Cancer Epidemiology, Biomarkers & Prevention

Use of Common Analgesics Is Not Associated with Ovarian Cancer Survival

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Abstract

Background: Use of analgesics has been associated with lower risk of ovarian cancer, but, to date, very few studies have explored the association between analgesics and ovarian cancer survival.

Methods: We examined the relationship between self-reported prediagnostic use of aspirin, ibuprofen, and acetaminophen and overall survival (OS), progression-free survival (PFS), ascites at the time of primary treatment, and persistence of disease after primary treatment among 699 women diagnosed with epithelial ovarian carcinoma. The associations between use of these medications and OS and PFS were estimated using Cox proportional hazards models. We utilized unconditional logistic regression models to estimate associations between medication use and presence of ascites and persistence of disease.

Results: Prediagnostic intake of aspirin, both low-dose and regular-dose, ibuprofen, and acetaminophen was not associated with any of the outcomes of interest.

Conclusions: Our results indicate a lack of association between prediagnostic intake of selected analgesics and OS, PFS, presence of ascites at the time of primary treatment, and persistence of disease after primary treatment.

Impact: Prediagnostic intake of analgesics may not be associated with ovarian cancer outcomes. *Cancer Epidemiol Biomarkers Prev; 24(8); 1291–4. ©2015 AACR.*

Introduction

Chronic inflammation is suspected to be one of the etiologic mechanisms of ovarian cancer initiation (1) and progression (2), with a majority of ovarian tumors overexpressing the proinflammatory mediator cyclooxygenase (COX)-2 (3). Analgesics, including nonsteroidal anti-inflammatory drugs (NSAID), may reduce inflammation by inhibiting the COX enzyme, which may subsequently interfere with synthesis of prostaglandins and tumor cells growth and proliferation (4). Therefore, analgesic intake could potentially reduce risk of ovarian cancer and improve survival after the diagnosis. An extensive body of research has shown that intake of analgesics, especially aspirin, is associated with a lower ovarian cancer risk (5, 6), but there has been little study regarding the relationship with ovarian cancer survival.

We examined the association of self-reported prediagnostic intake of aspirin, ibuprofen, and acetaminophen on ovarian cancer survival. We hypothesized that among ovarian cancer patients, prediagnostic intake of aspirin and ibuprofen would be associated with a lower risk of death, disease progression, presence of ascites, and persistent disease compared with nonusers. We also investigated associations with acetaminophen as a comparison drug.

Materials and Methods

The Hormones and Ovarian cancer PrEdiction (HOPE) study, a population-based case–control study, was conducted between February 2003 and November 2008 (7). Data on demographics, history of arthritis, diabetes, and intake of aspirin, nonaspirin NSAIDs, and acetaminophen were collected from study participants in an in-person interview. Data on disease characteristics and treatment were obtained from medical records that were collected until loss to follow-up, death, or end of follow-up on May 31, 2014. Vital status of the participants was determined from medical records abstraction or through National Death Index and Social Security Death Index search.

Out of the original sample of 902 patients, we excluded patients with nonepithelial ($n = 48$) or low malignant potential ($n = 81$) disease as well as those who did not receive surgery or chemotherapy ($n = 50$), who had missing treatment information ($n = 9$), and those who were lost to follow-up immediately following the interview ($n = 15$). We used the χ^2 or Student t test to compare characteristics of deceased and alive patients.

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Table 1. Characteristics of the HOPE study cases stratified by vital status after 5 years of follow-up[a]

