

Impact of Acetylsalicylic Acid on the Clinicopathological Characteristics and Prognosis of Patients with Invasive Breast Cancer

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Keywords

Aspirin · Acetylsalicylic acid · NSAIDs · Breast cancer

Summary

Background: The impact of acetylsalicylic acid (ASA) on the clinicopathological characteristics of breast cancer has not yet been elucidated in detail; we therefore aimed to investigate the effects of ASA on the clinicopathological characteristics of patients with breast cancer. **Patients and Methods:** Patients diagnosed with breast cancer were retrospectively analyzed. Breast cancer patients who were taking ASA at the time of breast cancer diagnosis were enrolled as ASA users (n = 84); matching patients with the same age who were not taking ASA were included as control group (n = 890). **Results:** The median age was 56 (range 34–82) years in both groups. ASA users had a significantly lower incidence of grade II–III tumors compared to non-users (P = 0.02). The other clinicopathological characteristics and treatment histories were similar in both groups. In patients using ASA, the disease-free survival (DFS) rate was 97.3%, 89.4%, and 79.9% and in non-users it was 94.1%, 81.8%, and 70.9% in the 1st, 3rd, and 5th year, respectively (P = 0.01). In aspirin users, the overall survival rate was 95.0%, 90.6%, and 87.6% and in non-users it was 98.1%, 91.2%, and 85.5% in the 1st, 3rd, and 5th year, respectively (P = 0.50). **Conclusion:** Using ASA at the time of breast cancer diagnosis was associated with significantly improved DFS in breast cancer patients.

Introduction

Breast cancer is the most common malignancy, expected to account for 29% of all new cancer cases among women [1]. Thus, risk reduction strategies and preventive approaches for breast cancer have been attractive for researchers in the recent years. The enzyme cyclooxygenase (COX) rapidly induces inflammation, growth factors, cytokines, and endotoxins, resulting in cell proliferation and carcinogenesis [2]. Prostaglandins also have deleterious effects on carcinogenesis by promoting cell proliferation and angiogenesis [3, 4].

Acetylsalicylic acid (ASA) can interfere with breast cancer carcinogenesis mainly by inhibiting the production of prostaglandins and by inhibiting both the COX-1 and COX-2 isoenzymes [5]. Blocking COX-1 and COX-2 may inhibit breast carcinogenesis via interfering with DNA adduct formation, inhibiting angiogenesis and aromatase expression, and via increased apoptosis [6–9]. Other important ASA-based inhibitory mechanisms of carcinogenesis are the up-regulation of tumor suppressor genes such as those coding for TP53 and Bax and the down-regulation of antiapoptotic genes such as the Bcl2 gene [10]. Also, ASA can induce cell apoptosis by altered gene transcription, cell cycle arrest, modulation of protein synthesis, and interference with signaling pathways via COX-independent effects [11–14]. Other probable chemopreventive mechanisms of ASA are the inhibition of tumor proliferation by inhibiting the mitochondrial calcium uptake and the reduction of DNA damage by decreasing oxidative stress [15, 16]. In vitro studies showed that ASA can repair the immune damage caused by radiation therapy for breast cancer [17]. In a mouse model study, treatment with COX inhibitors resulted in less tumor growth [18]. Holmes et al. [19] reported that COX-2 expression in a tumor was associated

with higher diagnostic stage and worse breast cancer prognosis in a study of 2,001 patients with invasive breast cancer. An *in vitro* study showed that the combination of ASA with exemestane compared to exemestane alone increased the response rate in breast cancer cells with high COX-1 and COX-2 expression [20].

Observational studies showed that using ASA for at least 5 years reduces the incidence and mortality of colorectal cancer [21–23]. With regular use of ASA, also the incidences of esophagus, gastric, biliary, lung, ovary, and prostate cancers were reduced [24–26]. In a recently published study, no association was found between the regular use of ASA and non-steroidal anti-inflammatory drugs (NSAIDs) and the risk of postmenopausal breast cancer [27]. In another recently published study, the large U.S. Cancer Prevention Study II

