Regular Aspirin Use and Risk of Multiple Myeloma: A Prospective Analysis in the Health Professionals Follow-up Study and Nurses’ Health Study

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Abstract
Multiple myeloma is a lethal malignancy with an unknown etiology and no prevention strategy. Aspirin inhibits several pathways mediated by NF-κB, COX-2, or their targets that are important in multiple myeloma pathogenesis. We conducted prospective analyses in the Health Professionals Follow-up Study and Nurses’ Health Study cohorts to examine whether regular aspirin use influences multiple myeloma risk. We used biennially updated data to characterize aspirin use from baseline through a cancer diagnosis, death, or 2008. We applied a 4-year lag in exposure classification to diminish the influence of preclinical multiple myeloma on aspirin use habits. We obtained HRs and 95% confidence intervals (CI) from multivariable proportional hazard models to assess the association of aspirin use with multiple myeloma risk. We tested for trend across increasing quantity and duration of use. During 2,395,458 person-years, we confirmed 328 incident multiple myeloma diagnoses, including 265 with prospective information on typical aspirin dose and frequency. Participants with a cumulative average of ≥5 adult strength (325 mg) tablets per week had a 39% lower multiple myeloma risk than nonusers (HR; 95% CI, 0.61, 0.39–0.94; tablets per week, \( P_{\text{trend}} = 0.06 \)). Persons with ≥11 years of continuous regular aspirin use also had a lower multiple myeloma risk (HR; 95% CI, 0.63, 0.41–0.95; duration, \( P_{\text{trend}} = 0.17 \)). The associations appeared stronger in men than in women, possibly reflecting gender differences in aspirin use patterns. This prospective study of aspirin use and multiple myeloma supports an etiologic role for aspirin-inhibited (i.e., NF-κB- or COX-2 mediated) pathways. The utility of aspirin for multiple myeloma chemoprevention warrants further evaluation. Cancer Prev Res; 7(1): 33–41. ©2013 AACR.

Introduction
Multiple myeloma is a B-cell neoplasm that is expected to account for 22,350 new cancer diagnoses and 10,710 cancer deaths in the United States (U.S.) in 2013 (1). A premalignant condition called monoclonal gammopathy of undetermined significance (MGUS) precedes the development of all diagnoses of multiple myeloma (2, 3), but little is known about the etiology of MGUS or multiple myeloma, or about predictors of progression to malignancy in patients with MGUS (4). Multiple myeloma incidence rises sharply in older adulthood and is higher in men, African Americans, persons with a family history of hematologic malignancy, farmers, people with pesticide and solvent exposure, and persons with a higher body mass index (BMI; refs. 5, 6). Although multiple myeloma survival has improved recently with the development of more effective therapies (7), 5-year relative survival is still lower than 45% for patients diagnosed between 2003 and 2009 (5), and current knowledge of multiple myeloma etiology remains inadequate to develop prevention strategies.

In contrast, advances in knowledge of multiple myeloma pathogenesis have identified numerous signaling pathways with important roles, several of which are inhibited by aspirin. Of particular interest, aspirin suppresses NF-κB, a family of transcription factors that mediate normal B-cell development and are upregulated in multiple myeloma cell lines (8, 9). Aspirin can also inhibit COX-2, which metabolizes arachidonic acid to numerous proinflammatory and potentially tumorigenic molecules (10). COX-2 is highly expressed in multiple myeloma cells, predicts poor outcome in patients with multiple myeloma (11), and is a molecular target of NF-κB. Aspirin may also suppress other targets of NF-κB or COX-2 involved in multiple myeloma pathogenesis, including interleukin (IL)-6, a pleiotropic proinflammatory cytokine and an important growth factor for multiple myeloma (12), and cyclin D1, which influences normal
and malignant cell proliferation and is dysregulated in multiple myeloma (13, 14).