Characteristic	Deceased, $n = 343$ (%)	Alive, $n = 338$ (%)	P^b
Age at diagnosis (years), mean (SD)	62.5 (11.6)	56.9 (11.8)	<0.001
Race			
White	328 (95.6)	325 (96.1)	0.73
Non-white	15 (4.4)	13 (3.9)	
Education			
High school or less	154 (44.9)	144 (42.6)	0.54
More than high school	189 (55.1)	194 (57.4)	
History of arthritis			
No	205 (59.8)	217 (64.2)	0.23
Yes	138 (40.2)	121 (35.8)	
History of diabetes			
No	304 (88.6)	317 (93.8)	0.02
Yes	39 (11.4)	21 (6.2)	
FIGO stage			
I	11 (3.2)	116 (34.3)	<0.001
II	22 (6.4)	60 (17.7)	
III	245 (71.4)	140 (41.4)	
IV	63 (18.4)	17 (5.0)	
Unknown	2 (0.6)	5 (1.5)	
Grade			
Well differentiated	6 (1.8)	40 (11.8)	<0.001
Moderately differentiated	68 (19.8)	95 (28.1)	
Poorly differentiated	255 (74.3)	184 (54.4)	
Unknown	14 (4.1)	19 (5.6)	
Histology			
Serous	253 (74.0)	176 (52.1)	<0.001
Mucinous	5 (1.5)	16 (4.7)	
Endometrioid	19 (5.5)	58 (17.2)	
Clear cell	15 (4.4)	33 (9.8)	
Mixed	49 (14.3)	54 (16.0)	
Other	2 (0.6)	1 (0.3)	
Presence of ascites			
No	76 (22.2)	165 (49.4)	<0.001
Yes	266 (77.8)	169 (50.6)	
Missing	1	4	
All gross disease removed during primary surgery			
No	231 (67.5)	96 (28.4)	<0.001
Yes	96 (28.1)	231 (68.3)	
Unknown	16 (4.4)	11 (3.3)	
Persistence of disease			
No	179 (54.1)	312 (92.6)	<0.001
Yes	152 (45.9)	25 (7.4)	
Missing	12	1	
Recurrence of disease			
No	141 (43.2)	198 (58.8)	<0.001
Yes	185 (56.8)	139 (41.2)	
Missing	17	1	

[a]Excluding 18 cases lost to follow-up within the first 5 years of follow-up.
[b]*P* value for the *t* test for age at diagnosis and χ^2 test for categorical variables.

Overall survival (OS) was defined as the number of days from the date of primary surgery to the date of death or date of last contact. Progression-free survival (PFS) was defined as the number of days between the date of diagnosis and the date when progression status (persistence, recurrence, or death) was determined.

Using the Cox proportional hazards model adjusted for age and Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage, we examined the association between ever use, type of use (recent or past), average frequency, and duration of use for regular strength aspirin (>81 mg, excluding those using low-dose aspirin), ibuprofen, and acetaminophen, and the OS and PFS after ovarian cancer diagnosis by calculating hazard ratios (HR) and 95% confidence intervals (CI) associated with survival. For low-dose aspirin, we examined ever use only due to small cell frequencies for the type and duration of use and no variation for average frequency of intake. Using unconditional logistic regression, we estimated odds ratios (OR) and 95% CIs using age-, stage-, and histology-adjusted models for the presence of ascites, and age- and stage-adjusted models for persistence of disease as the outcomes. Those who reported no regular intake of any NSAIDs or acetaminophen were referent category for these analyses. We also conducted our analyses separately among patients with serous and advanced tumors.

We had 80% power to detect risk estimates of 0.73, 0.68, and 0.68 for ever use of aspirin, ibuprofen, and acetaminophen

Table 2. Intake of aspirin, ibuprofen, and acetaminophen and OS, PFS, presence of ascites at the time of primary treatment, and persistence of disease after primary treatment among HOPE study cases[a]

