RESEARCH ARTICLE

The relation between cigarette smoking and risk of acute myeloid leukemia: An updated meta-analysis of epidemiological studies

Sophia Fircanis,[1] Priscilla Merriam,[1] Naushaba Khan,[2] and Jorge J. Castillo[3]*

Smoking has been postulated as an environmental risk factor for acute myeloid leukemia (AML). The primary objective of this meta-analysis of observational studies was to evaluate the epidemiologic relationship between smoking and the risk of development of AML. Twenty-three studies published between January 1993 and December 2013 were included in our analysis, and accounted for 7,746 cases of AML. The outcome of interest was the relative risk (RR) with 95% confidence interval (CI) of developing AML in adult cigarette smokers in comparison with non-smokers, and was estimated using the random-effects model. Our results showed that current and ever smokers have 40% (RR 1.40, 95% CI 1.22–1.60; $P<0.001$) and 25% (RR 1.25, 95% CI 1.15–1.36; $P<0.001$) increased risk of developing AML when compared with non-smokers. The increased RR of AML was increased regardless of sex, study design, geographical region, and quality of the studies. Intensity of smoking of <10, 10–20, 20–30, and >30 cigarettes per day was associated with RRs of AML of 1.27, 1.36, 1.55, and 1.77, respectively ($P<0.001$ for trend). Duration of smoking of <20 and >20 years was associated with RRs of 1.07 and 1.44, respectively ($P<0.001$ for trend). Cumulative smoking of <10, 10–20, 20–30, and >30 pack-years was associated with RRs of 1.13, 1.23, 1.39, and 1.71, respectively ($P<0.001$ for trend). Overall, cigarette smoking proves to be a significant risk factor for the development of AML in adults.
Am. J. Hematol. 89:E125–E132, 2014.

Introduction

AML is the most common acute leukemia in adults, accounting for 80% of the cases of acute leukemia in this group. According to Surveillance, Epidemiology, and End Results (SEER) data, the median age at diagnosis is 67 years, and the age adjusted incidence rate is 3.7 per 100,000 men and women per year [1], with ~14,590 new cases diagnosed each year in the United States (US) [2]. Currently, standard of care regimens, which include intensive chemotherapy and allogeneic stem cell transplantation, are associated with dismal cure rates in patients with AML, especially in older patients [3]. A recent population-based study revealed a 5-year survival rate of 15%, which varied greatly based on age [4]. This study showed a 5-year survival rate of 50% in patients younger than 40 years but <5% in patients older than 70 years.

There are some well-described risk factors for the development of AML, including a history of prior chemotherapy exposure, exposure to ionizing radiation, or pre-existing hematologic disorders [5]. Typically, however, these risk factors are found in only a small percentage of patients that develop the disease. Outside of benzene exposure, little is described regarding the association between AML and environmental exposures, especially smoking. Because smoking-related diseases are preventable, the association between smoking and the development of AML is worth of further investigation. A meta-analysis by Brownson et al. has previously established an association between AML and smoking [6]. However, differences according to sex, geographical region or intensity and duration of smoking were not investigated. Furthermore, the prevalence of smoking has steadily decreased in the US in the last decade [7], which could have affected the relation between smoking and AML.

The main objective of the present study was to more fully describe the relation between smoking and AML through a meta-analysis of observational epidemiologic studies published since 1993. Additionally, we explored the effects of smoking on the risk of AML according to sex and geographical region, and further analyzed the effects of intensity and duration of smoking on the risk of developing of AML.

Methods

Literature search. A PubMed search from January 1, 1993 to December 31, 2013 was undertaken using the keywords: "(smoking OR tobacco OR cigarette) AND leukemia." The titles and abstracts of the resulting articles were examined and, after excluding non-related articles, full-text articles were retrieved. If an article was selected for inclusion, the references were reviewed looking for additional studies. The electronic and by-hand literature searches were independently performed by at least two of the investigators. Additional search of EMBASE, Google Scholar and the Cochrane Database of Systematic Reviews did not provide additional studies.

Inclusion and exclusion criteria. Prospective cohort and case-control studies reporting on the relation between cigarette smoking and incidence of AML were included, regardless of language. Studies reporting on acute promyelocytic leukemia, acute leukemia without specifying a myeloid origin and myeloid leukemia without specifying an acute subtype were excluded. Reviews or letters to the editor without original data, editorials, case reports, and cross-sectional studies were excluded. Studies included in a

[1]Division of Hematology and Oncology, The Miriam Hospital, Providence, Rhode Island; [2]Department of Medicine, The Miriam Hospital, Providence, Rhode Island; [3]Division of Hematologic Malignancies, Dana-Farber Cancer Institute, Boston, Massachusetts

Conflict of interest: Nothing to report
***Correspondence to:** Jorge J. Castillo, MD, 450 Brookline Ave, M221, Boston, MA 02215, USA. E-mail: JorgeJ_Castillo@dfci.harvard.edu
Received for publication: 7 April 2014; **Accepted:** 18 April 2014
Am. J. Hematol. 89:E125–E132, 2014.
Published online: 19 April 2014 in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/ajh.23744