Regular aspirin users may have a reduced risk of Hodgkin lymphoma (15, 16), non-Hodgkin lymphoma (NHL; refs. 17, 18), and several solid tumors (19), as well as a reduced risk of mortality from hematologic malignancies with 5 or more years of regular use (20). An etiologic association of aspirin use with multiple myeloma is also plausible and has been examined to date in four studies: one hospital-based (117 cases, 483 matched controls; ref. 21) and one population-based case–control study (179 cases, 691 frequency-matched controls; ref. 22), and two prospective studies: the Vitamins and Lifestyle (VITAL) cohort (6–8 years follow-up, 66 cases of plasma cell disorders, cohort \( N = 64,839; \) ref. 23) and the American Cancer Society Cancer Prevention Study (CPS)-II Nutrition cohort (15 years follow-up, 310 cases, cohort \( N = 184,188; \) ref. 24). Neither case–control study reported an association of aspirin use with multiple myeloma; duration of regular use was not associated with multiple myeloma risk in the hospital-based study (21) and was not reported in the population-based study (22). The VITAL study reported a significant inverse association of regular use of 81 mg aspirin with risk of plasma cell disorders (\( P_{\text{trend}} = 0.02 \)), but no association of plasma cell disorder risk with use of regular strength aspirin (23). In the CPS-II study, neither quantity nor duration of aspirin use was associated with multiple myeloma (24). We undertook the present prospective study in the Nurses’ Health Study (NHS) and Health Professionals Follow-up Study (HPFS) cohorts to further examine the association of regular aspirin use with risk of multiple myeloma, taking advantage of biennially updated, detailed information on aspirin use and relevant covariates.

Materials and Methods

Study population

The HPFS began in 1986 when 51,529 male U.S. health professionals ages 40 to 75 years completed the enrollment questionnaire. The NHS began in 1976 when 121,701 female U.S. registered nurses ages 30 to 55 years returned the initial questionnaire (25). The design and methods of the two cohorts are similar. Biennial follow-up questionnaires update cohort members’ information on lifestyle and disease history. The study was approved by the Human Subjects Research Committees at the Harvard School of Public Health and Brigham and Women’s Hospital (Boston, MA) and was performed in accord with an assurance filed with and approved by the U.S. Department of Health and Human Services. Informed consent was implied by participants’ completion and return of the enrollment questionnaire.

Baseline populations were defined according to the year of first query of the relevant aspirin use details (Fig. 1). To diminish the potential influence of preclinical multiple myeloma on aspirin use habits, we applied a 4-year (two follow-up cycle) lag when classifying aspirin use. For example, person-time and cases occurring from 1990–1992 were classified according to aspirin use reported in 1986, those observed from 1992–1994 were classified by aspirin use status as of 1988, etc. We excluded participants who were deceased, had a history of cancer other than nonmelanoma skin cancer, or had missing exposure data at baseline (Fig. 1). Specifically, for the analysis of duration of aspirin use in HPFS (baseline year = 1990 as explained below), we excluded 3,265 men with a baseline history of cancer, 1,075 who were deceased, 149 men with a missing year of birth, and 11 with an unknown date of death. For the analysis of quantity of aspirin use in HPFS (baseline = 1996), we excluded 4,984 men with a history of cancer, 4,099 who were deceased, 6,632 with missing baseline questionnaires, and 4,815 with missing data on aspirin quantity in addition to the aforementioned 160 men with missing dates of birth or death. For both types of analysis in NHS (baseline year = 1984), we excluded 5,369 women with a baseline history of cancer, 1,873 who were deceased, 21,787 with missing baseline questionnaires, 6,606 with missing data on aspirin use, and 124 with missing year of birth. Thus, the baseline population comprised 30,839 and 47,029 men for analyses of quantity and duration of regular aspirin use, respectively, and 85,942 women for both analyses.

Assessment of regular aspirin use

The timing and nature of the aspirin use questions have been described previously in detail (26, 27), and the questionnaires are publicly available (28, 29). Men were asked about regular aspirin use from 1986 onward but were not queried about dose (81 mg “baby” vs. 325 mg “adult” strength) or frequency until 1992. Women were asked detailed aspirin use questions from 1980 onward, except in 1986. In 1994, 1996, and 1998, participants in both cohorts converted baby aspirin intake to adult strength equivalents (four baby tablets = one adult strength tablet). To identify the primary indications for aspirin use by cohort members, we conducted surveys among randomly selected self-reported regular aspirin users (Table 1; refs. 27, 30).

