A Pooled Analysis of Cigarette Smoking and Risk of Multiple Myeloma from the International Multiple Myeloma Consortium

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Abstract

Background: Past investigations of cigarette smoking and multiple myeloma have been underpowered to detect moderate associations, particularly within subgroups. To clarify this association, we conducted a pooled analysis of nine case–control studies in the International Multiple Myeloma Consortium, with individual-level questionnaire data on cigarette smoking history and other covariates.

Methods: Using a pooled population of 2,670 cases and 11,913 controls, we computed odds ratios (OR) and 95% confidence intervals (CI) relating smoking to multiple myeloma risk using unconditional logistic regression adjusting for gender, age group, race, education, body mass index, alcohol consumption, and study center.

Results: Neither ever smokers (OR, 0.95; 95% CI, 0.87–1.05), current smokers (OR, 0.82; 95% CI, 0.73–0.93), nor former smokers (OR, 1.03; 95% CI, 0.92–1.14) had increased risks of multiple myeloma compared with never smokers. Analyses of smoking frequency, pack-years, and duration did not reveal significant or consistent patterns, and there was no significant effect modification by subgroups.

Conclusion: Findings from this large pooled analysis do not support the hypothesis of cigarette smoking as a causal factor for multiple myeloma.

Impact: Cigarette smoking is one of the most important risk factors for cancer, but the association with multiple myeloma was inconclusive. This study had excellent power to detect modest associations, and had individual-level data to evaluate confounding and effect modification by potentially important factors that were not evaluated in previous studies. Our findings confirm that smoking is not a risk factor for multiple myeloma. Cancer Epidemiol Biomarkers Prev; 24(3); 1–4. ©2014 AACR.
Introduction

Multiple myeloma is a B-cell malignancy characterized by abnormal monoclonal plasma cells in the bone marrow, monoclonal immunoglobulin in serum and/or urine, and lytic bone lesions. The etiology of this malignancy remains poorly understood. Past investigations of cigarette smoking and multiple myeloma have generally yielded null results (1, 2), although most studies have been underpowered to detect moderate associations, particularly within population subgroups. To clarify the relationship between cigarette smoking and multiple myeloma, we conducted a pooled analysis of case–control studies participating in the International Multiple Myeloma Consortium (IMMC).

Materials and Methods

We pooled individual-level questionnaire data from nine case–control studies in the IMMC that collected data on cigarette smoking (2,670 cases and 11,913 controls). The methods of the participating studies and this pooled analysis have been previously described (3). Smoking status was based on participants’ usual behavior before the diagnosis of multiple myeloma or index date for controls; and former/current smoking status was based on direct questions or calculated from smoking duration. In sensitivity analyses, participants who reported quitting within the 2 years before study interview were regrouped as current smokers.

Data were checked for consistency, outliers, and missing values before pooling. Within each study, we computed odds ratios (OR) and 95% confidence intervals (95% CI) for ever versus never smoking using unconditional logistic regression with adjustment for gender and age group. We conducted a meta-analysis of study-specific findings using random- and fixed-effects models (4); random effects results are shown in Fig. 1. Because the statistical heterogeneity between studies was not significant ($Q_{\text{statistic}} = 0.10$), we pooled the data into a harmonized dataset. Pooled ORs and 95% CIs were adjusted for gender, age group, race, education (indicator of socioeconomic status), body mass index (BMI), alcohol consumption, and study center. Tests of trend for categorical variables were calculated by modeling category numbers as continuous parameters. We conducted stratified analyses by study.

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Cases/controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>1.32 (1.00–1.74)</td>
<td>252/969</td>
</tr>
<tr>
<td>EpiLymph</td>
<td>1.02 (0.76–1.36)</td>
<td>151/1,364</td>
</tr>
<tr>
<td>FHCRC</td>
<td>0.87 (0.71–1.06)</td>
<td>375/961</td>
</tr>
<tr>
<td>Italy</td>
<td>0.94 (0.68–1.29)</td>
<td>140/656</td>
</tr>
<tr>
<td>NCI Population Health Study</td>
<td>0.98 (0.80–1.21)</td>
<td>313/1,294</td>
</tr>
<tr>
<td>NCI–Connecticut</td>
<td>0.71 (0.50–1.01)</td>
<td>80/393</td>
</tr>
<tr>
<td>Nebraska</td>
<td>0.97 (0.57–1.66)</td>
<td>32/697</td>
</tr>
<tr>
<td>RPCI</td>
<td>0.76 (0.51–1.11)</td>
<td>75/338</td>
</tr>
<tr>
<td>Utah</td>
<td>0.54 (0.29–1.01)</td>
<td>30/9</td>
</tr>
<tr>
<td>Overall</td>
<td>0.92 (0.81–1.05)</td>
<td>1,448/6,741</td>
</tr>
</tbody>
</table>

Figure 1.