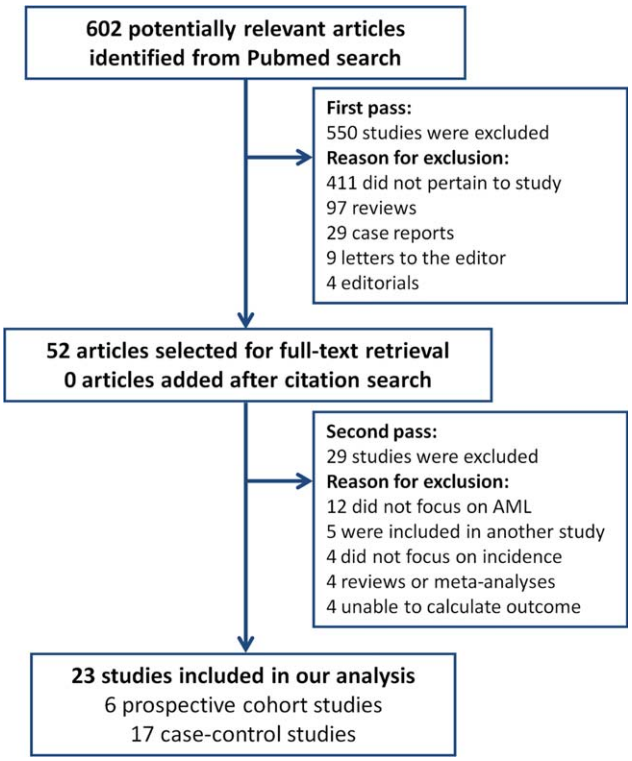

Figure 1. Search strategy. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

previous meta-analysis by Brownson et al. [6] were also excluded. If there were multiple publications from the same study, the most relevant was selected while using the other publications to clarify methodology, if necessary. The study selection was performed independently by at least two of the investigators.

Data gathering. Data extraction was performed independently by at least two of the investigators, and included author, year of publication, country of origin, sample size, method of ascertainment of smoking, and method of diagnosis of AML. For case-control studies, we extracted years of inclusion, the source and definition of cases and controls, the outcome measured (odds ratio) with 95% CIs, and the variables used for matching and/or adjustment. For cohort studies, we extracted the source of the exposed and the nonexposed cohort, years of follow-up, the outcome measured with 95% CIs, and the variables used for adjustment.

Quality assessment. Two investigators, using the Newcastle Ottawa Scale (NOS) [8], independently assessed the quality of each study. The NOS consists of three parameters of quality: selection, comparability, and exposure (case-control studies) or outcome (cohort studies). The NOS assigns a maximum of four points for selection, two points for comparability, and three points for exposure/outcome. Arbitrarily, NOS scores of 1–3, 4–6, and 7–9 were considered low, intermediate and high quality, respectively.

Statistical analysis. Because the risk of AML in the general population is low, the relative risk (RR) and the odds ratio (OR) are virtually equivalent [9], allowing the pooling of cohort and case-control studies (i.e., rare disease assumption). The outcome of interest was the maximally adjusted RR with 95% confidence interval (CI) of developing AML in cigarette smokers compared with never smokers. The random effects model (REM) [10], which accounts for intra and inter-study heterogeneity, was used to estimate the combined outcome. The presence of heterogeneity was assessed using the Cochran's Q statistic [11], and further quantified using the I^2 [12]. For the Q statistic, a P value <0.10 was considered significant for heterogeneity. I^2 values of 25, 50, and 75% were considered as mild, moderate, and severe heterogeneity, respectively. Publication bias was investigated by funnel plot observation [13], and assessed by the trim-and-fill analysis [14]. The trim-and-fill method assumes that the effect sizes of all the studies distribute normally around the center of a funnel plot; if asymmetry is found, it generates imputed studies that would balance such asymmetry and re-calculates the measured outcome. Stratified analyses were performed in current smokers and ever smokers. Sensitivity analyses were performed according to sex, study design, geographical region, study quality, number of cigarettes smoked, number of years of smoking and cumulative smoking in pack-years. All calculations and graphs were obtained using Comprehensive Meta-Analysis version 2.2.050 (Biostat, Englewood, NJ). The results of this meta-analysis are presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses proposed checklist [15].

Results

Search results

Twenty-three studies were included in this meta-analysis from which 6 (26%) were prospective cohort [16–21] and 17 (74%) were case-control studies [22–38]. Ten studies (43%) were from Europe, ten (43%) from Canada/USA and three (14%) from Asia. The search flow diagram is shown in Fig. 1.

Characteristics of the cohort studies

The main characteristics of the cohort studies are shown in Table I. Studies were published between 1993 and 2012. Three studies (50%) originated from the US, two (33%) from Europe and one (17%) from Asia. A total of 2,139 cases of AML were identified from a cohort of 3,654,041 individuals. The diagnosis of AML was assessed using national and/or regional cancer registries in all cases. Smoking was assessed by questionnaire in three studies (50%) and by personal interview in three studies (50%). All the studies adjusted the outcome analyses for age, two studies (33%) adjusted for sex and two (33%) for body mass index. Based on the NOS, all the studies were considered of high quality.