Covariates

Adult height and current weight were self-reported at enrollment in both cohorts; current weight was updated biennially. Validation studies in these cohorts showed high correlations of the self-reported data with measured height and weight (31). We computed current BMI (current weight divided by adult height squared, or kg/m\(^2\)) and age at the start of each follow-up interval. We characterized cohort members as regular users of acetaminophen (no/yes/missing) and ibuprofen (no/yes/missing) if they reported use at least twice per week. In the HPFS, separate questions on the use of these other analgesics were included in the enrollment questionnaire and biennially thereafter. In the NHS, a question on the regular use of other nonsteroidal analgesics was asked in 1980; the separate classification of acetaminophen and ibuprofen use was possible from 1990 onward.

Identification of cases

We identified most new diagnoses of cancer through the biennial questionnaires. Deaths were identified using the
National Death Index, which is highly sensitive and specific in these cohorts (32, 33). For each potential case of multiple myeloma, we sought permission to obtain the medical records, which we reviewed to confirm the diagnosis according to criteria specified by the International Myeloma Working Group (34) and the diagnosis date. The present analysis included all confirmed incident diagnoses of multiple myeloma that occurred during follow-up through the mailing date of the 2008 follow-up questionnaires (January for men and June for women).

**Statistical analysis**

Accrual of person-time began in 1996 (aspirin quantity analysis) or 1990 (duration of use analysis) for men and in 1984 for women (both analyses) due to the 4-year lag (Fig. 1). We followed participants through the earliest of three dates: diagnosis of cancer other than nonmelanoma skin cancer, death, or January (HPFS) or July (NHS) 2008.

![Figure 1. Definition of the baseline populations for studies of quantity and duration of regular aspirin use among HPFS and NHS cohort members.](image-url)
We computed HRs and 95% confidence intervals (CI) using Cox proportional hazard regression to estimate the relative risk of multiple myeloma associated with regular aspirin use quantity (nonuse, <2, 2–<5, ≥5 tablets/week) and duration (nonuse, <5, 6–10, ≥11 years). We analyzed pooled data from both cohorts and conducted gender-(cohort)-specific analyses. All statistical models were stratified by age (months) and adjusted for BMI (kg/m²) to control for potential confounding. Analyses performed in the combined dataset also adjusted for gender (cohort). To obtain a \( P \) trend, we entered ordinal variables created from the medians of the quantity and duration variable categories into additional multivariable Cox models.

To assess potential confounding by concurrent use of other analgesics, we performed additional analyses in which the age-stratified, BMI-adjusted Cox models were further adjusted for regular use of acetaminophen and/or ibuprofen. In women, those analyses were restricted to the follow-up intervals in which acetaminophen and ibuprofen use could be classified separately, i.e., 1994–2008 after incorporating the exposure lag, the prevalence of regular use of acetaminophen (42.7%) and ibuprofen (36.5%) was lower than that of aspirin (46.5%); use of both aspirin and another analgesic was infrequent (aspirin and acetaminophen, 15%; aspirin and ibuprofen, 14%).

We observed 328 incident diagnoses of multiple myeloma (132 male, 196 female) during 2,395,458 person-years of observation (Table 3). Of those, 265 cases (72 male, 193 female) that occurred over 1,997,506 person-years could be classified with regard to regular aspirin quantity. The sex-specific age-incidence rates for multiple myeloma in the analyzed HPFS and NHS populations were not significantly different from expected; the SIR (95% CI) was 0.90 (0.71–1.14) in men in the aspirin quantity analysis (1996 baseline). All \( P \) values were two-tailed.

### Results

At baseline for the aspirin quantity analysis, regular aspirin use was generally more common in men, although regular use of five or more 325 mg tablets per week was reported more frequently in women than in men (Table 2). Mean age and BMI did not vary notably by baseline aspirin use status among men or women. In men, the use of other analgesics was rare at baseline; fewer than 5% (1,468) reported use of acetaminophen at least twice per week, and fewer than 10% (2,905) reported regular use of ibuprofen. In women in 1994—the earliest follow-up cycle for which the two other analgesics could be classified separately after incorporating the exposure lag—the prevalence of regular use of acetaminophen (42.7%) and ibuprofen (36.5%) was lower than that of aspirin (46.5%); use of both aspirin and another analgesic was infrequent (aspirin and acetaminophen, 15%; aspirin and ibuprofen, 14%).

