for individuals in Norway including date of dispensing and medications dispensed (identified by Anatomical Therapeutic Chemical [ATC] code), strength (i.e., active ingredient per unit, e.g., mg per tablet), and the number of defined daily dose (DDD) units which is defined as the average maintenance dose per day for a medication used for its main indication.

Information on body mass index (BMI) was available for a subset of the population ($n = 2814$) and extracted from four large Norwegian health surveys. Data S1 provides further description of the registries and health surveys used in our study.

2.1 | Study population

We identified individuals between the ages of 18–94, with a diagnosis of invasive EC (ICD-code C54) between 2004 and 2018 and with no prior history of other invasive cancers (except non-melanoma skin cancer C44). Patients were excluded if they were not residing in Norway at the time of diagnosis, immigrated to Norway <6 months before diagnosis or if the morphology code showed a non-malignant histology. Histologies such as sarcomas (ICD-O3 code: 8890/, 8891/3, 8896/3, 8900/3, 8933/3, 8935/3, 8950/3) were excluded. Lastly, we excluded patients who died or were lost to follow-up due to emigration within the first 10 months of diagnosis. The final study population included 7751 individuals (Figure 1).

2.2 | Exposure, follow-up and outcome

Baseline exposure to aspirin and NA-NSAIDs was defined as post-diagnostic use with at least three consecutive prescriptions between

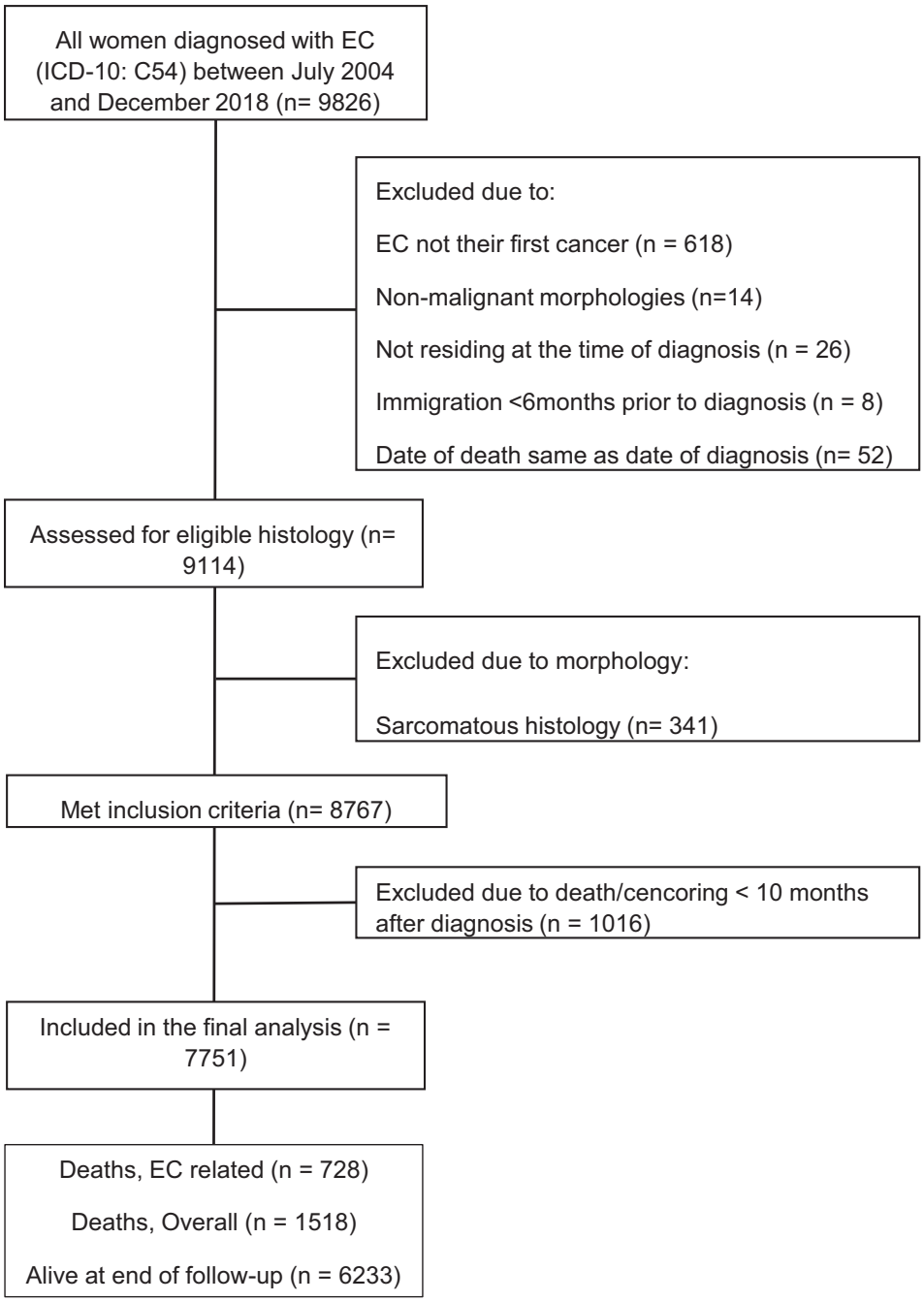

FIGURE 1 Flowchart of the selection of the study population from the Cancer Registry of Norway including all women diagnosed with endometrial cancer in the time period 2004–2018.

