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Aspirin and risk of multiple myeloma in adults: A systematic review and meta-analysis

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ABSTRACT

Multiple myeloma is a relatively uncommon plasma cell malignancy. Preclinical and clinical studies have suggested that aspirin might modify the risk of multiple myeloma. We performed a systematic review and meta-analysis of studies to examine the association between regular aspirin use and risk of multiple myeloma. Five observational studies including 332,660 adults were evaluated. The pooled estimate had a hazard ratio of 0.90 (95% confidence interval $=0.58-1.39$; $P=0.638$). Odds ratios from the two case-control studies were similar. The findings demonstrated that there was no significant association between aspirin use and the risk of multiple myeloma.

1. Introduction

Multiple myeloma is a malignant plasma cell disorder, comprising approximately 10% of all haematological malignancies, and its incidence is increasing [1]. The pathogenesis is complex, culminating in malignant transformation of clonal plasma cells. The aetiology is not well established, although a number of case-control and cohort studies have reported on the possible associations.

Previous studies reported no consistent association between multiple myeloma and socioeconomic status, income, and education [2,3]. However, a familial history of myeloma in a first-degree relative has been reported to increase the risk of myeloma by 2–6 times [4,5]. A previous study reported that the incidence of multiple myeloma was approximately 60% lower in a Chinese population compared with a non-Chinese population, and that the lower rates were maintained in migrants, showing a strong genetic component as evidenced by ethnic differences [6]. Furthermore, an association between increasing body mass index (BMI) and the risk of myeloma has been detected in several studies [7–9]. Aetiological evidence on the effects of alcohol consumption and tobacco use on the risk of multiple myeloma is limited [10–14]. There is currently inconsistent or limited evidence regarding the association between the risk of myeloma and various factors, including reproductive and hormonal factors [15], occupational exposure [16], chronic immune stimulation [17], and autoimmune disorders [5,18].

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of drugs that inhibit cyclooxygenase (COX) activity and its production of inflammatory prostaglandins. COX-2 expression is associated with inflammation and numerous neoplasms, including multiple myeloma, and COX-2 positivity has been shown to be associated with a poor outcome [19,20]. COX-2 is also expressed in pre-malignant neoplasms, and an animal study showed that the up-regulation of COX-2 was sufficient to stimulate the transformation of normal cells into invasive cancer and metastatic disease [21]. Chronic inflammation can activate stromal fibroblasts leading to enhanced COX-2 expression and the secretion of inflammatory prostaglandins. In turn, stromal cells expressing COX-2 and inflammatory prostaglandins can induce hematopoietic neoplasms to become malignant [22].

Aspirin, which is a commonly used drug, can irreversibly inactivate COX-1 and COX-2 via covalent bond formation [23]. Aspirin may also inhibit nuclear factor-kappaB [24] and interleukin-6 [25], which have been implicated in the development of multiple myeloma. Epidemiological studies have shown that regular aspirin use may be associated with a lower risk of Hodgkin lymphoma [26,27], and non-Hodgkin lymphoma [28,29]. Studies investigating the risk of multiple myeloma have suggested that aspirin might be chemopreventive [30], whereas others have shown no beneficial effect [31–34]. In order to understand the association, and to evaluate the magnitude and quality of the supporting evidence, we performed a systematic review and meta-analyses of observational studies that evaluated the effect of regular aspirin use on the risk of developing multiple myeloma.

2. Materials and methods

2.1. Search strategy

Studies were identified from EMBASE and MEDLINE databases via

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the OVID platform, the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov (www.clinicaltrials.gov), and the World Health Organization International Clinical Trials Registry Platform. Search terms for each database are shown in the Appendix. We did not apply limits to the language, date, or study size in our search, although only journal articles in English were included in the analysis. We performed the final search of all databases on 11 April 2016.

2.2. Inclusion and exclusion criteria

First, titles and abstracts were reviewed to exclude studies unrelated to the objective of this meta-analysis. Articles were considered for full reading if authors reported data from an original peer-reviewed study (i.e., not case reports, comments, letters, meeting abstracts, or review articles), and if the study design included a prospective or retrospective cohort, or if it was a case-control study. Full texts of the selected studies were then retrieved and read in full in an unblinded and independent manner by two authors (S.F.L. and T.Y.N.). Studies were considered eligible for full data extraction if they met the following criteria: i) evaluated and clearly defined exposure to aspirin; (ii) reported the risk of multiple myeloma incidence in adults (18 years or older); and (iii) reported relative risk, odds ratios (ORs), or hazard ratios (HRs), or provided data for their calculation. We excluded studies that did not provide quantification data or sufficient statistical parameters for analysis.