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### Table 1. Primary indications for regular aspirin use among randomly selected subsets of self-reported aspirin users in the HPFS and NHS cohorts

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Quantity not specified</th>
<th>1–6 tablets/wk</th>
<th>7+ tablets/wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPFS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N surveyed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin use indication (%)(^c)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment/management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain(^d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache and musculoskeletal pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| NHS   |                        |                |              |
| N surveyed |                        |                |              |
| Aspirin use indication (%)\(^c\) |                |                |              |
| Cardiovascular disease |                |                |              |
| Treatment/management |                |                |              |
| Prevention |                |                |              |
| Musculoskeletal pain\(^d\) |                |                |              |
| Headache |                |                |              |
| Headache and musculoskeletal pain |                |                |              |
| Other |                |                |              |

Abbreviation: NR, not reported.

\(^a\)The HPFS survey was conducted among randomly selected men who reported regular use of aspirin on surveys from 1986–1990 and was first reported in ref. (27).

\(^b\)The NHS survey was conducted among randomly selected women who reported the indicated level of regular aspirin use on surveys from 1980–1984 and was first reported in ref. (30).

\(^c\)Men were allowed to report more than one indication; women selected only one.

\(^d\)The musculoskeletal pain category included arthritis on the NHS survey.
In analyses performed in the combined HPFS and NHS population, we observed a 39% lower multiple myeloma risk in persons who used an average of five or more adult strength tablets per week compared with individuals who did not use aspirin regularly (HR = 0.61; 95% CI, 0.39–0.94; P_trend = 0.06). Weekly use of fewer than five tablets did not seem to predict multiple myeloma risk (Table 3). An inverse association was also suggested for quantity of aspirin use among men. Compared with male nonusers, multiple myeloma risk was 72% lower in men who used a cumulative average of five or more tablets per week, based on three exposed cases (HR = 0.28; 95% CI, 0.08–0.95; P_trend = 0.11). A significant association of regular aspirin quantity with multiple myeloma was not apparent in women, although those who reported regular use of five or more tablets per week had a nonsignificant 29% reduction in multiple myeloma risk (Table 3). An inverse association with multiple myeloma was apparent for duration of continuous regular aspirin use, but the P_trend was statistically.

### Table 2. Selected characteristics at baseline^a^ in men and women by regular quantity of aspirin use

<table>
<thead>
<tr>
<th>Adult strength tablets/wk</th>
<th>Men (HPFS; N = 30,839)</th>
<th>Women (NHS; N = 85,942)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonuser</td>
<td>&lt;2</td>
</tr>
<tr>
<td>N (%)</td>
<td>10,111 (32.8)</td>
<td>13,594 (44.1)</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>62.1</td>
<td>62.4</td>
</tr>
<tr>
<td>Mean BMI, kg/m^2^</td>
<td>25.1</td>
<td>25.5</td>
</tr>
</tbody>
</table>

^a^Because of the use of a 4-year lag, baseline for the analysis of cumulative average tablets per week of aspirin use is defined as 1996 in men and 1984 in women.

^b^Calculated by converting reported usual dose and weekly quantity of tablets to 325 mg equivalents per week.

^c^Standardized to the baseline age distribution of the specified cohort.

### Table 3. HRs and 95% CIs for risk of multiple myeloma according to quantity and duration of regular aspirin use in men and women