Nutrition Cohort study among 77,413 women, neither aspirin nor NSAIDs were associated with the incidence of breast cancer [28]. In a Canadian cohort study, it was shown that using ASA at > 100 mg/day may result in a lower risk of breast cancer whereas using ASA at ≤ 100 mg/day did not affect the incidence of breast cancer [29]. In the Women's Health Initiative (WHI) trial, using ASA on alternate days did not show any reduction in any cancer incidence [30]. In another prospective cohort study on 26,580 postmenopausal women, using ASA was associated with a 20% risk reduction of postmenopausal breast cancer incidence [31]. A recent meta-analysis of 19 cohort studies, 13 case-control studies, and 1 randomized control study showed that regular use of ASA may be associated with a lower breast cancer risk (relative risk (RR) = 0.86).

Table 1. Baseline characteristics by ASA use

Characteristic	ASA use				P value
	Yes (n = 84)		No (n = 890)		
	n	%	n	%	
Age					
≤ 50 years	24	28.6	305	34.3	0.33
> 50 years	60	71.4	585	65.7	
Body mass index					
< 25.0 kg/m ²	14	18.2	187	23.7	0.54
25.0–29.9 kg/m ²	32	41.5	309	39.2	
≥ 30 kg/m ²	31	40.3	292	37.1	
Smoking					
No	70	83.3	713	80.1	0.48
Yes	14	16.7	177	19.9	
Parity					
Nulliparous	4	4.8	19	2.1	0.38
Parous	80	95.2	871	97.9	
Menopausal status					
Premenopausal	17	20.2	217	24.6	0.33
Perimenopausal	3	3.6	57	6.5	
Postmenopausal	64	76.2	608	69.9	
Family history of breast cancer					
No	81	96.4	863	97.0	0.86
Yes	3	3.6	27	3.0	
Diabetes mellitus					
No	62	73.8	731	82.1	0.07
Yes	22	26.2	159	17.9	
Hypertension					
No	32	38.1	481	54.0	0.006
Yes	52	61.9	409	46.0	
Hyperlipidemia					
No	67	79.8	818	91.9	0.001
Yes	17	20.2	72	8.1	
Hormone replacement therapy					
No	71	84.5	738	85.3	0.87
Yes	13	15.5	127	14.7	
Oral contraceptive use					
Never	70	83.3	681	79.0	0.60
0–12 months	9	10.7	106	12.3	
> 12 months	5	6.0	75	8.7	

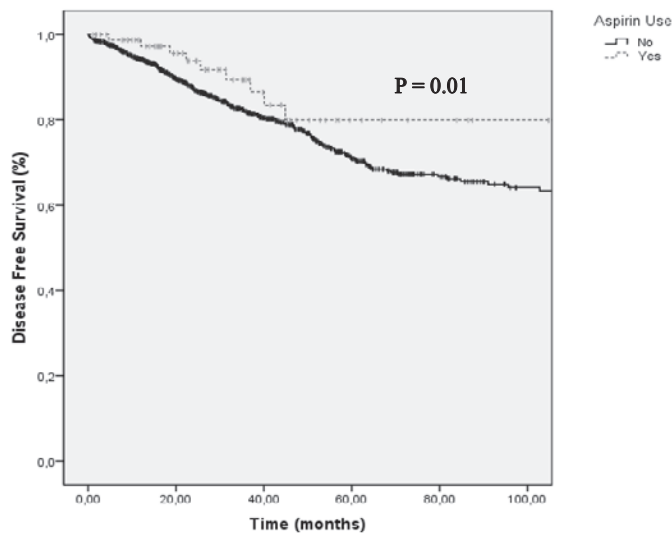


Fig. 1. Analysis of the DFS of ASA users and non-users.