Two independent authors (S.F.L. and T.Y.N.) assessed the methodological quality of the studies using the Newcastle-Ottawa scale [35,36]. In this scale, studies were scored across three categories by answering certain questions: the selection (four questions) and comparability (two questions) of study groups, and the determination of the outcomes or exposures of interest (three questions). All questions were given a score of one except for the comparability of study groups, in which separate points were awarded for controlling for age and sex (maximum score of two). Any discrepancy was resolved via a consensus.

2.3. Data Extraction

Two reviewers (S.F.L. and T.Y.N.) independently performed data extraction. We used a customized form to record the first author of the study, year of publication, study design, country of study population, duration of follow-up, outcome measures, dose and duration of aspirin use (if reported), information regarding exposure ascertainment and outcome assessment, the total number of people in each group (exposed and non-exposed), and effect estimates and 95% confidence intervals (CIs), with and without adjustment for confounding factors. When data for men and women were reported separately, the data were pooled to obtain a summary estimate. For analysis, a reference group was composed of patients with multiple myeloma who were not exposed to aspirin. We derived standard deviations and standard errors from the p-values, according to the instructions in the Cochrane Handbook for Systematic Reviews of Interventions [37]. Conflicts in data extraction were resolved by a consensus.

2.4. Outcomes assessment

The primary outcome was the risk of multiple myeloma in adults based on usage of aspirin, as compared with non-users. Aspirin use for subclinical symptoms of early myeloma was a concern, and the latency period for the development of myeloma is largely unknown; thus, when data on duration of aspirin use were available, the myeloma risks associated with the longest duration of exposure to aspirin were assessed, to minimise the risk of reverse causality.

2.5. Statistical analysis

We used the random-effects model to calculate the meta-analytic estimate of risk of multiple myeloma and 95% CIs [38]. Outcomes were relatively rare events; HRs were considered approximations of relative risks. Adjusted estimates were used in the analysis to account for confounding variables. Heterogeneity between study-specific estimates was assessed using two methods [39,40]. First, the Cochran Q statistical test for heterogeneity, which assesses the null hypothesis that all studies in a meta-analysis have the same underlying magnitude of effect, was performed. A p-value was quoted as an indication of the extent of inter-study variability. It is widely accepted that the Cochran Q statistical test has poor power when the number of studies is small; thus, a p-value of < 0.10 was considered to indicate significant heterogeneity. Second, to estimate the proportion of total variation across studies due to heterogeneity rather than chance, the I^2 statistic was calculated. Higgins et al. [40] provided an informal categorisation of I^2 with values of 25%, 50%, and 75% representing 'low', 'moderate', and 'high' levels of heterogeneity, respectively.

Publication bias was evaluated quantitatively using the Egger regression test (wherein publication bias is present if $p \leq 0.10$), and qualitatively using funnel plots of the logarithmic HRs versus their standard errors [41,42]. Sensitivity analyses were performed to explain statistical heterogeneity if necessary.

All p-values were two tailed. For all tests (except for heterogeneity and publication bias), a p-value of < 0.05 was considered statistically significant. Analysis and reporting were performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines [43]. All analyses and graphs were produced using Stata version 12 software (Stata, College Station, TX, USA) [44].

3. Results

Fig. 1 shows the study inclusion process. We identified 368 studies from our literature search of the five databases. After removing 47 duplicates, we assessed 321 titles and abstracts, and excluded 296 records that did not meet the inclusion criteria. The full text of 25 citations was examined in more detail. Five studies fulfilled the inclusion criteria and were included in the systematic review. No unpublished relevant studies were obtained.

3.1. Characteristics and quality of the included studies

Table 1 shows the characteristics of the included studies. There were five studies, involving 332,660 adults and 901 cases of myeloma. The studies were published in English between 2006 and 2013; all were observational and conducted in the USA. Three of these studies were prospective cohort studies [30,33,34], while two were hospital- or population-based case-control studies [31,32].

The overall methodological quality of this body of evidence was moderate-to-high. Supplementary Tables 1 and 2 show the performance of studies on the Newcastle-Ottawa scale. For the majority of the studies, exposure was ascertained via questionnaires and interviews; outcome assessments were based on electronic databases. The duration and adequacy of follow-up in cohort studies, and the nonresponse rate in case-control studies, were often reported.

The majority of the studies were adjusted for the following confounders: age [30–34], sex [30,33,34], use of panadol/NSAIDs [30,34], race/ethnicity [31,33,34], BMI [30,31,34], education [31,33,34], and family history of haematopoietic cancer [33,34].

The doses of aspirin were 81 mg or 325 mg (regular dose), as reported in three of the studies [30,33,34]; only the outcomes of patients who received a regular dose were included in the analysis. For the two case-control studies [31,32], outcomes were evaluated using ORs, which are the odds of myeloma in the aspirin group compared with the non-aspirin group. An OR of < 1 indicates a lower risk of