<table>
<thead>
<tr>
<th>Aspirin use</th>
<th>Men (HPFS)</th>
<th>Women (NHS)</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Person-years</td>
<td>HR (95% CI)^a^</td>
</tr>
<tr>
<td>Cumulative average 325 mg tablets/wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>132</td>
<td>666,264</td>
<td>—</td>
</tr>
<tr>
<td>Nonusers</td>
<td>52</td>
<td>256,203</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>&lt;2</td>
<td>55</td>
<td>269,879</td>
<td>0.77 (0.53–1.14)</td>
</tr>
<tr>
<td>2–5</td>
<td>19</td>
<td>99,134</td>
<td>0.65 (0.38–1.10)</td>
</tr>
<tr>
<td>≥5</td>
<td>6</td>
<td>39,047</td>
<td>0.42 (0.18–0.98)</td>
</tr>
<tr>
<td>Continuous duration of regular use, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>132</td>
<td>666,264</td>
<td>—</td>
</tr>
<tr>
<td>Nonusers</td>
<td>52</td>
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<td>≥11</td>
<td>6</td>
<td>39,047</td>
<td>0.42 (0.18–0.98)</td>
</tr>
<tr>
<td>P_trend</td>
<td>—</td>
<td>—</td>
<td>P_trend = 0.02^c^</td>
</tr>
</tbody>
</table>

^a^HRs and 95% CIs were computed in Cox proportional hazard models that stratified on age in months and adjusted for current BMI in kg/m^2^.

^b^Cohort-combined Cox proportional hazard models were stratified on age in months and controlled for BMI (kg/m^2^) and cohort (gender).

^c^For the trend tests, cumulative average tablets per week or continuous duration of regular aspirin use was modeled as an ordinal variable using the midpoint of each category of the respective variable in Cox proportional hazard models stratified by age in months and adjusted for the covariables indicated.
significant only among men (Table 3); the suggested benefit in men was most notable in those with 11 or more continuous years of regular aspirin use (HR = 0.42; 95% CI, 0.18–0.98; \( P_{\text{trend}} = 0.02 \)).

Adjustment for regular use of acetaminophen and ibuprofen (individually or simultaneously) did not change the BMI-adjusted associations of aspirin use with multiple myeloma risk in men or women. In men who used a cumulative average of fewer than two, two to fewer than five, or five or more adult strength aspirin tablets per week, compared with nonusers, with simultaneous adjustment for BMI, acetaminophen and ibuprofen use, the HRs (95% CIs) for multiple myeloma risk were 0.79 (0.44–1.42), 0.87 (0.46–1.64), and 0.27 (0.08–0.94), respectively (\( P_{\text{trend}} = 0.10 \)). In those multivariable models, the corresponding HRs (95% CIs) for multiple myeloma risk with regular use of acetaminophen and ibuprofen compared with nonusers were 1.12 (0.48–2.63) and 1.03 (0.53–1.99), respectively, based on six and 11 exposed cases, respectively. In women, the BMI-adjusted, other analgesic use-unadjusted findings for cumulative average tablets per week of aspirin and multiple myeloma risk were very similar when examined in the restricted follow-up interval to those reported in Table 3 for the complete follow-up period. In the interval from 1994–2008, the HRs (95% CI) in women who reported a cumulative average of fewer than two, two to fewer than five, or five or more tablets per week of aspirin compared with nonusers were 1.11 (0.63–1.95), 1.22 (0.68–2.20), and 0.71 (0.36–1.39), respectively (\( P_{\text{trend}} = 0.24 \)), with stratification by age and control for BMI. With further adjustment for acetaminophen and ibuprofen use, the findings were virtually unchanged (vs. nonuse; HR = 1.09; 95% CI, 0.62–1.92 for <2 tablets/week; 2–<5 tablets/week = 1.19; 0.66–2.14; ≥5 tablets/week = 0.69; 0.35–1.35; \( P_{\text{trend}} = 0.20 \)). In those mutually adjusted models, the HR (95% CI) for regular use of acetaminophen and ibuprofen and multiple myeloma risk compared with nonuse were 0.68 (0.45–1.03) and 1.33 (0.92–1.92), respectively, based on 35 and 47 exposed cases, respectively. We had insufficient statistical power to examine their associations with multiple myeloma in greater detail.

We evaluated whether the association of regular aspirin use with multiple myeloma varied by category of BMI (<25 kg/m², ≥25 kg/m²) and did not observe evidence of heterogeneity (data not shown). The findings in the BMI-defined strata were similar to those observed in the main models (data not shown).