Characteristics of the case-control studies

The main characteristics of the case-control studies are shown in Table II. Studies were published between 1992 and 2013. Eight studies (47%) originated from Europe, seven (41%) from the US and Canada, and two (12%) from Asia. A total of 5,607 cases of AML and 22,784 controls were included in this meta-analysis. Controls were population-based in thirteen studies (76%), and were matched by age in all studies and by sex in 14 studies (82%). The diagnosis of AML was confirmed pathologically in twelve studies (71%) and assessed through medical record review in five (29%). Smoking habits were assessed using personal interview in 12 studies (71%) and using mailed questionnaires or chart review in 5 (29%). Based on the NOS, 11 studies (65%) were of high quality, and 5 (29%) and 1 (6%) were of intermediate and low quality, respectively.

Outcome assessment

Current smokers. Seventeen studies evaluated the relation between current cigarette smoking and AML incidence [16–21,23,24,26–29,32,34–36,38]. Current smokers had 40% higher risk of developing AML than the general population with moderate heterogeneity (Fig. 2). In the subset analyses, the risk of developing AML was similar in case-control and cohort studies with RRs at 1.35 and 1.53, respectively. An increased risk of developing AML was also seen regardless of sex with RR of 1.42 for men and 1.28 for women; there was mild heterogeneity between studies. In the geographical analysis, studies from Canada/USA had higher risk (RR 1.70) than studies from Europe and Asia (RR 1.28 and 1.21, respectively). There was however severe heterogeneity between the studies from Canada/USA, but no heterogeneity in European and Asian studies. When investigating studies based on their quality, the studies with low/intermediate quality rendered a higher effect size (RR 1.84) than studies of high quality (RR 1.36). Publication bias analysis identified the presence of bias, however, after adjusting for this, our results would have not changed. Complete results are shown in Table III.

Ever smokers. Twenty-two studies evaluated the association between ever smoking and AML incidence [16–33,35–38]. Ever smokers had an increased risk of developing AML than the general population (RR 1.25) with mild to moderate heterogeneity. Risk was similar in case-control and cohort studies (RR 1.24 and 1.34, respectively). Although the risk of AML was elevated in men and women, the RR in men was 1.45 and 1.14 in women. The geographical region

 doi:10.1002/ajh.23744

TABLE I. Main Characteristics of Cohort Studies Evaluating the Association Between Cigarette Smoking and Acute Myeloid Leukemia

Study	Year	Country	Source of cohort	AML assessment	Smoking assessment	Follow-up period (median)	Total cohort	No. of patients	Adjustments	NOS
Fernberg	2007	Sweden	Construction Industries Organization for Working Environment, Safety and Health	National Causes of Death Registry, Migration Registry, Cancer Registry	Personal interview	1971–1992 (22.2 years)	336,381	224	Age, body mass index	7
Friedman	1993	United States	Kaiser Permanente Medical Centers in San Francisco and Oakland	Surveillance, Epidemiology and End Results and Kaiser Registry	Self-administered questionnaire	1964–1988 (14 years)	175,112	594	Age	8
Jee	2004	Korea	National Health Insurance Corporation	National Cancer Registry and Hospital records	Personal interview	1993–2001 (Up to 9 years)	1,307,275	355	Age	7
Kroll	2012	United Kingdom	Million Women Study	National Health Services Central Registrar	Self-administered questionnaire	1996–2009 (10.4 years)	1,319,121	613	Age, body mass index, socio-economic status	9
Ma	2009	United States	National Institutes of Health – American Association of Retired Persons Diet and Health Study	State Cancer Registry Database	Self-administered questionnaire	1995–2003 (~6 years)	491,163	338	Age, sex	8
Xu	2007	United States	Three Mile Island Cohort	Pennsylvania Department of Health Cancer Registry and National Death Index	Personal interview	1979–1995 (Up to 16 years)	24,539	15	Age, sex, race, education, radiation exposure	7

doi:10.1002/ajh.23744

TABLE II. Main Characteristics of Case-control Studies Evaluating the Association Between Cigarette Smoking and Acute Myeloid Leukemia