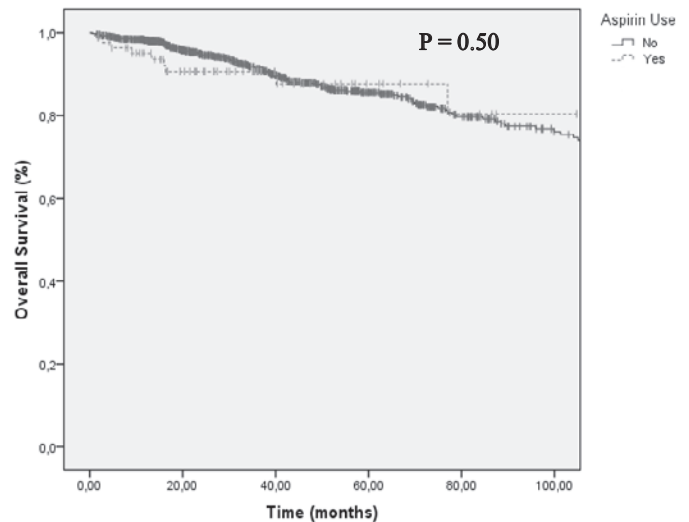


Fig. 2. Analysis of the OS of ASA users and non-users.

As a result of the published studies and meta-analyses, there were contradictory results regarding the impact of using ASA on the breast cancer risk. But the effects of ASA use on the clinicopathological properties of breast cancer have not yet been elucidated in detail. In this retrospective study, we aimed to investigate the impact of ASA on the demographic and clinicopathological characteristics of breast cancer patients at the time of diagnosis.

Patients and Methods

Breast cancer patients diagnosed between 2001 and 2013 in our clinic were analyzed retrospectively. A total of 3,000 patients with breast cancer were admitted to our clinic. Breast cancer patients who were taking ASA at the time of breast cancer diagnosis were enrolled as ASA users ($n = 84$), whereas matching patients with the same age who did not use ASA were included as control group ($n = 890$). Demographic and clinicopathological properties including age, menopausal status, weight, height, breast cancer treatment history, hormonal treatment history, and comorbidities were collected from the medical charts. Tumors were graded according to the modified Bloom-Richardson scoring system and staged according to the tumor-node-metastasis (TNM) criteria. The data on estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2)/neu expression were obtained through standard clinical testing, using immunohistochemistry (IHC) for ER and PR and the HercepTest™ (Dako) for HER2/neu. For the ER and PR, receptor positivity was based on more than 1% of cells testing positive. Patients were categorized as triple negative if they were negative for ER, PR, and HER2/neu.

Statistical Analysis

Statistical analyses were performed by using SPSS for Windows version 18.0 (SPSS, Chicago, IL, USA). The baseline characteristics of ASA users were compared with those of non-users by χ^2 tests (for categorical variables) or with 2-sample t-tests (for continuous variables). Tumors with missing values were omitted from the analyses. Kaplan-Meier sur-

vival analysis was carried out for disease-free survival (DFS) and overall survival (OS). The log-rank test was used to examine the statistical significance of the differences observed between the groups. 2-sided P values of < 0.05 were considered as statistically significant.

Results

A total of 974 patients were included to this study. The median age of both the ASA users and non-users was 56 (range 34–82) years. Breast cancer patients who were taking ASA for more than 1 year at the time of breast cancer diagnosis were enrolled as ASA users ($n = 84$); matching patients with the same age who had no history of using ASA were included as control group ($n = 890$). The baseline demographic characteristics of the participants are described in table 1. The frequency of hypertension was found to be significantly higher in the ASA users compared to the non-users (61.9% vs. 46.0%; $P = 0.006$). Also hyperlipidemia was found significantly more often in the ASA users compared to the non-users (20.2% vs. 8.1%; $P = 0.001$). Diabetes mellitus occurred non-significantly more often in the ASA users (26.2%) compared to the non-users (17.9%; $P = 0.07$). There were no apparent differences in the other baseline demographic characteristics between ASA users and non-users. The median follow-up of this study was 27.4 months.

The baseline tumor characteristics of the participants are described in table 2. In both groups, the histology of the primary tumor and the type of surgery were similar. Also, in both arms, the rates of lymphovascular invasion, perineural invasion, and extracapsular extension were similar. ASA users had a significantly lower incidence of histological grade II–III tumors compared to non-users ($P = 0.02$). There were no apparent differences in the baseline tumor size ($P = 0.91$), lymph node positivity ($P = 0.18$), and tumor stage ($P = 0.40$)