Discussion

We report results from our large (for multiple myeloma) prospective study on the association of regular aspirin use with multiple myeloma risk. Our findings suggest that individuals who regularly take five or more adult strength aspirin tablets per week have a nearly 40% lower multiple myeloma risk than persons who do not use aspirin regularly, and that this association is independent of use of other analgesics. Individuals with longer continuous regular aspirin use may also have a lower multiple myeloma risk, although the duration findings were only statistically significant among men.

Two previous case–control studies examined aspirin use and multiple myeloma risk with generally null findings. Neither frequency nor duration of regular aspirin use was associated with multiple myeloma in the hospital-based study (117 multiple myeloma patients, 483 controls; ref. 21). Participants reported their aspirin use frequency and duration before the onset of their illness, but the influence of preclinical multiple myeloma on aspirin use by cases could not be evaluated (21). In a population-based case–control study of women in Connecticut (179 multiple myeloma cases, 691 controls), regular aspirin use at least one year before diagnosis or interview was not associated with multiple myeloma risk; duration of aspirin use was not evaluated (22). The null findings in the Connecticut study may be explained in part by the relatively stringent definition of regular aspirin use: daily use for 6 months or more during the reference period. Only 9 multiple myeloma patients and 35 controls reported regular use by that definition (22). In contrast with the published case–control studies, the present analysis utilized biennially updated information on aspirin use that was prospectively acquired during up to 24 years of follow-up from health professionals likely to have accurate recall of their analgesic use patterns in any given 2-year period. The utilization of a 4-year lag diminished the influence of preclinical multiple myeloma on aspirin use by cases, although the true latency of multiple myeloma is unknown and may be longer than 4 years; we could not consider longer lag intervals well due to the loss of statistical power from the exclusion of more cases from the analysis. By computing an updated cumulative average aspirin tablets per week, we reduced the influence of misclassification of the tablets per week reported in a given follow-up interval (40).

Our report of an inverse association of quantity and duration of regular aspirin use with multiple myeloma is consistent with reported associations of regular aspirin use with risk of several solid tumors (19, 20) as well as of Hodgkin lymphoma (15, 16) and NHL (17, 18). The present findings are also consistent with those from a recent pooled analysis of data from seven randomized clinical trials (20), and with those from the VITAL cohort (23). In the meta-analysis of clinical trial participants followed for at least 5 years postrandomization, which included 50 hematologic cancer deaths, persons allocated to aspirin use had a nonsignificant 66% reduction in mortality from hematologic cancers compared with those allocated to placebo arms (20). In the VITAL cohort, regular use of baby aspirin during the 10 years before study enrollment was inversely associated with risk of plasma cell disorders (\( P_{\text{trend}} = 0.02 \)); “high” users of baby aspirin (i.e., ≥4 days/week for ≥4 years) had a marginally significant 60% lower risk of plasma cell disorders compared with nonusers (23). In contrast, Teras and colleagues (24) did not observe an association of regular aspirin quantity or duration with multiple myeloma risk in the CPS-II cohort in an analysis of comparable
sample size to the present study. Differences in the computation of CPS-II participants' usual aspirin quantity from self-reported baby versus adult strength tablets, and in the choice of exposure lag, may partially explain the discrepant findings. For example, the CPS-II analysis treated tablets per week of baby and adult strength aspirin as equivalent when computing usual pills per month, whereas in the HPFS and NHS, study participants converted baby aspirin use to adult strength equivalents as previously noted. In addition, the CPS-II analysis incorporated no exposure lag or a lag of only 2 years in contrast with the 4-year lag utilized in the present analysis.

Our findings and the aforementioned published reports of a reduced risk of multiple myeloma among regular aspirin users are biologically plausible and may be explained in part by suppression of NF-kB and several of its molecular targets such as COX-2, IL-6, and cyclin D1 by aspirin (14, 41, 42). These molecules regulate normal immune responses and B-cell development but are aberrantly expressed or activated in multiple myeloma (8–11, 43). Our findings are consistent with an etiologic role for one or more of these biologic pathways with known importance to multiple myeloma pathogenesis, although a role for any candidate molecule or pathway must be further explored with prospective biomarker-based studies. In one such study, we pooled individual level data across eight large prospective cohorts (493 cases of multiple myeloma, 978 matched controls with prediagnosis blood samples) and observed that the peripheral blood concentration of the soluble IL-6 receptor was positively associated with risk of a subsequent diagnosis of multiple myeloma within 6 years of blood collection (44). Those findings suggest that inflammation or IL-6 perturbations have an etiologic role in multiple myeloma and support the biologic plausibility of the aspirin-multiple myeloma associations we report in the present study.