Study	Year	Country	Ascertainment period	Cases source	No. of cases	Controls source	No. of controls	AML assessment	Smoking assessment	Matching	NOS
Bjork	2001	Sweden	1976–1993	Department of Clinical Genetics	333	Population-based	351	Medical record review by 3 pathologists, cytogenetic evaluation	Structured telephone interview	Age, sex, region	7
Bjork	2009	Sweden	2001–2004	Local laboratories, physicians Regional Cancer Registry	104	Population, hospital-based	240	Registry, cytogenetic evaluation	Structured interview	Age, sex, region	8
Ciccone	1993	Italy	1989–1990	Main Hospital of Torino	50	Population, hospital-based	246	Pathological and cytogenetic evaluation	Structured interview	Age, region of birth, residence	7
Crane	1992	United States	1982–1983	Texas Medical Center	34	Hospital-based	41	Pathological evaluation	Structured non-blinded interview	Age, sex, race, center	6
Kane	1999	United Kingdom	1991–1996	Leukaemia Research Fund	695	Population-based	1593	Pathological evaluation	Personal interview	Age, sex	7
Kasim	2005	Canada	1994–1997	Canadian National Enhanced Cancer Surveillance System	307	Population-based	5093	Pathological evaluation	Mailed questionnaire	Age, sex, race, education, residence, income, body mass index	7
Mele	1994	Italy	1986–1989	Hospitals from Rome, Bologna and Pavia	252	Hospital-based	1161	Medical record review by a hematologist	Personal interview	Age, education, residence	6
Musselman	2013	United States	2005–2009	Minnesota Cancer Surveillance System	414	Population-based	692	Pathological evaluation	Self-administered questionnaire	Age, sex, body mass index	8
Pasqualetti	1997	Italy	Not specified	Hospitals from L'Aquila and Avezzano	73	Hospital-based	73	Medical record review	Medical record review	Age, sex, center	5
Pogoda	2002	United States	1987–1994	University of Southern California Cancer Surveillance Program	412	Population-based	412	Pathological evaluation	Non-blinded interview	Age, sex, race	7
Richardson	2008	Germany	1986–1998	Seven cities in Germany	120	Population-based	1009	Medical record review	Personal interview	Age, sex, birth year, region	7
Sandler	1993	United States, Canada	1986–1989	CALGB clinical trials	423	Population-based	618	Pathological evaluation	Telephone interview	Age, sex, race, region	6
Speer	2002	United States	1984–1993	Cancer Surveillance Program of Orange County	604	Population-based	7112	Record linkage (SEER)	Medical record review	Age, race	5
Stagnaro	2001	Italy	1990–1993	Eleven provinces and city of Torino	351	Population-based	1779	Pathological evaluation	Personal blinded interview	Age, sex, residence, education	8
Strom	2012	United States	2003–2007	MD Anderson Cancer Center, Houston, TX	638	Population-based	636	Pathological evaluation	Personal interview	Age, sex, race, residence	7
Wakabayashi	1994	Japan	1981–1990	Department of Internal Medicine, Hyogo College of Medicine	75	Hospital-based	284	Medical record review	Medical record review	Age, sex	3
Wong	2009	China	2003–2007	29 hospitals in Shanghai	722	Hospital-based	1444	Pathological evaluation	Personal blinded interview	Age, sex	8

doi:10.1002/ajh.23744

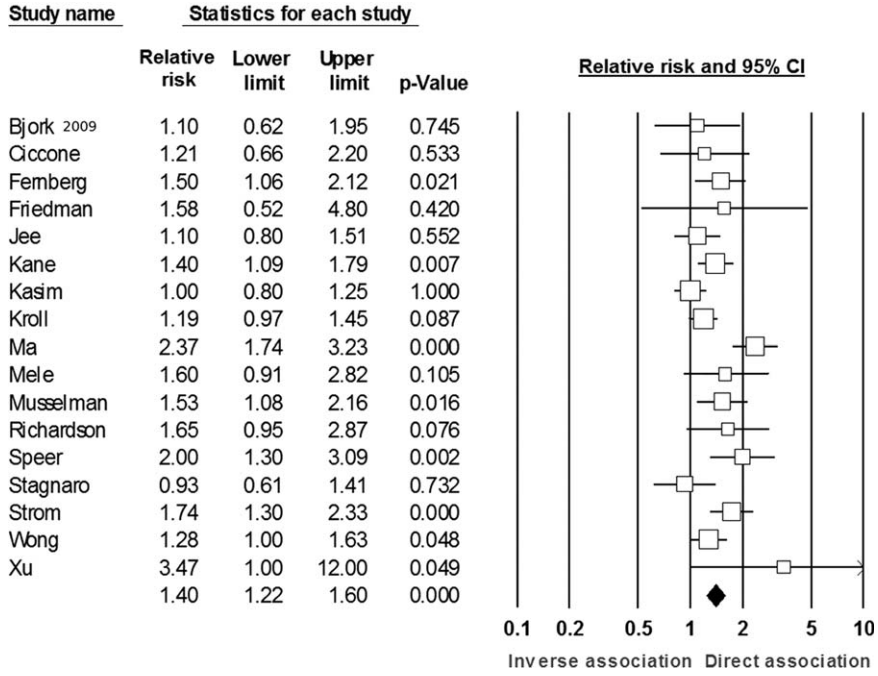

Figure 2. Estimates of the relative risk of developing acute myeloid leukemia in current smokers.

analysis showed a similar increase in the risk of developing AML in European (RR 1.17), Canada/USA (RR 1.31), and Asian studies (RR 1.29). When evaluating studies according to their quality, studies considered of low/intermediate and high quality showed an increase in the risk of AML in ever smokers (RR 1.31 and 1.24, respectively); however, the risk of AML in low/intermediate quality studies did not reach statistical significance. Complete results are shown in Table IV.