30 days and 10 months after the diagnosis of EC. The assumption was that those who refilled a prescription at least twice were more likely to represent regular users than those with fewer refills. Consequently, all patients with <3 prescriptions between 30 days and 10 months after the diagnosis of EC were classified as non-users. Individuals were classified as "users" based on post-diagnosis use, regardless of whether they used these medications prior to diagnosis (Figure 2).

Pre-diagnosis use was defined as at least two filled prescriptions in the 6 months prior to diagnosis.

Updated exposure to NSAIDs allowed the assessment of the exposure in a time-dependent manner. Individuals were initially classified as non-users at baseline if <3 prescriptions were filled in the period 30 days to 10 months after EC diagnosis, and user with ≥3 prescription during that period. After start of follow-up any non-user became user from the time of filling the third prescription during follow-up. For example, an individual with two prescriptions in the period 30 days to 10 months after EC diagnosis would be defined as a non-user from start of follow-up until the next prescription fill (3 prescriptions in total) and user from that time until end of follow-up. Dose–response was evaluated by cumulating the number of defined daily doses (DDD) in each prescription. The users were then categorized according to the median cumulative amount used, either <median DDD or ≥median DDD; the median DDD threshold was defined as the median of the total cumulative DDDs among users.

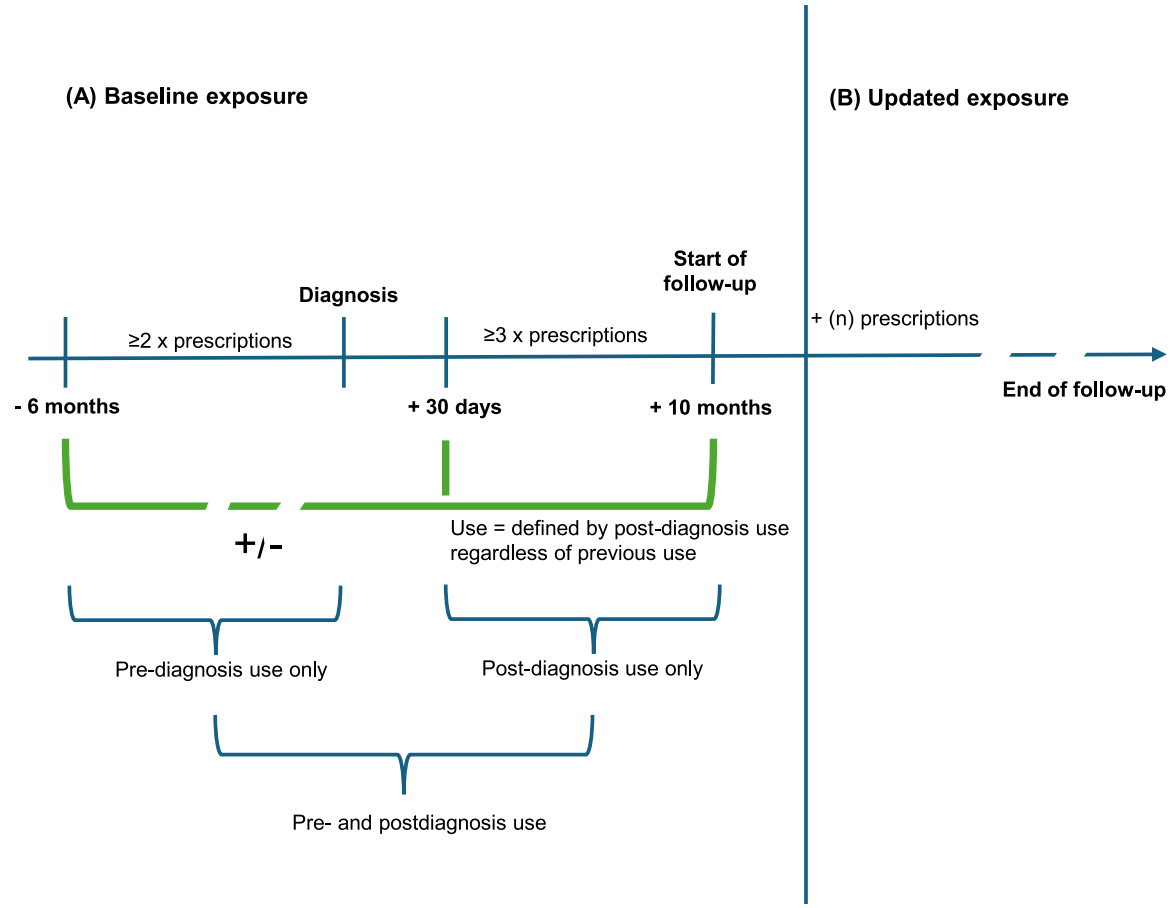

FIGURE 2 A schematic overview over (A) Baseline exposure and (B) updated exposure.

