No association between cigarette smoking and incidence of plasma cell myeloma: A meta-analysis of 17 observational studies

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Plasma cell myeloma (PCM) is a lymphoproliferative disorder characterized by the malignant growth of monoclonal plasma cells within the bone marrow. Although risk factors for the development of PCM have been identified, the etiology on the majority of patients with PCM remains unclear. Cigarette smoking has been postulated as a potential risk factor for lymphoid malignancies; however, the association with PCM is inconclusive. We have carried out a meta-analysis of observational studies to assess the relationship, if any, between cigarette smoking and PCM. A literature search through December 2011 rendered 4 prospective cohort and 13 case–control studies evaluating such association. Our categorical meta-analysis showed that there is no association between ever, current, and former smokers and PCM. This lack of association was maintained when analyzing by study design, study quality, and geographical area of report. Similarly, meta-regression analysis showed no association with the number of cigarettes smoked per day. In conclusion, our meta-analysis shows that there is no relationship between cigarette smoking and an increased incidence of PCM. Future studies should focus on other potential risk factors for PCM.

PCM is a lymphoproliferative disorder characterized by the malignant accumulation of monoclonal plasma cells within the bone marrow. Patients with PCM can present with anemia, renal dysfunction, hypercalcemia, and bony lytic lesions, and can develop disabling effects from this disease, such as bone fractures or permanent renal insufficiency. In the United States (US) alone, it has been estimated that 21,700 individuals will be diagnosed and 10,710 will die from PCM in 2012 [1]. Despite recent advances in the therapy of PCM (i.e., immunomodulators and proteasome inhibitors), PCM is considered incurable and the majority of patients will ultimately die from PCM-related complications. The etiology of PCM has been an area of active research and few risk factors have been described, such as older age, male sex, African descent, a positive family history, and increased body mass index [2]. However, the large majority of patients diagnosed with PCM do not have an identifiable risk factor. Cigarette smoking has been associated with an increased risk of developing lymphoproliferative disorders [3,4]. The purpose of our study was to evaluate the potential association that cigarette smoking could have on the incidence of PCM by performing a meta-analysis of observational studies.

Our literature search through December 2011 rendered 161 returns, from which 133 were excluded because they were case reports, reviews, or did not pertain to our study. The reference list of the remaining 28 studies provided 7 additional studies for a total of 35. From these, 18 were excluded because they did not provide enough data to calculate the outcome, were already included in other studies, or did not focus on PCM or smoking. From these 17 studies, 4 were prospective cohort [5–8] and 13 were case–control studies [9–21]. The prospective studies were published between 1990 and 2007, and included 1,232 cases identified in a total cohort of 789,000 individuals. Three studies were from the US and 1 from Europe. Two studies were of high quality and two were considered intermediate. The case–control studies were published between 1987 and 2008, and included 4,484 cases and 19,810 controls. Six studies were from the US, six from Europe, and one from Asia. Eight studies were considered of intermediate quality and five of high quality. There was no statistical association between cigarette smoking and incidence of PCM identified in ever smokers, former smokers, or current smokers (Table I). Forests plots are shown in Fig. 1. Similarly, when evaluating subset analyses by study design, study quality, or geographic region, no statistical association was found (Table I). Data were insufficient to perform meta-analysis by sex. Meta-regression analyses evaluating the number of cigarettes smoked per day showed no linear association with incidence of PCM (data not shown). Data were insufficient to perform meta-regression analyses on duration (years) or cumulative smoking (pack-years).

Based on the results of our study, cigarette smoking does not appear to increase the incidence of PCM. Subset analyses by study design and geographical region also failed to show an association. To the best of our knowledge, this is the first meta-analysis evaluating the potential role of cigarette smoking on the incidence of PCM. Cigarette smoking has been associated with an increased risk of developing Hodgkin lymphoma (HL) in a previous meta-analysis from our group [4]. In such study, there was a clear dose-dependent relationship between the incidence of HL and duration and intensity of smoking. Although to a lesser degree, cigarette smoking has also been associated with a small but statistically significant increase in the incidence of non-Hodgkin lymphoma (NHL), specifically in women, identified only in case–control studies [3].

The lack of association between cigarette smoking and PCM incidence likely is a reflection of a clear pathophysiological, molecular, and genetic distinction between PCM and HL or NHL. Cigarette smoking has shown to increase the risk of several malignancies thought to be secondary to the multiple carcinogenic substances contained in cigarettes such as benzene, formaldehyde, and chromium, just to name a few, which have specific effects on apoptosis, cell cycle, and differentiation [22]. Cigarette smoking is also thought not only to produce a chronic inflammatory environment but also to dysregulate the function of lymphocytes and macrophages rendering an immunodeficiency-like state [23]. However, chronic antigenic stimulation (e.g., autoimmune diseases) and immunodeficient states (e.g., HIV infection) have not been associated with an increased risk of PCM. Plasma cells are, on the other hand, resistant against toxic exposures, and utilize a series of protecting mechanisms such as overexpression of P-glycoprotein, which serves as a chemotherapy efflux pump [24]. The clinical translation of such cellular characteristics is the fact that systemic PCM is incurable by means of standard chemotherapy, even at higher doses. One could hypothesize that plasma cells use these and other means against the carcinogenic effects of smoking, which could provide a plausible explanation for the lack of association between smoking and PCM.