	Deceased			Progression			Ascites			Persistence		
Variables	**Yes**	**No**	**HR (95% CI)[b]**	**Yes**	**No**	**HR (95% CI)[b]**	**Yes**	**No**	**OR (95% CI)[c]**	**Yes**	**No**	**OR (95% CI)[d]**
Aspirin												
Nonusers	190	130	1.00 (referent)	238	82	1.00 (referent)	207	111	1.00 (referent)	79	234	1.00 (referent)
Regular users	145	77	1.06 (0.84–1.35)	168	53	0.99 (0.80–1.22)	137	82	0.94 (0.63–1.41)	59	159	1.01 (0.65–1.55)
Type of users[e]												
Nonusers	190	130	1.00 (referent)	238	82	1.00 (referent)	207	111	1.00 (referent)	79	234	1.00 (referent)
Past	48	29	0.88 (0.64–1.21)	59	17	1.00 (0.75–1.34)	49	26	1.10 (0.61–1.99)	23	54	1.12 (0.62–2.04)
Recent	93	45	1.19 (0.92–1.55)	104	34	0.98 (0.77–1.25)	83	54	0.89 (0.56–1.42)	34	100	0.93 (0.56–1.54)
Duration												
Nonusers	190	130	1.00 (referent)	238	82	1.00 (referent)	207	111	1.00 (referent)	79	234	1.00 (referent)
0.5–5 y	62	41	0.94 (0.70–1.27)	71	31	0.92 (0.70–1.21)	63	39	1.01 (0.60–1.70)	31	71	1.33 (0.77–2.29)
≥5 y	83	36	1.19 (0.91–1.55)	97	22	1.06 (0.83–1.36)	74	43	0.94 (0.57–1.55)	28	88	0.79 (0.46–1.35)
P_{trend}			0.28			0.72			0.83			0.54
Aspirin: 81 mg												
Nonusers	190	130	1.00 (referent)	238	82	1.00 (referent)	207	111	1.00 (referent)	79	234	1.04 (referent)
Regular users	61	27	1.17 (0.86–1.60)	70	18	0.98 (0.74–1.31)	55	32	1.06 (0.60–1.87)	23	62	1.02 (0.56–1.86)
Aspirin: >81 mg												
Nonusers	190	130	1.00 (referent)	238	82	1.00 (referent)	207	111	1.00 (referent)	79	234	1.00 (referent)
Regular users	73	41	1.04 (0.79–1.36)	85	29	0.99 (0.77–1.27)	71	42	0.95 (0.57–1.58)	31	82	1.00 (0.59–1.69)
Tablets per week[f]												
Nonusers	190	130	1.00 (referent)	239	82	1.00 (referent)	207	111	1.00 (referent)	79	234	1.00 (referent)
≤7	40	25	1.12 (0.79–1.59)	46	19	0.89 (0.65–1.23)	40	24	1.09 (0.57–2.08)	12	52	0.59 (0.28–1.22)
>7	33	16	0.95 (0.66–1.38)	39	10	1.14 (0.81–1.60)	31	18	0.80 (0.39–1.61)	19	30	1.68 (0.85–3.32)
P_{trend}			0.99			0.73			0.66			0.40
Type of users[e]												
Nonusers	190	130	1.00 (referent)	238	82	1.00 (referent)	207	111	1.00 (referent)	79	234	1.00 (referent)
Past	39	18	0.83 (0.53–1.29)	46	11	1.03 (0.75–1.42)	35	21	0.85 (0.44–1.66)	20	37	1.27 (0.66–2.41)
Recent	33	22	1.05 (0.68–1.64)	38	17	0.97 (0.69–1.37)	35	20	1.08 (0.55–2.14)	11	43	0.76 (0.36–1.63)
Duration												
Nonusers	190	130	1.00 (referent)	238	82	1.00 (referent)	207	111	1.00 (referent)	79	234	1.00 (referent)
0.5–5 y	24	15	0.99 (0.65–1.52)	27	12	0.95 (0.64–1.41)	26	13	1.18 (0.54–2.61)	13	26	1.34 (0.61–2.92)
≥5 y	49	26	1.09 (0.79–1.49)	58	17	1.02 (0.77–1.38)	45	29	0.86 (0.47–1.56)	18	56	0.85 (0.45–1.60)
P_{trend}			0.67			0.91			0.71			0.76
Ibuprofen												
Nonusers	190	130	1.00 (referent)	238	82	1.00 (referent)	207	111	1.00 (referent)	79	234	1.00 (referent)
Regular users	69	68	0.97 (0.74–1.28)	84	53	0.86 (0.67–1.11)	81	55	0.98 (0.61–1.56)	28	108	0.99 (0.58–1.69)
Tablets per week[g]												
Nonusers	190	130	1.00 (referent)	238	82	1.00 (referent)	207	111	1.00 (referent)	79	234	1.00 (referent)
≤14	47	49	0.98 (0.71–1.35)	59	37	0.94 (0.70–1.25)	59	361	1.21 (0.70–2.08)	17	78	0.91 (0.48–1.72)
>14	22	19	0.97 (0.62–1.51)	25	16	0.72 (0.48–1.10)	22	19	0.62 (0.30–1.28)	11	30	1.15 (0.51–2.60)
P_{trend}			0.87			0.14			0.49			0.88
Type of users[e]												
Nonusers	190	130	1.00 (referent)	238	82	1.00 (referent)	207	111	1.00 (referent)	79	234	1.00 (referent)
Past	38	31	1.12 (0.79–1.59)	43	26	0.88 (0.64–1.22)	45	23	1.46 (0.78–2.73)	15	53	1.16 (0.58–2.32)
Recent	30	35	0.85 (0.58–1.25)	39	26	0.85 (0.61–1.20)	33	32	0.62 (0.34–1.13)	13	52	0.90 (0.44–1.85)
Duration												
Nonusers	190	130	1.00 (referent)	238	82	1.00 (referent)	207	111	1.00 (referent)	79	234	1.00 (referent)
0.5–5 y	28	33	1.01 (0.67–1.51)	35	26	0.96 (0.67–1.38)	37	24	1.22 (0.64–2.33)	13	48	1.29 (0.61–2.74)
≥5 y	40	35	0.94 (0.67–1.33)	48	27	0.81 (0.59–1.11)	44	30	0.87 (0.48–1.55)	15	59	0.84 (0.43–1.65)
P_{trend}			0.78			0.20			0.79			0.78
Acetaminophen												
Nonusers	190	130	1.00 (referent)	238	82	1.00 (referent)	207	111	1.00 (referent)	79	234	1.00 (referent)
Regular users	73	50	1.03 (0.78–1.35)	87	36	0.91 (0.71–1.17)	81	41	1.19 (0.71–1.98)	33	89	1.14 (0.68–1.90)
Tablets per week[h]												
Nonusers	190	130	1.00 (referent)	238	82	1.00 (referent)	207	111	1.00 (referent)	79	234	1.00 (referent)
≤9	35	26	0.97 (0.68–1.40)	44	17	0.96 (0.69–1.33)	45	16	1.89 (0.93–3.86)	18	43	1.31 (0.68–2.54)
>9	38	24	1.08 (0.76–1.54)	43	19	0.87 (0.63–1.21)	36	25	0.79 (0.42–1.51)	15	46	0.98 (0.49–1.94)
P_{trend}			0.71			0.40			0.93			0.83
Type of users[e]												
Nonusers	190	130	1.00 (referent)	238	82	1.00 (referent)	207	111	1.00 (referent)	79	234	1.00 (referent)
Past	34	17	1.32 (0.92–1.91)	38	13	1.06 (0.75–1.49)	36	15	1.47 (0.70–3.08)	14	36	1.24 (0.60–2.55)
Recent	36	30	0.86 (0.60–1.23)	44	22	0.78 (0.57–1.08)	43	22	1.15 (0.60–2.21)	17	49	1.01 (0.53–1.94)
Duration												
Nonusers	190	130	1.00 (referent)	238	82	1.00 (referent)	207	111	1.00 (referent)	79	234	1.00 (referent)
0.5–5 y	30	25	0.92 (0.63–1.36)	38	17	0.95 (0.67–1.34)	31	23	0.87 (0.44–1.72)	13	42	1.03 (0.50–2.13)
≥5 y	43	25	1.12 (0.80–1.56)	49	19	0.89 (0.65–1.21)	50	18	1.57 (0.80–3.04)	20	47	1.23 (0.65–2.30)
P_{trend}			0.62			0.43			0.28			0.55