All aspirin prescriptions had low dose formulations of ≤75 mg or 160 mg. A detailed overview over the aspirin and NA-NSAIDs included in this study is provided in the Table S1.

NorPD was further used to identify medications as proxies for comorbidity; these included pre- and postdiagnosis statins (C10), anti-diabetics (A10) and cardiovascular drugs (e.g., antihypertensives, C01–C09) as shown in Table S2.

Follow-up time for all individuals started at 10 months after the diagnosis to allow sufficient exposure time as defined above. The patients were followed up until death, emigration or end of study (December 31, 2018), whichever came first. The primary outcome of the study was risk of cancer-specific death, with risk of all-cause death as secondary outcome.

2.3 | Statistical analysis

Cox-proportional hazard regression models were used to estimate hazard ratios (HR) with 95% confidence intervals (CIs) for the association between use of aspirin or NA-NSAIDs and risk of cancer - specific death and risk of all - cause death. Hazard ratios were adjusted for age at diagnosis and in the multivariable models (fully adjusted) adjusted for age at diagnosis, stage, tumor morphology (endometroid vs. non-endometroid), comorbidities (use of statins, anti-diabetics and cardiovascular drugs used as proxies for comorbidities), concomitant use of other types of NSAIDs (aspirin and NA-NSAIDs), education, marital status, income and parity. For education, the following categories were used: "None/mandatory" (up to 10 years of primary education), "secondary" (up to 13 years of education) and "higher" which includes all levels of tertiary education. Marital status included the following categories: "Married/partnered", "unmarried/no partner", "divorced" and "widowed." Income was categorized as low, medium and high using tertiles. Parity was categorized according to "no children", "1–2 children" or "≥3 children." The proportional hazard assumption was assessed by evaluating scaled Schoenfeld residuals.

Associations were evaluated in predefined subgroups by age groups, tumor morphology, stage and by concomitant use of medications used for cardiovascular disease in addition to anti-diabetics and statins. The associations were also evaluated in subgroups by categories of BMI ≥25 or <25 in the subset of the population where this information was available (36%). Interactions between aspirin or NA-NSAID use, and the abovementioned variables were evaluated with likelihood ratio tests comparing models with and without interaction terms. Two sensitivity analysis were conducted. We restricted the study sample to the individuals with available data on BMI and

evaluated the associations without and with adjustment for BMI. We also conducted analyses restricting the study population to individuals aged ≥50 years to especially study individuals with the highest likelihood to be exposed to NSAIDs as primary prophylaxis, as the initiation for prophylactic low-dose aspirin for cardiovascular disease is recommended after the age of 50.[29]

All analyses were performed in R version 4.2.3.

3 | RESULTS

In the total study population of 7751 individuals diagnosed with a primary, histologically verified EC, 685 individuals (8.8%) were aspirin users and 620 (8.0%) were NA-NSAIDs users at baseline; 36 individuals (0.5%) were using both aspirin and NA-NSAIDs. During median follow-up of 5.0 years (range: 1 month to 13 years), 1518 (19.6%) deaths were observed, of which 728 (9.4%) were due to EC. Among aspirin users, 194 (28.3%) deaths occurred, of these 77 (11.2%) were EC-specific. Among NA-NSAIDs users, 132 (21.3%) deaths occurred, of which 81 (13.1%) were EC-specific.

3.1 | Aspirin users

Individuals classified as aspirin users at baseline were older at diagnosis (median 73.3 vs. 65.3 years) and more likely to be a widow (30.5% vs. 17.3%) compared to non-users. There were more aspirin users with lower education levels (41% vs. 30% "none/mandatory"), lower income (43.2% vs. 32.0% "low") and a noticeably higher use of concomitant drug use indicating more comorbidities compared to non-users. The proportion of individuals that used anti-diabetic medication (16.9% vs. 7.7%), cardiovascular drugs (82.6% vs. 37.3%) and drugs against hypercholesterolemia (50.8% vs. 11.5%) were all higher among aspirin users compared to non-users (Table 1). Distribution of stage and histology was similar between aspirin users and non-users.