Strengths from our meta-analysis include the number of cases analyzed and the multinational origin of the studies. Additionally, heterogeneity was minimal and publication bias did not seem to alter our results. From the study design perspective, 10 out of 13 case–control studies used population-based controls (77%) minimizing selection bias, and 3 of the cohort studies (75%) had >20 years of follow-up, allowing a reasonable amount of time for the

TABLE I. Meta-Analyses of the Incidence of Multiple Myeloma by Smoking Status, Study Design, and Geographical Region

Smoking status	Analyses	OR (95% CI)	*P*-value	I^2	Publication bias
Ever smokers	All studies	0.97 (0.90–1.05)	0.51	18%	NS
Study design	Cohort	1.05 (0.84–1.31)	0.66	74%	NS
	Case–control	0.96 (0.88–1.06)	0.42	0%	NS
Study quality	NOS ≥7	1.03 (0.88–1.21)	0.69	45%	NS
	NOS <7	0.93 (0.86–1.01)	0.09	0%	NS
Region	America	0.99 (0.88–1.12)	0.89	45%	NS
	Europe	0.98 (0.87–1.11)	0.75	0%	NS
Former smokers	All studies	1.05 (0.95–1.18)	0.34	5%	NS
Study design	Cohort	1.07 (0.87–1.32)	0.54	25%	NS
	Case–control	1.05 (0.91–1.21)	0.49	5%	NS
Study quality	NOS ≥ 7	1.22 (0.97–1.54)	0.10	31%	NS
	NOS < 7	0.99 (0.86–1.12)	0.79	0%	NS
Region	America	1.04 (0.90–1.19)	0.62	6%	NS
	Europe	1.09 (0.89–1.34)	0.41	17%	NS
Current smokers	All studies	0.97 (0.62–1.34)	0.63	49%	NS
Study design	Cohort	0.98 (0.80–1.20)	0.84	45%	NS
	Case–control	0.98 (0.82–1.17)	0.79	54%	NS
Study quality	NOS ≥7	1.09 (0.83–1.43)	0.53	59%	NS
	NOS <7	0.89 (0.80–0.99)	0.03	22%	NS
Region	America	0.92 (0.80–1.06)	0.27	53%	NS
	Europe	1.09 (0.84–1.42)	0.51	42%	NS

OR: odds ratio; CI: confidence interval; NS: not significant; NOS: Newcastle–Ottawa scale