Dose response analysis

We evaluated the risk of developing AML in cigarette smokers according to intensity (i.e., number of cigarettes smoked per day), duration (i.e., number of years of smoking), and cumulative smoking (i.e., number of pack-years of smoking). In our intensity analysis, which included data from 14 studies [16,19–24,28–31,35,37,38], individuals who smoked <10, 10–20, 20–30, and >30 cigarettes per day had a RR of AML of 1.27, 1.36, 1.55, and 1.77, respectively ($P < 0.001$ for trend). In our duration analysis, which included nine studies [21–23,26,29–31,35,38], individuals who smoked for <20 and >20 years had RR of AML of 1.07 (NS) and 1.44, respectively ($P < 0.001$ for trend). Finally, in the cumulative smoking analysis, which included nine studies [21–23,27,29,31,33,36,38], individuals who smoked <10, 10–20, 20–30, and >30 pack-years had RR of AML of 1.13, 1.23, 1.39, and 1.71, respectively ($P < 0.001$ for trend). Heterogeneity was non-existing to moderate, and adjustment for publication bias would have not altered our results. Complete results from our analysis are shown in Table V.

Discussion

The association between smoking and AML has been recognized [39]. In a previous meta-analysis, such relation was further evaluated [6]; however, the available data at the time did not allow for the evaluation of sex and geographic differences. Also, dose-response analyses were not performed. We present the results of an updated meta-analysis aimed at comprehensively evaluating the association between cigarette smoking and the development of AML. In this study, which included over 7,500 cases of AML, we found that smoking increases the risk of developing AML regardless of sex, geographical region, study design and quality of studies. Our dose-response analysis suggests an increase in the risk of AML with higher intensity and longer duration of smoking. Furthermore, analyses of heterogeneity and publication bias had minimal impact on our results.

TABLE III. Relative Risk Estimates of AML in Current Smokers Compared With Nonsmokers

	No. studies	RR (95% CI)	*P* value	I^2	Publication bias	Adjusted RR (95% CI)
All studies	17	1.40 (1.22–1.60)	<0.001	57%	Yes	1.39 (1.21–1.59)
Study design						
Case-control	11	1.35 (1.17–1.56)	<0.001	45%	No	
Cohort	6	1.53 (1.13–2.08)	0.007	73%	Yes	1.47 (1.08–1.98)
Sex						
Male	5	1.42 (1.12–1.81)	0.004	28%	No	
Female	5	1.28 (1.03–1.60)	0.03	27%	Yes	1.46 (1.15–1.86)
Region						
Europe	8	1.28 (1.14–1.45)	<0.001	0%	Yes	1.26 (1.12–1.42)
Canada/USA	7	1.70 (1.24–2.32)	0.001	76%	Yes	1.63 (1.21–2.21)
Asia	2	1.21 (1.00–1.47)	0.05	0%	UTC	
Quality						
High	15	1.36 (1.18–1.57)	<0.001	58%	No	
Low/intermediate	2	1.84 (1.30–2.60)	0.001	0%	UTC	

RR: relative risk; CI: confidence interval; UTC: unable to calculate.

TABLE IV. Relative Risk Estimates of AML in Ever Smokers Compared With Nonsmokers

	No. studies	RR (95% CI)	*P* value	I^2	Publication bias	Adjusted RR (95% CI)
All studies	22	1.25 (1.15–1.36)	<0.001	34%	No	
Study design						
Case-control	16	1.24 (1.12–1.36)	<0.001	31%	Yes	1.31 (1.17–1.46)
Cohort	6	1.34 (1.09–1.65)	0.006	50%	Yes	1.17 (0.93–1.48)
Sex						
Male	5	1.45 (1.14–1.85)	0.002	49%	Yes	1.50 (1.20–1.88)
Female	4	1.14 (1.00–1.29)	0.046	0%	Yes	1.14 (1.01–1.30)
Region						
Europe	10	1.17 (1.06–1.29)	0.002	0%	Yes	1.17 (1.07–1.29)
Canada/USA	9	1.31 (1.08–1.58)	0.005	67%	Yes	1.23 (1.01–1.49)
Asia	3	1.29 (1.09–1.51)	0.003	0%	No	
Quality						
High	17	1.24 (1.14–1.36)	<0.001	30%	No	
Low/intermediate	5	1.31 (0.96–1.78)	0.09	54%	No	

RR: relative risk; CI: confidence interval.

Our analysis reveals a 40% increase in the risk of AML in current smokers, and of 25% in ever smokers. Such risk was equally increased in case-control and prospective cohort studies and when removing low and intermediate quality studies, supporting the consistency and strength of our analysis. Although our study did not include a "former smoker" category due to lack of data, one could hypothesize that the risk of AML in former smokers might be lower than in current smokers. This suggests that stopping smoking might be associated with a decrease in the risk AML. The risk of AML was increased in male and female smokers. The risk of AML appears slightly higher in men than women, especially in the ever smoker category, which could be a reflection of specific gender disparities that deserve further attention. Similarly, the risk of AML was increased regardless of geographical region, although it appeared higher in studies from Canada/USA than in European or Asian studies, specifically in current smokers.