3.2 | NA-NSAIDs users

The individuals who used NA-NSAIDs had a similar age distribution at diagnosis as the non-users of NA-NSAIDs (median 64.3 vs. 66.3 years) and a similar distribution of socioeconomical factors and comorbidities. However, NA-NSAIDs users had more metastatic disease at the time of diagnosis compared to non-users (14.8% vs. 9.3%).

3.3 | Association of aspirin use and risk of death

There was no significant association between aspirin use and risk of cancer-specific death in the multivariable baseline exposure analysis (users compared to non-users, HR 1.17, 95% CI 0.90–1.51; Table 2). Individuals with both pre-and post-diagnosis aspirin use had a significantly higher risk of cancer-specific death (HR of 1.43, 95% CI 1.07–1.92), as compared to non-users. For all-cause death, aspirin use was significantly associated with a 19% higher risk (HR 1.19, 95% CI 1.01–1.41) compared to non-users. The increased risk of all-cause death was also observed in the group of patients with both pre- and post-diagnosis use (HR 1.35, 95% CI 1.12–1.64). Exclusive post-diagnosis aspirin use was not associated with cancer-specific or all-cause death. However, there were a limited number of deaths within that subgroup ($n = 19$ cancer-specific, $n = 57$ overall). No associations were observed in the updated exposure analysis for cancer-specific or all-cause death.

3.4 | Association of NA-NSAIDs use and risk of death

In multivariable analysis NA-NSAIDs users had a higher risk of cancer-specific death (HR 1.25, 95% CI 0.99–1.58), relative to non-users, in the baseline exposure analysis (Table 3). No significant association was found with cancer-specific death in individuals with pre-and post-diagnosis NA-NSAIDs use (HR 1.19, 95% CI 0.80–1.76), however exclusive post-diagnosis use of NA-NSAIDs indicated a higher risk of cancer-specific death (HR 1.31, 95% CI: 0.99–1.73). This trend was also observed in the updated exposure analysis (HR 1.17, 95% CI 0.97–1.42). These findings were further supported by the observation of statistically significant higher risk of cancer-specific death with at or above the median prescribed DDD of NA-NSAIDs (HR 1.33, 95%CI 1.02–1.75) compared to below the median DDD where no significant association was found (HR 1.08, 95% CI 0.85–1.36), both relative to non-users. There was no significant association between NA-NSAIDs use and all-cause death in neither the fixed baseline exposure analysis nor the updated exposure analysis.

3.5 | Subgroup analysis

We evaluated baseline exposure to aspirin and NA-NSAIDs and risk of death in groups defined by tumor histology, stage and by concomitant use of medications as proxy for comorbidities (Tables S3 and S4). Aspirin users with endometroid and localized EC had a significantly higher risk of all-cause death (HR 1.33, 95% CI 1.09–1.61 and HR 1.29, 95% CI 1.04–1.60, respectively) compared to non-users. No significant associations were noted between aspirin use and cancer-specific death in these subgroups. Higher risk of cancer-specific death in NA-NSAIDs users was observed in patients with metastatic disease (HR 1.37, 95%CI 1.02–1.84), with a significant interaction by stage ($p_{\text{interaction}} = 0.044$). There was some variation in the hazard ratios observed in subgroups by use of concomitant medication use, but none of these reached statistical significance (Tables S3 and S4).

In the age restricted analysis of individuals ≥50 years, estimates of the associations remained unchanged (Tables S5 and S6). Stratified analysis by age revealed no consistent pattern (Table S7). Analyses in subgroups by BMI did not show any significant associations between aspirin use and risk of cancer-specific- or all-cause death (Table S8).

TABLE 1 Characteristics of the study cohort based on baseline exposure of aspirin and NA-NSAID use[a]: Registry-based cohort of endometrial cancers diagnosed in Norway 2004–2018.