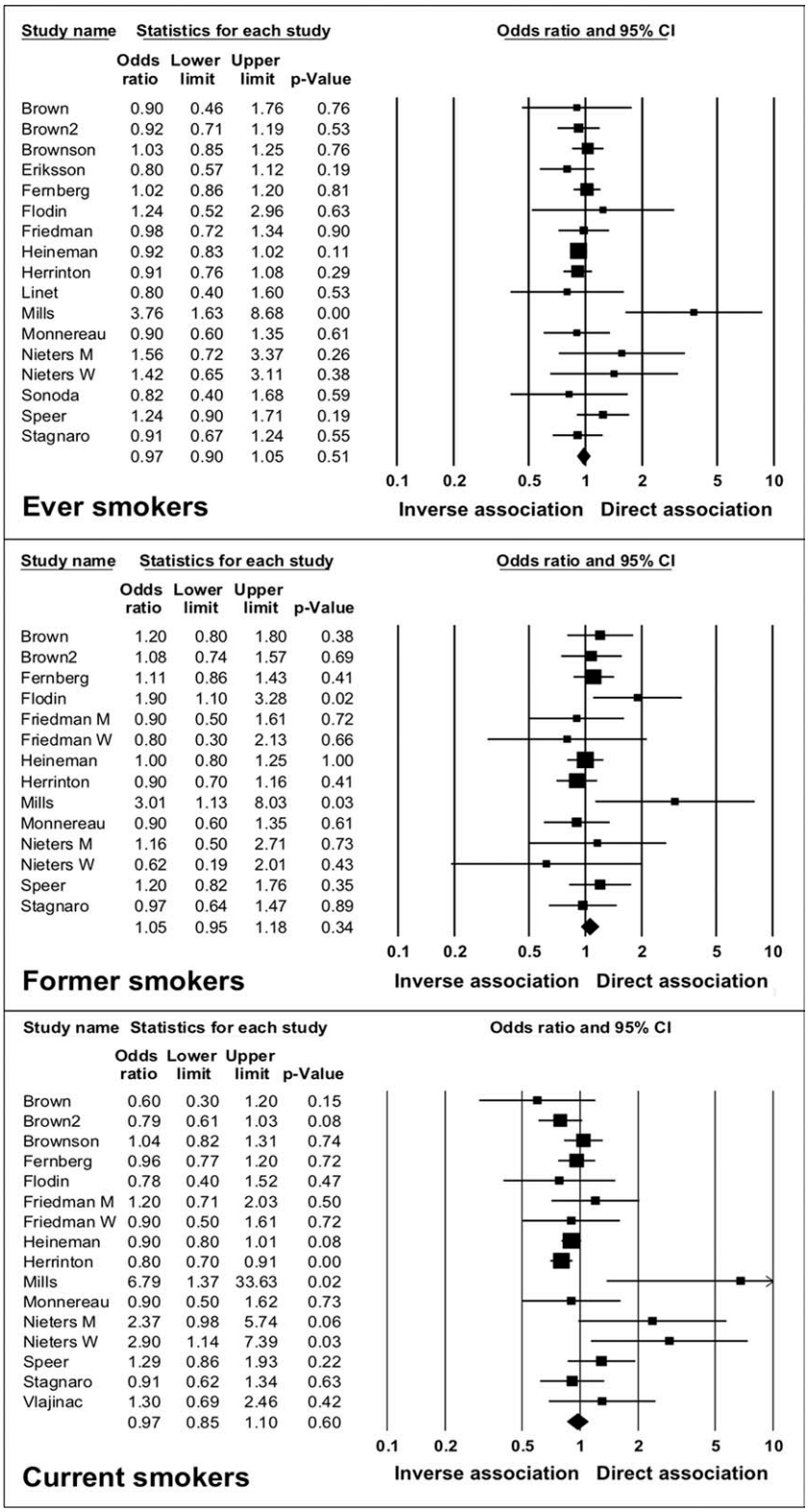

Figure 1. Forests plots on the association of smoking status (ever, former, and current smokers) and the incidence of PCM.

outcome of interest to occur. Our study has, however, several weaknesses, mainly related to the quality of the studies included. We were not able to perform relevant subset analyses according to sex or duration of smoking. Smoking status and intensity and duration assessment relies on self-report, which could have introduced recall and exposure bias depending on the study design. However, smoking status self-report has shown to be reliable in virtually 100% of the participants in a large observational prospective study [25]. Two approaches could help address the weaknesses of our analysis. First, a study including a much larger number of cases could show a true association between smoking and PCM that we could have failed to identify. Second, a patient-level meta-analysis could overcome the specific caveats associated with ecological bias inherent to study-level meta-analyses.

In conclusion, our meta-analysis has failed to show an association between cigarette smoking and incidence of PCM. Future studies should

focus on identifying other risk factors for PCM incidence, or could focus on investigating the role of cigarette smoking on the outcome of patients with PCM. Despite the results of our study, cigarette-smoking cessation will affect positively the health of the general population and should be encouraged globally.

Methods

Two authors independently performed a literature search using PubMed through December 31, 2011. The keywords used were (*smoking OR tobacco OR cigarette*) *AND myeloma*. If a paper was selected for inclusion, the references were scrutinized to look for additional studies. An article was deemed relevant if it originated from prospective cohort or case–control studies and reported original data, regardless of its language, on the association between cigarette smoking and incidence of PCM. Cross-sectional studies, case reports, and reviews were excluded. If there were multiple publications from the same study, the most relevant was selected, using the other publications to clarify methodology or characteristics of the population. The data extraction was performed independently by three authors, and included author, year of publication, country of origin, sample size, method of ascertainment of smoking, method of diagnosis of PCM, source of the exposed and non-exposed cohorts, source of cases and controls, years of follow-up, the outcome measured with 95% confidence interval (CI), the variables used for matching and adjustment, and intensity and duration of smoking. The quality of each study was assessed independently by three authors using the Newcastle–Ottawa Scale (NOS) [26]. The NOS consists of three parameters of quality: selection, comparability, and outcome (cohort studies) or exposure (case–control studies) for a maximum score of 9 points. NOS scores of 7–9, 4–6, and 1–3 were considered high, intermediate, and low quality, respectively. Any discrepancies between reviewers were addressed by a joint re-evaluation of the original article. Because the risk of PCM is low, the relative risk in prospective cohort studies mathematically approximates the odds ratio (OR), therefore permitting the combination of case–control and cohort studies. The primary outcome was calculated as the maximally adjusted OR with 95% CI of developing PCM in cigarette smokers using the random-effects model [27]. Never smokers were the reference group in all calculations. We assessed for heterogeneity using the I^2 index [28]; I^2 values of 25%, 50%, and 75% represent mild, moderate and severe heterogeneity, respectively. Publication bias was assessed using the trim-and-fill method [29]. Subset analyses were performed by smoking status (ever, current, and former), study design (case–control and prospective cohort), and geographical region. Regression analyses were used to assess the dose-relationship between smoking and incidence of PCM. All calculations and graphs were obtained using Comprehensive Meta-Analysis (Biostat, Englewood, NJ). Data will be presented in accordance to the checklist proposed by the Meta-analysis of Observational Studies in Epidemiology group [30].

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