Interestingly, our dose-response analysis shows a direct relation between intensity and duration of smoking and risk of AML. The risk of AML increased from 27% in smokers who smoke <10 cigarettes per day to 77% in smokers who smoke >30 cigarettes per day. Also, the risk of AML increased from 7 to 44% in smokers who smoked for <20 years and >20 years, respectively. Finally, the risk of AML increased with cumulative smoking form 13% in smokers who smoked <10 pack-years to 71% in smokers who smoked >30 pack-years. The trends in AML risk for intensity, duration and cumulative smoking were all statistically significant. These findings support a direct coherent association between smoking and risk of AML. Based on these results, one could hypothesize that intensity of smoking (i.e., cigarettes smoked per day) is a stronger risk factor for AML than the duration of smoking (i.e., number of years of smoking). However, the available data does not permit additional analysis in this regard.

There is a biologically plausible association between smoking and AML. Cigarette smoking exposes the smoker to over 7,000 chemicals, from which 70 can be associated with the development of cancer [40]. A limited list of the toxic agents found in cigarette smoke includes benzene, formaldehyde, polonium 210, arsenic, lead, and ammonia. Benzene is probably the strongest carcinogen associated with leukemogenesis. This matter has been recently reviewed [41]. In a recent laboratory study, hydroquinone, the major metabolite of benzene in humans, increased expression of the p53 protein, increased apoptosis and induced DNA double strand breaks in human bone marrow stem cells as well as decreased stem cell differentiation and proliferation [42]. Interestingly, in this study yolk sac stem cells seemed to be especially sensitive to the effects of hydroquinone, which is supported by evidence that exposure to smoking during pregnancy increases the risk of leukemia during childhood [43].

Ionizing radiation, similar to the one emitted by polonium 210, has also been implicated in carcinogenesis and leukemogenesis. A recent meta-analysis found an increased risk of leukemia among workers receiving protracted exposure to low-dose gamma radiation [44]. On the other hand, a study in radiology technologists identified an increased risk of leukemia among workers employed before 1950, when radiation exposures were higher. However, there was no convincing evidence of an increased risk of leukemia in medical radiation workers exposed to current levels of radiation [45].

TABLE V. Relative Risk Estimates of AML in Smokers According to Cigarettes per Day, Years of Smoking and Cumulative Smoking (Pack-Years)

	No. of studies	RR (95% CI)	*P* value	I^2	Publication bias	Adjusted RR (95% CI)
Cigarettes per day						
<10	9	1.27 (1.03–1.56)	0.027	0%	No	
10–20	7	1.36 (1.12–1.64)	0.002	0%	Yes	1.30 (1.08–1.56)
20–30	14	1.55 (1.25–1.92)	<0.001	53%	No	
>30	13	1.77 (1.44–2.18)	<0.001	27%	Yes	1.71 (1.39–2.12)
Years of smoking						
<20	5	1.07 (0.91–1.25)	0.415	9%	Yes	1.06 (0.89–1.25)
>20	9	1.44 (1.23–1.68)	<0.001	9%	Yes	1.42 (1.21–1.67)
Pack-years						
<10	6	1.13 (0.95–1.36)	0.175	0%	Yes	1.11 (0.93–1.32)
10–20	5	1.23 (1.04–1.44)	0.015	12%	No	
20–30	8	1.39 (1.19–1.63)	<0.001	0%	Yes	1.42 (1.22–1.65)
>30	7	1.71 (1.43–2.05)	<0.001	0%	Yes	1.54 (1.26–1.88)

RR: relative risk; CI: confidence interval.

Smoking also directly affects the central and peripheral hematopoietic system. Smoking has shown to decrease the number of circulating CD34+ progenitor cells in healthy individuals [46]. In the bone marrow, cigarette smoke extract exposure diminishes the number of erythrocyte and granulocyte colony-forming units, up-regulates toll-like receptor expression and increases NF-kB, AKT and ERK expression inducing IL-8 and TGF-b1 production [47]. Finally, current epidemiological data support a connection between smoking and the development of myelodysplastic syndromes (MDS) [48,49], which in turn are associated with an increased risk of AML transformation. Whether the increased risk of AML in smokers is dependent on the increased risk of MDS is unclear.

As with any meta-analytic approach, our study carries inherent weaknesses based on the quality of the included studies. First, the history of smoking habits was most commonly obtained from questioning rather than direct observation or blood levels of cotinine, which could have introduced recall bias; however, self-reporting of smoking habits seem to be reliable based on recent experience in a large prospective study [50]. Additionally, there are no data to support that smoking increases the risk of other leukemia subtypes arguing against recall bias as a cause for a false positive relation with AML. Second, based on our study design, we cannot categorically demonstrate causality between smoking and AML; however, the dose-response relationship found as well as the fact that the majority of prospective studies are considered of long follow-up (>10 years) supports a causal role of smoking in AML. Third, several studies have attempted on evaluating the association between smoking and the development of AML with specific cytogenetic abnormalities with mixed results [51]. However, the existing data are rather limited and did not allow for deeper analysis but should be subject of further study. Finally, we must acknowledge that our results might have been affected by statistical multiplicity and therefore be biased. However, the statistically significant dose-dependent relation identified between risk of AML and the duration, intensity and cumulative smoking supports the validity of our results.