Characteristics	Aspirin use				NA-NSAIDs use			
	Yes ($n = 685$)		No ($n = 7066$)		Yes ($n = 620$)		No ($n = 7131$)	
	73.3 (37.8–91.9)		65.3 (25.5–92.5)		64.3 (31.2–85.3)		66.1 (25.5–92.5)	
Median age at diagnosis (min, max)	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Tumor histology								
Endometroid	575	83.9	5938	84.0	497	80.2	6016	84.0
Serous, clear cell	79	11.5	745	10.5	75	12.1	749	10.6
Other	31	4.5	383	5.4	48	7.7	366	5.3
Clinical stage								
Local	533	77.8	5343	75.6	442	71.3	5434	75.8
Regional	63	9.2	565	8.0	44	7.1	584	8.1
Metastatic	49	7.2	709	10.0	92	14.8	666	9.8
Unknown	40	5.8	449	6.4	42	6.8	447	6.3
Medications[b]								
Anti-diabetics	116	16.9	544	7.7	61	9.8	599	8.5
Cardiovascular drugs	566	82.6	2635	37.3	256	41.3	2945	41.3
Statins	348	50.8	811	11.5	87	14.0	1072	14.9
BMI								
<25 kg/m^2	60	8.8	825	11.7	61	9.8	824	11.4
≥25 kg/m^2	185	27.0	1744	24.7	169	27.3	1760	24.9
Unknown	440	64.2	4497	63.6	390	62.9	4547	63.7
Education								
None/mandatory	282	41.2	2093	29.6	183	29.5	2192	30.7
Secondary	312	45.6	3306	46.8	296	47.7	3322	46.7
Higher	89	13.0	1627	23.0	138	22.3	1578	22.1
Unknown	2	0.3	40	0.6	3	0.5	39	0.5
Marital status								
Married	345	50.4	4069	57.6	368	59.3	4046	56.9
Unmarried	56	8.2	789	11.2	59	9.5	786	10.9
Divorced	75	11.0	984	13.9	91	14.7	968	13.7
Widow	209	30.5	1221	17.3	102	16.5	1328	18.5
Income[c]								
Low	296	43.2	2260	32.0	191	30.8	2365	33.0
Medium	255	37.2	2306	32.6	226	36.5	2335	33.0
High	134	19.6	2500	35.4	203	32.7	2431	34.0
Parity								
0	83	12.1	1142	16.2	90	14.5	1135	15.8
1–2	345	50.4	3562	50.4	342	55.2	3565	50.4
≥3	257	37.5	2362	33.4	188	30.3	2431	33.8

[a]Baseline exposure; defined by post-diagnosis exposure at least three consecutive prescriptions between 30 days and 10 months after the diagnosis of endometrial cancer, regardless of previous use.
[b]Recorded at the time of diagnosis.
[c]According to tertiles of income in Norwegian Krone (low <242,849; medium 242,849–343,752 and high >343,753).

Multivariable analysis showed an increased risk of cancer-specific death in patients with BMI ≤25 using NA-NSAIDs (HR 2.55, 95% CI 1.24–5.23; Table S9). No statistically significant interaction was observed by BMI. Overall, the associations were similar in the sensitivity analysis in the subgroup of individuals with data on BMI, however the point estimates were higher (Tables S10 and S11).

TABLE 2 Association between aspirin use and risk of death among individuals with endometrial cancer: Registry-based cohort of endometrial cancers diagnosed in Norway 2004–2018.

Exposure	Person years	Cancer specific deaths	Overall deaths	Age-adjusted analysis		Multivariable analysis[a]	
				Cancer-specific death	All-cause death	Cancer-specific death	All-cause death
				HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Aspirin-baseline exposure[b]							
No use (ref)	40,394	651	1324	1	1	1	1
Use	3302	77	194	1.01 (0.80–1.29)	1.20 (1.03–1.40)	1.17 (0.90–1.51)	1.19 (1.01–1.41)
Pre- and post	2171	58	137	1.10 (0.84–1.45)	1.26 (1.05–1.50)	1.43 (1.07–1.92)	1.35 (1.12–1.64)
Post only	1131	19	57	0.80 (0.51–1.28)	1.09 (0.83–1.42)	0.74 (0.47–1.19)	0.93 (0.70–1.22)
No pre-diagnosis use (ref)	39,457	614	1244	1	1	1	1
Pre-diagnosis use	4239	114	274	1.16 (0.94–1.42)	1.30 (1.14–1.49)	1.19 (0.96–1.48)	1.24 (1.08–1.43)
Aspirin-updated exposure							
No use (ref)	35,825	609	1154	1	1	1	1
Ever use	7882	119	364	0.95 (0.77–1.17)	1.14 (1.00–1.29)	1.01 (0.81–1.26)	1.06 (0.93–1.21)
No use (ref)	35,825	609	1154	1	1	1	1
<Median DDD	4655	98	241	0.98 (0.79–1.23)	1.14 (0.99–1.32)	1.06 (0.84–1.34)	1.10 (0.95–1.28)
≥Median DDD	3226	21	123	0.81 (0.51–1.30)	1.12 (0.92–1.38)	0.81 (0.51–1.31)	0.98 (0.79–1.20)

Abbreviation: CI, confidence interval; HR, hazard ratio.

[a]Models adjusted for age at diagnosis, stage, tumor morphology, marital status, education, income, comorbidities (medications as proxy for cardiovascular disease, diabetes and hypercholesterolemia) and concomitant use of NA-NSAIDs.

[b]Baseline exposure: Use: defined by post-diagnosis use with at least three consecutive prescriptions between 30 days and 10 months after the diagnosis of endometrial cancer, regardless of previous use. Pre- and post: defined by both post-diagnosis use and pre-diagnosis use; at least two filled prescriptions in the 6 months prior to diagnosis. Post only: use recorded only in the postdiagnosis period. Pre-diagnosis use: defined by pre-diagnosis use, patients with <2 prescriptions were defined as non-users.