Table 2. Baseline tumor characteristics by ASA use

Characteristics	ASA use				
	Yes (n = 84)		No (n = 890)		P value
	n	%	n	%	
Type of surgery					
None	0	0	10	1.2	0.45
Breast-conserving surgery	20	25.0	244	28.8	
Modified radical mastectomy	60	75.0	592	70.0	
Histology of the primary tumor					
Invasive ductal carcinoma	58	70.7	611	69.5	0.27
Invasive lobular carcinoma	8	9.8	55	6.3	
Mixed	7	8.5	119	13.5	
Others	9	11.0	94	10.7	
ER					
Positive	63	75.0	640	73.2	0.61
Negative	21	25.0	250	26.8	
PR					
Positive	61	72.6	593	66.6	0.27
Negative	23	27.4	297	33.4	
HER2					
Positive	14	16.7	144	16.2	0.74
Negative	70	83.3	746	83.8	
Triple negative					
Yes	8	8.5	112	12.6	0.70
No	76	91.5	778	87.4	
Grade					
I	19	25.0	100	13.4	0.02
II	31	40.8	364	48.6	
III	26	34.2	285	38.1	
Lymphovascular invasion					
Positive	20	23.8	211	23.7	0.98
Negative	64	76.2	679	76.3	
Perineural invasion					
Positive	15	17.9	107	12.0	0.12
Negative	69	82.1	783	88.0	
Extracapsular extension					
Positive	6	7.1	91	10.2	0.44
Negative	78	92.9	759	89.8	
T stage at diagnosis					
T1	25	31.2	298	34.9	0.91
T2	43	53.8	415	48.5	
T3	9	11.3	112	13.1	
T4	3	3.7	30	3.5	
Lymph node status					
N0	39	46.4	438	49.3	0.18
N1	23	27.4	242	27.2	
N2	15	17.9	101	11.3	
N3	7	8.3	109	12.2	
TNM stage					
I	15	19.0	208	24.0	0.40
II	37	46.8	362	41.7	
III	23	29.1	211	24.3	
IV	4	5.1	87	10.0	
Adjuvant chemotherapy					
Yes	50	59.5	584	65.6	0.37
No	34	40.5	306	34.4	
Adjuvant radiotherapy					
Yes	53	63.1	549	61.7	0.98
No	31	36.9	341	38.3	
Adjuvant hormonal treatment					
Yes	70	83.3	665	74.7	0.21
No	14	16.7	225	25.3	

between the 2 groups. ER positivity was observed in 75.0% and 73.2% of the ASA users and non-users, respectively ($P = 0.61$). Regarding the PR status, 72.6% and 66.6% positivity were observed in the ASA users and non-users, respectively ($P = 0.27$). In the subgroup analysis, 65.0% and 62.5% of the patients had both ER and PR positivity in case of ASA users and non-users, respectively ($P = 0.28$). Only ER positivity was found in 3.6% of the ASA users whereas it was found in 8.5% of the non-users ($P = 0.14$). Only PR positivity was found at similar frequencies in the 2 groups (3.1% vs. 5.3%; $P = 0.76$). HER2 positivity ($P = 0.74$) and the incidence of triple-negative tumors ($P = 0.70$) were similar in both groups. The treatment histories with adjuvant chemotherapy and radiotherapy were also similar and not significantly different between the ASA users and the non-users. In both groups, adjuvant chemotherapy and radiotherapy were used similarly. Hormonal treatment was used in 83.3% and 74.7% of the ASA users and non-users, respectively ($P = 0.21$).

In the ASA users, the DFS rates were 97.3%, 89.4%, and 79.9%, whereas they were 94.1%, 81.8%, and 70.9% in the non-users in the 1st, 3rd, and 5th year, respectively ($P = 0.01$) (fig. 1). In the subgroup analysis, no effects of hypertension ($P = 0.54$), hyperlipidemia ($P = 0.14$), or diabetes mellitus ($P = 0.69$) were found on the risk of recurrence. The median OS could not be obtained due to the low number of events and the short follow-up period. The OS rates of the ASA users and non-users were 95.0%, 90.6%, and 87.6% and 98.1%, 91.2%, and 85.5% the 1st, 3rd, and 5th year, respectively ($P = 0.50$) (fig. 2).