Study-specific risks of multiple myeloma for ever versus never cigarette smoking, adjusted for gender and age group. $P_{\text{heterogeneity}} = 0.10$. 

Published OnlineFirst December 23, 2014; DOI: 10.1158/1055-9965.EPI-14-1145
we did recategorized as current smokers from former smokers. However, within 2 years before the completion of the questionnaire were not change measurably when participants who ceased smoking compared with never smokers (Table 1). These associations did

95% CI, 0.92
(OR, 0.82; 95% CI, 0.73–0.93)

ever smokers (OR, 0.95; 95% CI, 0.87–1.05)

Among ever smokers.

Among former smokers.

Among ever smokers.

excludes participants who ceased smoking within 2 years before completions of questionnaire.

Stratified analyses and tests of interaction did not suggest any effect modification by subgroups. However, female ever smokers (OR, 0.83; 95% CI, 0.72–0.96) and current smokers (OR, 0.71; 95% CI, 0.58–0.86) had significantly lower risks than female never smokers. Among women, additional stratified analyses and tests of interaction did not reveal evidence of effect modification. We did not observe a difference in the Pearson correlations between smoking status and alcohol frequency by gender (male $r = 0.11$; $P < 0.001$; female $r = 0.11$; $P = 0.003$).

Discussion

In this pooled analysis of 2,670 cases and 11,913 controls, we found no convincing evidence of an association between cigarette smoking multiple myeloma. Null associations between smoking and multiple myeloma were also reported in two recent meta-analyses (1, 2), which included two and four studies from our analysis, respectively. Unlike our study, these meta-analyses did not have access to individual-level data, and therefore were limited in their ability to conduct subgroup analyses.
It is unclear why we observed lower risks of multiple myeloma among women who were ever and current smokers, but not former smokers. The null exposure–response relationships with smoking frequency, pack-years, and duration of smoking among women argue against smoking being a real protective factor. Moreover, these findings could be due to a possible disease effect with the current smokers being healthier than the former smokers. Disease effect may also explain the higher risk with older age at smoking cessation.

Strengths of our study include the relatively large sample size and the availability of individual-level risk factor data, enabling us to adjust for a variety of potential confounders and investigate associations within subgroups. Inherent limitations of the case-control design of the participating studies are the potential recall bias of past smoking, exposure misclassification, using controls that are not representative of the case source population.

The consistency of our findings with previous cohort studies (5–7), which are less susceptible to these design limitations, argues against bias as a major explanation for our findings. In conclusion, the totality of evidence from our pooled analysis confirms that smoking is not associated with multiple myeloma.

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

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Study supervision: G. Andreotti, B.M. Birmann, P. Pahwa, J.R. McLaughlin, A. Neters, T. Zheng, G. Tricot, M.P. Purdue
Other (supervision of data cleaning, constructing database, and computation of derived variables for the Cross-Canada Study of Pesticide and Health):
P. Pahwa
Other (co-PI of the Cross-Canada Study of Pesticides and Health): J.A. Dosman

Grant Support
Funding for the Utah study was, in part, from the Leukemia and Lymphoma Society 6067–09 (to N.J. Camp) and the NCI CA152336 (to N.J. Camp). Data collection for the Utah resource was made possible by the Utah Population Database (UPDB) and the Utah Cancer Registry (UCR). Partial support for all datasets within the UPDB was provided by the University of Utah Huntsman Cancer Institute (HCI) and the HCI Cancer Center Support grant, P30 CA42014 from the NCI. The UCR is funded by contract HHSN261201000026C from the NCI SEER program with additional support from the Utah State Department of Health and the University of Utah.

The work was supported by the European Regional Development Fund and the State Budget of the Czech Republic (RECAMO, CZ.1.05/2.1.00/ 03.0101). The work conducted by B.M. Birmann was supported, in part, by grants from the NCI (K07 CA115687, CA119443) and the American Cancer Society (RSG-11-020-01-CNE).


This work was supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics of the National Cancer Institute.

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Received October 9, 2014; revised December 10, 2014; accepted December 15, 2014; published OnlineFirst December 23, 2014.
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Cancer Epidemiol Biomarkers Prev  Published OnlineFirst December 23, 2014.

Updated version  Access the most recent version of this article at: doi:10.1158/1055-9965.EPI-14-1145

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