Despite our limitations, we were able to show that cigarette smoking is associated with an increased risk of developing AML, which appears statistically and clinically significant regardless of sex and geographical region. Additional studies should focus on racial disparities, the evaluation of potential cytogenetic abnormalities associated with smoking, and the effects of smoking cessation on the risk of AML. Smoking cessation should be advised globally.

References

1. Surveillance, Epidemiology, and End Results [website]. SEER Stat Fact Sheets: Age Adjusted and US Death Rates and 5 year relative survival by Primary cancer site, sex and age. Available at: http://seer.cancer.gov/csr/1975_2010/results_single/sect_01_table.05_2pgs.pdf. Accessed on October 23, 2013.
2. American Cancer Society [website]. Cancer Facts and Figures 2013. Atlanta, GA. Available at: http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-036845.pdf. Accessed on October 23, 2013.
3. Juliusson G, Antunovic P, Derolf A, et al. Age and acute myeloid leukemia: Real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. Blood 2009;113:4179–4187.
4. Shah A, Andersson TM, Rachet B, et al. Survival and cure of acute myeloid leukaemia in England, 1971–2006: A population-based study. Br J Haematol 2013;162:509–516.
5. Pagano L, Pulsoni A, Mele L, et al. Acute myeloid leukemia in patients previously diagnosed with breast cancer: Experience of the GIMEMA group. Ann Oncol 2001;12:203–207.
6. Brownson RC, Novotny TE, Perry MC. Cigarette smoking and adult leukemia: A meta-analysis. Arch Intern Med 1993;153:469–475.
7. Centers for Disease Control and Prevention [website]. Morbidity and Mortality Weekly Report. "Current Cigarette Smoking Among Adults- United States 2011." Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6144a2.htm?s_cid= mm6144a2.htm_w. Accessed on October 23, 2013.
8. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses [website]. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed on January 1, 2014.
9. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 1998;280:1690–1691.
10. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–188.
11. Cochran WG. The combination of estimates from different experments. Biometrics 1954;10:101–129.
12. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–1558.
13. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Br Med J 1997;315:629–634.
14. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455–463.
15. PRISMA [website]. Transparent Reporting of Systematic Reviews and Meta-Analyses. Available at: http://www.prisma-statement.org/. Accessed on October 23, 2013.
16. Fernberg P, Odenbro A, Bellocco R, et al. Tobacco use, body mass index, and the risk of leukemia and multiple myeloma: A nationwide cohort study in Sweden. Cancer Res 2007;67:5983–5986.
17. Friedman GD. Cigarette smoking, leukemia, and multiple myeloma. Ann Epidemiol 1993;3:425–428.
18. Jee SH, Ohrr H, Sull JW, Samet JM. Cigarette smoking, alcohol drinking, hepatitis B, and risk for hepatocellular carcinoma in Korea. J Natl Cancer Inst 2004;96:1851–1856.
19. Kroll ME, Murphy F, Pirie K, et al. Alcohol drinking, tobacco smoking and subtypes of haematological malignancy in the UK Million Women Study. Br J Cancer 2012;107:879–887.
20. Ma X, Park Y, Mayne ST, et al. Diet, lifestyle, and acute myeloid leukemia in the NIH-AARP cohort. Am J Epidemiol 2009;171:312–322.
21. Xu X, Talbott EO, Zborowski JV, Rager JR. Cigarette smoking and the risk of adult leukemia: Results from the Three Mile Island cohort study. Arch Environ Occup Health 2007;62:131–137.
22. Bjork J, Albin M, Mauritzson N, et al. Smoking and acute myeloid leukemia: Associations with morphology and karyotypic patterns and evaluation of dose-response relations. Leuk Res 2001;25:865–872.
23. Bjork J, Johansson B, Broberg K, Albin M. Smoking as a risk factor for myelodysplastic syndromes and acute myeloid leukemia and its relation to cytogenetic findings: A case-control study. Leuk Res 2009;33:788–791.
24. Ciccone G, Mirabelli D, Levis A, et al. Myeloid leukemias and myelodysplastic syndromes: Chemocal exposure, histologic subtype and cytogenetics in a case-control study. Cancer Genet Cytogenet 1993;68:135–193.
25. Crane MM, Godwin JE, Annegers JF, Keating MJ. Is histological subtype a marker for environmental exposures in acute myelogenous leukemia? Cancer Epidemiol Biomarkers Prev 1992;1:183–188.
26. Kane EV, Roman E, Cartwright R, et al. Tobacco and the risk of acute leukaemia in adults. Br J Cancer 1999;81:1228–1233.
27. Kasim K, Levallois P, Abdous B, et al. Lifestyle factors and the risk of adult leukemia in Canada. Cancer Causes Control 2005;16:489–500.
28. Mele A, Szklo M, Visani G, et al. Hair dye use and other risk factors for leukemia and pre-leukemia: A case-control study. Italian Leukemia Study Group. Am J Epidemiol 1994;139:609–619.
29. Musselman JR, Blair CK, Cerhan JR, et al. Risk of adult acute and chronic myeloid leukemia with cigarette smoking and cessation. Cancer Epidemiol 2013;37:410–416.
30. Pasqualetti P, Festuccia V, Acitelli P, et al. Tobacco smoking and risk of haematological malignancies in adults: A case-control study. Br J Haematol 1997;97:659–662.
31. Pogoda JM, Preston-Martin S, Nichols PW, Ross RK. Smoking and risk of acute myeloid leukemia: Results from a Los Angeles County case-control study. Am J Epidemiol 2002;155:546–553.
32. Richardson DB, Terschuren C, Pohlabeln H, et al. Temporal patterns of association between cigarette smoking and leukemia risk. Cancer Causes Control 2008;19:43–50.
33. Sandler DP, Shore DL, Anderson JR, et al. Cigarette smoking and risk of acute leukemia: Associations with morphology and cytogenetic abnormalities in bone marrow. J Natl Cancer Inst 1993;85:1994–2003.
34. Speer SA, Semenza JC, Kurosaki T, Anton-Culver H. Risk factors for acute myeloid leukemia and multiple myeloma: A combination of GIS and case-control studies. J Environ Health 2002;64:9–16; quiz 35–16.
35. Stagnaro E, Ramazzotti V, Crosignani P, et al. Smoking and hematolymphopoietic malignancies. Cancer Causes Control 2001;12:325–334.
36. Strom SS, Oum R, Elhor Gbito KY, et al. De novo acute myeloid leukemia risk factors: A Texas case-control study. Cancer 2012;118:4589–4596.
37. Wakabayashi I, Sakamoto K, Masui H, et al. A case-control study on risk factors for leukemia in a district of Japan. Intern Med 1994;33:198–203.
38. Wong O, Harris F, Yiying W, Hua F. A hospital-based case-control study of acute myeloid leukemia in Shanghai: Analysis of personal characteristics, lifestyle and environmental risk factors by subtypes of the WHO classification. Regul Toxicol Pharmacol 2009;55:340–352.
39. Centers of Disease Control and Prevention [website]. 50th Anniversary Report on Smoking and Health. Available at: http://www.cdc.gov/features/2014smokingreport. Accessed on February 28, 2014.
40. Centers for Disease Control and Prevention [website]. 2010 Surgeon Generals' Report—Chemicals in Tobacco Smoke. Available at:

http://www.cdc.gov/tobacco/data_statistics/sgr/2010/consumer_booklet/chemicals_smoke. Accessed on February 28, 2014.
41. Snyder R. Leukemia and benzene. Int J Environ Res Public Health 2012;9:2875–2893.
42. Zhu J, Wang H, Yang S, et al. Comparison of toxicity of benzene metabolite hydroquinone in hematopoietic stem cells derived from murine embryonic yolk sac and adult bone marrow. PLoS One 2013;8:e71153.
43. Mucci LA, Granath F, Cnattingius S. Maternal smoking and childhood leukemia and lymphoma risk among 1,440,542 Swedish children. Cancer Epidemiol Biomarkers Prev 2004;13:1528–1533.
44. Daniels RD, Schubauer-Berigan MK. A meta-analysis of leukaemia risk from protracted exposure to low-dose gamma radiation. Occup Environ Med 2011;68:457–464.
45. Yoshinaga S, Mabuchi K, Sigurdson AJ, et al. Cancer risks among radiologists and radiologic technologists: Review of epidemiologic studies. Radiology 2004;233:313–321.
46. Ludwig A, Jochmann N, Kertesz A, et al. Smoking decreases the level of circulating CD34+ progenitor cells in young healthy women—A pilot study. BMC Womens Health 2010;10:20.
47. Zhou J, Eksioglu EA, Fortenbery NR, et al. Bone marrow mononuclear cells up-regulate toll-like receptor expression and produce inflammatory mediators in response to cigarette smoke extract. PLoS One 2011;6:e21173.
48. Du Y, Fryzek J, Sekeres MA, Taioli E. Smoking and alcohol intake as risk factors for myelodysplastic syndromes (MDS). Leuk Res 2010;34:1–5.
49. Tong H, Hu C, Yin X, et al. A meta-analysis of the relationship between cigarette smoking and incidence of myelodysplastic syndromes. PLoS One 2013;8:e67537.
50. Yeager DS, Krosnick JA. The validity of self-reported nicotine product use in the 2001–2008 National Health and Nutrition Examination Survey. Med Care 2010;48:1128–1132.
51. Lichtman MA. Cigarette smoking, cytogenetic abnormalities, and acute myelogenous leukemia. Leukemia 2007;21:1137–1140.