Adjusting for BMI in this subset of the cohort did not substantially change the results.

4 | DISCUSSION

The aim of this nationwide cohort study was to investigate the association between the use of aspirin and NA-NSAIDs and endometrial cancer-specific and all-cause death. We observed a higher risk of cancer-specific death among individuals that used aspirin both before and after the diagnosis. We also found that post-diagnosis aspirin use, regardless of pre-diagnosis use, was associated with higher risk of all-cause death. The use of NA-NSAIDs was associated with higher risk of cancer-specific death, supported by a dose-dependent association in the updated exposure analysis. There was no association between NA-NSAIDs use and risk of all-cause death.

4.1 | Aspirin

Studies to date have shown mixed results on the association between the use of aspirin and EC survival.[18–22] These studies differ vastly in design and exposure definitions making comparison of the findings across studies challenging. Only two studies have evaluated post-diagnosis aspirin use utilizing prescription data for the exposure definition.[21,22] A registry-based cohort study from Denmark evaluating post-diagnosis low-dose aspirin use and EC survival found no association between low dose aspirin and risk of cancer-specific death (HR 1.10, 95% CI 0.90–1.33).[21] In line with our results, the study also reported a higher risk of all-cause death with aspirin use (HR 1.28, 95% CI 1.07–1.53). Our study had several similarities with the Danish study with regards to study design, the ability to control for confounding factors, and use of prescription registry data for exposure assessment. One of the main methodological differences is the stricter definition of post-diagnosis exposure in our study with at least three filled prescriptions in the current study compared to one or more filled prescriptions in the Danish study. This explains the smaller proportion of patients with exclusive post-diagnostic use in our study. However, the approach used here increased the likelihood to capture chronic exposure beyond the time of diagnosis. As in our study, many of the individuals in the Danish study defined as post-diagnosis users of aspirin, also used aspirin prior to the diagnosis. The Danish paper address this in a stratified analysis by pre-diagnosis use, with no significant association with EC-specific death in either stratum of pre-diagnosis use. In contrast, our study found a significantly higher risk of EC-specific death in individuals that used aspirin both before and after the diagnosis. No associations were observed between exclusive post-diagnosis use and risk of death, thus we do not find evidence to suggest that starting aspirin is detrimental, but rather provide evidence that individuals already using aspirin had poorer outcomes.

TABLE 3 Association between NA-NSAIDs use and risk of death among individuals with endometrial cancer: Registry-based cohort of endometrial cancers diagnosed in Norway 2004–2018.

Exposure	Person years	Cancer specific deaths	Overall deaths	Age adjusted analysis		Multivariable analysis[a]	
				Cancer-specific death	All-cause death	Cancer-specific death	All-cause death
				HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
NA-NSAIDs-baseline exposure[b]							
No use (ref)	39,942	647	1386	1	1	1	1
Use	3754	81	132	1.50 (1.19–1.89)	1.14 (0.96–1.37)	1.25 (0.99–1.58)	1.04 (0.87–1.25)
Pre and post	1571	26	49	1.10 (0.74–1.62)	0.95 (0.71–1.26)	1.19 (0.80–1.76)	1.04 (0.78–1.38)
Post only	2183	55	83	1.81 (1.37–2.39)	1.30 (1.04–1.63)	1.31 (0.99–1.73)	1.06 (0.84–1.32)
No pre-diagnosis use (ref)	40,320	673	1406	1	1	1	1
Pre-diagnosis use	3376	55	112	0.98 (0.75–1.30)	0.94 (0.78–1.14)	0.96 (0.73–1.27)	0.94 (0.77–1.14)
NA-NSAIDs-updated exposure							
No use (ref)	31,427	577	1187	1	1	1	1
Ever use	12,279	151	331	1.37 (1.13–1.65)	0.97 (0.85–1.11)	1.17 (0.97–1.42)	0.90 (0.79–1.03)
No use (ref)	31,427	577	1187	1	1	1	1
<Median DDD	6528	86	181	1.40 (1.11–1.77)	1.01 (0.86–1.19)	1.08 (0.85–1.36)	0.88 (0.75–1.04)
≥Median DDD	5751	65	150	1.32 (1.01–1.72)	0.93 (0.78–1.11)	1.33 (1.02–1.75)	0.93 (0.78–1.11)

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Models adjusted for age at diagnosis, stage, tumor morphology, marital status, education, income, comorbidities (medications as proxy for cardiovascular disease, diabetes and hypercholesterolemia) and concomitant use of aspirin.

[b]Baseline exposure: Use: defined by post-diagnosis use with at least three consecutive prescriptions between 30 days and 10 months after the diagnosis of endometrial cancer, regardless of previous use. Pre and post: defined by both post-diagnosis use and pre-diagnosis use; at least two filled prescriptions in the 6 months prior to diagnosis. Post only: use recorded only in the postdiagnosis period. Pre-diagnosis use: defined by pre-diagnosis use, patients with <2 prescriptions were defined as non-users.