Discussion

In this study, we showed that using ASA at the time of breast cancer diagnosis corresponded with a significantly lower incidence of histological grade II–III tumors compared to non-users. Other clinical and pathological features were similar between ASA users and non-users. Hormone receptor positivity was also similar in both groups. The DFS rate was significantly better in ASA users compared to non-users, but the difference in the OS rate was not statistically significant. Despite the higher rate of hypertension, hyperlipidemia, and diabetes mellitus seen in ASA users, no effect on the DFS was found in the subgroup analysis of these comorbidities.

Evidence from published studies showed that regular use of ASA for at least 5 years is associated with a risk reduction of colorectal cancer by 20–30% [32]. For other gastrointestinal system cancers, the risk reduction was reported as approximately 30% by regular ASA use, whereas the risk reduction was modest in both breast and prostate cancer [32]. Due to the heterogeneity of the case-control and cohort studies in breast cancer, no association was found between the dose and duration of ASA use. Thus, the absolute duration and the optimal dose of ASA for the prevention of breast cancer are still not known.

Both preclinical and epidemiologic data support the notion that ASA has anticancer activity in the case of breast cancer. Preclinical studies showed that adding ASA to aromatase inhibitors can increase the response rate compared to single-agent aromatase inhibitors in breast cancer cells with high COX-1 and COX-2 expression [20]. Treatment of wild-type mice with a selective COX-2 inhibitor showed a reduction of tumor growth and additionally a reduction of vascular endothelial growth factor (VEGF) production by 92% [18]. Hudson et al. [33] reported significantly lower levels of serum estradiol in postmenopausal breast cancer patients who used ASA and NSAIDs compared to non-users. In our study, we found that the DFS rate was significantly improved with using ASA, but the OS rate was not significantly improved. Consistent with the results of our study, Rothwell et al. [34], in an observational study of randomized controlled trials, reported that daily use of ASA reduced the risk of all distant metastases of all cancer types. Compared to our study, the Nurses' Health Study with 4,164 participants showed that using ASA after breast cancer diagnosis was associated with decreased rates of death and distant recurrence of breast cancer [35]. Previous studies also demonstrated a decreased risk of recurrence of early breast cancer with using NSAIDs other than ASA [36]. In another study, Li et al. [37] reported that using pre-diagnostic ASA or NSAIDs was not associated with survival following breast cancer diagnosis like in our study.

There is limited data about the association of COX-2 expression with ER, PR, and HER2 expression. Thus, using ASA seems to have an effect on the risk of both ER-positive and -negative tumors. Zhang et al. [27] reported that ASA had no role in breast cancer molecular subtypes. In the subgroup analyses of the Women's Health Study (WHS), no effect of ASA was found on the tumor size, lymph node metastasis, histology, the hormonal status, and the grading [38]. In another study, the use of ASA was associated with a reduced risk of breast cancer, with no effects on molecular subtypes [39]. In comparison to previous studies, ASA users in our study had a significantly lower incidence of histological grade II–III tumors, but no other effect on the pathological properties was found.

Our study has some limitations due to the retrospective design. In our study, there is no data about the definite time of the beginning of ASA use and the exact dosage of ASA. And there is no data on whether the patients continued to use ASA after breast cancer diagnosis. It is not possible to estimate the dose-response effect or the duration of ASA use in our breast cancer patients. The information on the ASA usage was self-reported. Also, in our study, we do not have data on whether or not the patients used additional NSAIDs for chronic pain. Thus, we do not know whether NSAIDs had an additive effect. In our study, we observed a DFS advantage by using ASA, but this advantage was not observed for OS. This controversy can be explained by significantly higher comorbidities in the group of ASA users. Another limitation of our

study is that ASA users may be more likely to use mammography screening programs than non-users. Recent studies show that both angiotensin and beta-blockage may have an important role in breast cancer carcinogenesis [40, 41]. Thus, the unspecified usage of angiotensin-converting enzyme inhibitors and beta-blockers may have had additive effects to those of ASA usage.

In conclusion, despite the contradictory results regarding ASA use and breast cancer incidence, using ASA at the time of breast cancer diagnosis was associated with an improved

DFS in our study. ASA users have a significantly lower incidence of histological grade II–III tumors, but no effect was found on other clinicopathological properties. This retrospective study requires further prospective confirmative cohort studies.

Disclosure Statement

The authors declare no potential conflicts of interest.

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