We noted somewhat stronger associations of aspirin use with multiple myeloma in men compared with women, although the associations were generally inverse across both genders. The incidence rates for multiple myeloma in our cohort samples were similar to expected on the basis of SEER age-incidence rates, which suggest that unusual patterns of incidence do not explain the gender discrepancies. Rather, the apparent gender differences may be due to chance or may reflect true differences in aspirin use patterns or the physiologic effects of regular aspirin use. The surveys obtained from randomly selected regular aspirin users in our cohorts indicated gender differences in the primary reasons for aspirin use: cardiovascular disease prevention was cited considerably more frequently in men than women (nearly 60% vs. <10%, respectively), whereas headache, arthritis, and musculoskeletal pain comprised the primary indications in women (approximately 80% in women vs. 25% in men; refs. 27, 30). Thus, the typical patterns of aspirin use may also differ by gender in our cohort populations. For example, daily use of baby aspirin may be more common among men, whereas women may achieve a similar weekly dose by taking adult strength aspirin more sporadically. These gender-specific patterns of use may result in different physiologic effects on COX-2, NF-kB, or other relevant pathways. Of interest, in the VITAL study risk of plasma cell disorders was associated with baby aspirin but not with regular strength aspirin use (23). We could not directly evaluate multiple myeloma risk associated with regular use of baby versus adult strength aspirin because baby aspirin use was reported in adult strength equivalents for most of the follow-up period covered in the present analysis.

The inability to explore gender-specific aspirin use patterns or control for primary indication are important limitations of the present analysis. Other limitations include an inability to jointly examine the use of acetaminophen (21) and other nonsteroidal anti-inflammatory drugs (45) due to inadequate statistical power. The secondary analyses in which we evaluated potential confounding by acetaminophen and ibuprofen use suggested that the aspirin-multiple myeloma associations we observed are not strongly confounded by concurrent use of those other medications; however, we were not able to examine use of the other analgesics in detail and cannot rule out the possibility that they have independent associations with multiple myeloma or may interact with aspirin to influence multiple myeloma risk. Finally, we had inadequate statistical power to evaluate exposure lags of more than 4 years, to separately examine the higher quantities of regular aspirin use (i.e., as high as >14 tablets/week) that predicted a reduced risk of colorectal cancer in the same cohorts (35, 46), or to jointly examine quantity and duration of regular aspirin use. The considerable strengths of our study have already been noted in detail and include the prospective design, biennially updated exposure classification, and accurate reporting of medication use by the health professionals in our cohorts. Because the cohort members are predominantly Caucasian (approximately 95%), residual confounding by race is unlikely.

The aforementioned limitations call for caution in the interpretation of our findings. With no available cure for multiple myeloma, it is encouraging to consider that persons who regularly use aspirin for other purposes may also have a lower risk of multiple myeloma. However, confirmation of our findings in other large populations is necessary, as is further exploration of the apparent gender differences we observed. As has been noted in other studies of regular aspirin use and cancer risk, the aspirin dose and frequency that would provide the most favorable risk/benefit ratio is not known (19, 41), and neither is the biologic mechanism by which aspirin use may influence multiple myeloma risk. A clinical trial in patients with MGUS or smoldering multiple myeloma would be informative to evaluate the influence of regular aspirin use on risk of malignant progression, and whether any confirmed benefit of regular aspirin use varies by progression risk as characterized recently by Kyle and colleagues (4). In conclusion, the prospective evidence from the present study supports the further exploration of aspirin use, and of the biologic pathways affected by regular aspirin use, in the etiology and
prevention of multiple myeloma. An investment in carefully
designed prospective studies of MGUS and multiple
myeloma is warranted to obtain further insights into the
etiology and prevention of this lethal malignancy.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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