However, the number of EC deaths among aspirin users was limited and these results should be interpreted in that context.

Another registry-based prospective cohort study from the UK evaluating post-diagnosis low-dose aspirin use in a time-dependent manner observed no association between the use of aspirin and neither cancer-specific nor all-cause death.[22] Pre-diagnosis use in the UK study was evaluated in an analysis stratified by pre-diagnosis use and did not observe significant associations for EC-specific- or all-cause death in either stratum.

Several studies have evaluated pre- or peri-diagnosis use of aspirin,[18–20] with inconsistent findings. Our study showed the strongest associations with EC-specific and all-cause death in patients with both pre- and post-diagnostic use. It is unclear what role aspirin plays in the etiology, carcinogenesis, progression and survival of EC, but it may be postulated that pre-diagnosis use could promote development of a more aggressive tumor or influence progression of a developing tumor to a more aggressive phenotype, whereas post-diagnosis use could impact progression or treatment. Although we adjusted for comorbidities to reduce bias due to confounding by indication in the analysis, this could still be an explanation for our findings; that is, patients that are prescribed aspirin are more frail and at a greater risk of death.

The main mechanism of action of NSAIDs including aspirin is through inhibition of COX 1 and COX 2. These enzymes are involved in the biosynthesis of different prostaglandins that play a role in endometrial carcinogenesis.[30] COX 2 is usually induced and upregulated in nucleated cells as a response to inflammation and injury while COX 1 is highly expressed in platelets.[31] Very high doses of aspirin are required to fully inhibit COX 2.[32] The chemo-preventative mechanism of low dose aspirin is mainly through the COX 1 pathway and works by inhibiting platelet aggregates that are paramount to the metastatic process in endometrial cancer.[32] Although low dose aspirin irreversibly inactivates both isoforms of COX, nucleated cells can reverse this inactivation by synthesizing more enzyme, mainly COX 2.[32] Platelets are not nucleated and not able to synthesize more COX 1. One could hypothesize from this that low dose aspirin triggers a relative increase in COX2 levels in a similar way to how cytotoxic therapies have been shown to upregulate COX-2/PGE2-levels in cancer cells,[33] and thereby potentially leading to further cancer progression or worse outcomes in endometrial cancer.

The role of aspirin in the tertiary prevention of cancer in general seems to differ by the type of cancer. A Norwegian registry-based study, using a very similar approach to us, found low dose aspirin use to be associated with lower risk of death of colorectal cancer.[13] This inverse association was also shown in studies of ovarian cancer.[16,17] Even though colorectal and endometrial cancer share some similarities in terms of carcinogenesis (i.e., loss of mismatch repair [MMR] function protein), there are also other drivers in endometrial cancer such as p53 abnormality.[34] The new International Federation of Gynecology and Obstetrics (FIGO) classification system of endometrial cancer

encourages complete molecular classification of all endometrial cancers, and future studies may explore the role of aspirin and other NSAIDs in molecular subtypes of EC.[35]

4.2 | NA-NSAIDs

Our results observing a higher risk of cancer-specific death among individuals with EC using NA-NSAIDs are in line with another registry-based study from Denmark reporting a detrimental effect of NA-NSAIDs and EC mortality.[23] In the Danish study the association between NA-NSAIDs and poorer EC survival was dose dependent with highest risk associated with large cumulative doses of NA-NSAIDs. We observed the highest risk of EC-specific and all-cause death among baseline NA-NSAIDS users with BMI ≤25 kg/m^2.

The differential association in subgroups of BMI was not observed in the Danish study. In our study, patients using NA-NSAIDS were more likely to be diagnosed with more advanced disease compared to non-users. We observed significant interaction between NA-NSAID use and stage for the association risk of all-cause death, with strongest associations observed for individuals with metastatic disease at diagnosis. NA-NSAIDS are not commonly used as pain medication in cancer patients, and we consider the risk of end-of life use bias or confounding by indication as low and not a likely explanation for this result.