[a]Those who reported no regular use of any medications were chosen as a referent category.
[b]Cox proportional hazards model adjusted for age and FIGO stage.
[c]Unconditional logistic regression model adjusted for age, FIGO stage, and histology.
[d]Unconditional logistic regression model adjusted for age and FIGO stage.
[e]Type of users: past users (stopped using medications at least 1 year before the reference date) and recent users (used medications for at least 1 year continuously through the reference date).
[f]Standardized as 325 mg.
[g]Standardized as 200 mg.
[h]Standardized as 500 mg.

correspondingly for OS, and 0.75, 0.71, and 0.71, respectively, for PFS.

Results

Characteristics of participants by 5-year survival status are shown in Table 1. By the end of the fifth year of follow-up, 343 patients were deceased. The median follow-up time was 1,759 days for OS and 540 days for PFS.

No statistically significant associations between use of these analgesics and any of the outcomes of interest were observed (Table 2). There was a weak suggestion of an inverse relationship for past intake of aspirin and ibuprofen; however, the estimated HR did not reach statistical significance. Results were not substantially changed when analyses were conducted separately among patients with serous and advanced tumors.

Discussion

In this study, we found no associations between ever use, frequency, type and duration of use of self-reported prediagnostic intake of analgesics, and OS or PFS in women with epithelial ovarian cancer. These results are consistent with findings of a recent Australian study where aspirin, nonaspirin NSAIDs, and acetaminophen use 5 years prior to diagnosis were not related to ovarian cancer survival (8).

Limitations of our study include reliance on self-reported prediagnostic analgesics intake; they do not provide information as to the impact on survival of postdiagnostic intake.

In conclusion, we found no evidence that prediagnostic intake of commonly used analgesics influences OS, PFS, presence of ascites at diagnosis, and persistence of disease after primary treatment.

Disclosure of Potential Conflicts of Interest

R.B. Ness has provided expert testimony for Beasley Allen Law Firm. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: K. Grzankowski, K.B. Moysich
Development of methodology: K.B. Moysich
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): B. Diergaarde, F. Modugno, K. Odunsi, R.B. Ness, K.B. Moysich
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