In our study the most prescribed NA-NSAID was diclofenac which tends to have a higher affinity for inhibiting COX 2 relative to COX 1, followed by ibuprofen which has a greater affinity for COX 1.[36] Oxicam drugs were the third most prescribed NA-NSAID and inhibit both forms of COX. These NA-NSAIDs are typically used on a chronic basis among individuals with musculoskeletal disorders and rheumatic diseases with autoimmune pathogenesis.[37] A higher incidence of certain types of cancers have been reported in these patients, however, studies have not specifically reported on endometrial cancer incidence.[38,39] Whether this higher incidence of cancer is due to the underlying autoimmune disease, or the use of medications used to treat the disease, is still largely unknown. Although EC has not been listed among the most common cancers associated with autoimmune diseases, the mounting evidence of efficacy of immunotherapy in patients with EC,[40] warrants further investigation on the biological mechanisms by which NSAIDs may act on the host immune system and thereby may influence EC progression and prognosis. The introduction of immunotherapy to endometrial cancer treatment has been a paradigm change, particularly for patients with MMRdeficient/microsatellite instability-high (MSI-H) tumors, and there is certainly a prognostic role in the host/tumor immune environment.[41]

NA-NSAIDs differ in their capacity to inhibit COX-1 or COX-2 depending on the concentration and the tissue involved. COX 2 has been shown to be elevated in malignant endometrial cells in laboratory studies[30] and it has been hypothesized that the chemopreventive effect of NA-NSAIDs is mainly linked to inhibition of COX 2. Experimental evidence has demonstrated that a selective COX 2-inhibitor both reduced the proliferative rate of endometrial cancer cells, but also upregulated COX 2.[42] There are some epidemiological data indicating increased risk of certain cancers with the use of NSAIDs. A study showed increased risk of renal cell carcinoma with prolonged analgesic use[43] and an increased risk of certain molecular subtypes of breast cancer with use of ibuprofen was reported in a population based case–control study.[44] However, as far as we know, no study to date have specifically explored the biological mechanisms by how NA-NSAIDs could play a role in cancer development,[45] and the potential lethal effect of NA-NSAIDs on tumor progression is unknown.

5 | STRENGTH AND LIMITATIONS

The most obvious strength of our study is the use of the high quality and complete Cancer Registry of Norway and the Norwegian Prescription Database, covering 99% of the Norwegian population.

Our study had some limitations. Firstly, this is an observational cohort study and no conclusion regarding the causality of the observed associations can be drawn. We lacked detailed information on other lifestyle factors and health behavior, but adjusted for co-medication as proxy for important comorbidities. The complex associations between BMI, co-medication use, molecular subgroup and prognosis may play a role in the observed heterogeneity in groups by co-medication use, but the lack of data on molecular subtypes of EC and the lack of a consistent difference in BMI between co-medication users vs. non-users in our study (data not shown) precludes any final conclusion. Secondly, data on BMI was only available for 36% of the included patients. Even though there is conflicting data on the association of BMI with EC survival,[46–48] low BMI has been reported to be more often associated with p53abnormal tumors, which have the poorest prognosis.[49]

Lastly, no individuals in our study were exposed to high doses of aspirin which prevented us from exploring different dose levels. We did not have any information about over-the-counter use of the evaluated drugs. However, we consider this to be a low risk of bias as most regular users of aspirin and NA-NSAIDs in Norway will obtain this through a prescription due to a national reimbursement system. Over-the counter aspirin and NA-NSAIDs are strictly regulated, sold in limited quantities, and not eligible for reimbursement, limiting their widespread use. Detailed treatment data was not available in this study population, but as gynecological cancer treatment is largely centralized in Norway, we anticipate little variation in treatment patterns and no association with NSAID use.

6 | CONCLUSION

We report a higher risk of cancer-specific death and all-cause death among individuals taking aspirin after a diagnosis of endometrial cancer, mainly driven by the use of aspirin prior to diagnosis. We further report a higher risk of cancer-specific death among individuals with endometrial cancer taking NA-NSAIDs. Further studies should explore the biological mechanisms behind the interaction between the use of

aspirin and NA-NSAIDs, the immune system and endometrial cancer development also including the association with molecular subgroups.

AUTHOR CONTRIBUTIONS

Ala Jabri Haug: Methodology; investigation; formal analysis; data curation; software; writing – original draft; writing – review and editing. **Nathalie Støer:** Methodology; conceptualization; software; data curation; investigation; validation; supervision; writing – original draft; writing – review and editing. **Hilde Langseth:** Conceptualization; methodology; writing – review and editing; project administration. **Franziska Siafarikas:** Writing – review and editing; supervision. **Edoardo Botteri:** Conceptualization; methodology; writing – review and editing; project administration. **Renée Turzanski Fortner:** Methodology; supervision; writing – original draft; writing – review and editing; conceptualization. **Kristina Lindemann:** Conceptualization; supervision; methodology; project administration; resources; writing – original draft; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data can be requested to the registry holders in Norway. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

The study was approved by the Regional Committee for Medical and Health research Ethics South East (S-09113b 2009/2062, 2009/594, 214/1854/REK sør-østB). Informed written consent is in Norway waived for studies using de-identified data through registries, as regulated by the Personal Health Data Filing System Act in Norway. The data was disclosed with legal basis in *the Cancer Registry Regulations section 3–1 and the Personal Health Data Filing System Act section 19 a to 19 h* and regulations on population-based health surveys 6–1.

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