Relationship between cigarette smoking and risk of chronic myeloid leukaemia: a meta-analysis of epidemiological studies

Ling Qin\textsuperscript{a}, Hui-Yang Deng\textsuperscript{a}, Sheng-Jiang Chen\textsuperscript{b} and Wei Wei\textsuperscript{a}

\textsuperscript{a}Department of Hematology, First Affiliated Hospital, College of Clinical Medicine, Henan University of Science and Technology, Luoyang, Henan, China; \textsuperscript{b}Department of Ultrasound, First Affiliated Hospital, College of Clinical Medicine, Henan University of Science and Technology, Luoyang, Henan, China

\section*{ABSTRACT}

\textbf{Objective:} Previous epidemiologic studies that have been reported on the association between cigarette smoking and risk of chronic myeloid leukaemia (CML) have remained controversial. A comprehensive meta-analysis was performed to evaluate smoking as a potential relationship factor and incidence of CML.

\textbf{Methods:} Systematic literatures collected from articles published before August 2015 were searched from PubMed, EMBASE and the Cochrane Library. A total of 10 studies (nine case-controls and one cohort) met inclusion criteria of this meta-analysis. Odds ratios (ORs) with 95\% confidence interval (CI) were calculated to assess the strength of the association between cigarette smoking and risk of CML in this study. Quality assessments were performed on the studies with the Newcastle-Ottawa Scale. I\textsuperscript{2} index was used to evaluate heterogeneity. Finally, publication bias was assessed through funnel plots and Begger’s test.

\textbf{Results:} No significant association was observed between ever-smokers and CML when compared among non-smokers (OR = 1.13, 95\% CI: 0.99–1.29) or between subgroups stratified by smoking history, gender, geographical region, study design and source of patients. Our results demonstrate that this association was stronger in individuals who smoked <20 cigarettes/day (OR = 1.72, 95\% CI: 1.06–2.79) vs. individuals who smoked >20 cigarettes/day (OR = 1.24, 95\% CI: 0.55–2.81). Moreover, cumulative smoking of <15, 15–30 and >30 pack-years was associated with ORs of 1.22, 1.32 and 1.39, respectively (P < 0.001, for trend).

\textbf{Conclusion:} This meta-analysis suggests that smoking may significantly increase the risk of CML in a dose-dependent manner. However, additional well-designed, prospective cohort studies are required to verify these findings and identify other risk factors associated with CML.

\section*{Introduction}

Chronic myeloid leukaemia (CML) is a myeloproliferative disorder, caused by expression of the BCR-ABL tyrosine kinase oncogene, which arising from a translocation t(9;22)(q34;q11) Philadelphia chromosome [1–4]. It is universally acknowledged that gene mutation is a necessary but insufficient risk factor for the development of CML. Therefore, some studies on benzene, radiation and prior chemotherapy exposure are well-established risk factors for CML [5–7]. Other exposures that have been suggested as risk factors include treatment with DNA topoisomerase II inhibitors, tobacco smoking, personal use of hair dye and other organic solvents, extremely low frequency electromagnetic fields, viruses and pesticides [8–13]. With the development of allogeneic SCT and with BCR-ABL tyrosine kinase inhibitors, CML seems curable. However, a better understanding of the etiology of this disease may lead to the significant reduction in CML incidence.

Previous studies have confirmed that cigarette smoking has a strong link between exposure to cigarette smoke and increased risk of developing myeloid leukaemia in adults [14,15]. Tobacco use may result in an imbalance in the haematopoietic system such as changes in the erythrocyte–leukocyte ratio and composition of mature leukocytes in peripheral blood [16]. No detailed biological mechanism has been proposed, but a causal link has made plausible by evidence of the systemic effects of cigarette smoke and the presence of chemicals in cigarette smoke that have been associated with leukaemia risk [17,18].

By including cohorts and case–control epidemiological studies, these findings were inconclusive. Some studies of CML have reported a dose–response effect according to the duration and/or intensity of smoking, while others revealed no such effect [19,20]. Seven studies suggest a positive correlation between cigarette smoking and CML [20–26]. Furthermore, there are controversial reports reflective of the complex effects of smoking on the human body, as well as the heterogeneity of the parameters used.
among different studies. Therefore, our main objective was to investigate the relationship of cigarette smoking and the development of CML, and conduct a meta-analysis of published literatures to investigate whether an epidemiologic relationship, if any, exists between the risk of CML and cigarette smoking. Additionally, we explored the effects of smoking on the risk of CML according to gender and geographical region; and further analyzed the effects of the intensity and duration of smoking on the risk of developing CML.

**Materials and methods**

A systematic literature search in the Cochrane Library, PubMed and EMBASE databases was undertaken using keywords ‘(smoking OR tobacco OR cigarette) AND (leukaemia OR chronic myelogenous leukaemia OR CML OR chronic myeloid leukaemia)’ for papers published between 1980 and 31 July 2015. Titles and abstracts of the resulting articles were examined, after excluding non-related articles; and full-text articles were retrieved. References were reviewed for additional articles when an article was selected for inclusion. Electronic and by-hand literature searches were conducted by two independent reviewers.

**Inclusion and exclusion criteria**

Inclusion criteria for this meta-analysis were as follows: (1) prospective cohort or case–control studies; (2) articles that evaluated the association between cigarette smoking and risk of CML; (3) studies that provide data on risk and corresponding 95% confidence intervals (CI) or data on the frequency of cigarette smoking in both cases and controls that could be calculated; (4) studies written in any language.

Study selection was independently performed by at least two of the reviewers to ensure the accuracy of the extracted information. If there were multiple publications from the same study or overlapping study populations, only the most relevant study with the largest number of cases was eligible for inclusion in the meta-analysis. Editorials or reviews, letters to the editor without original data, case reports and cross-sectional studies were excluded.

**Data gathering**

Data extraction was performed independently by at least two of the investigators. The following data were extracted from each study and included in the final analysis: first author’s name, year of publication, country of origin, study design, gender, age, sample size, method of ascertainment of smoking and method of diagnosis of CML. Furthermore, years of inclusion, source and definition of cases and controls, and the variables used for matching and adjusting covariates we extracted from all studies (cohort and case–control studies). If the eligible date for the meta-analysis was not available, the author was contacted, when necessary. Any disagreements were resolved through a third investigator to attain a consensus. Two reviewers independently assessed the quality of each study with the nine-score Newcastle-Ottawa Scale (NOS) [27].

**Statistical analysis**

In this study, measurement tests employed for statistical heterogeneity were either fixed-effect or random-effect models, which were appropriately used to calculate a pooled odds ratio (OR) with 95% CI [28]. There was no heterogeneity when a fixed-effects model was used to calculate a pooled OR with 95% CI. Otherwise, the random-effect model was used. Heterogeneity was assessed using Q-test and I2 index. \( p > 0.05 \) for the Q-test indicated a lack of heterogeneity among studies. The presence of heterogeneity was assessed using the Cochran’s Q statistic, and was further quantified using the I2. For the Q statistic, a \( p \)-value <0.10 was considered significant for heterogeneity. I2 values of 25, 50 and 75% were considered as mild, moderate and severe heterogeneity, respectively. Estimation of potential publication bias was investigated by funnel plot. Sensitivity analysis was performed by sequential omission of individual studies under various contrasts to reflect the influence of individual data to the pooled ORs, and evaluate the stability of results. Stratified analyses were performed on current smokers and ever-smokers. Subgroup analyses were performed and categorized by study quality, geographical regions, gender, the number of cigarettes smoked per day, years of smoking and pack-years. An asymmetrical plot suggested a possible publication bias. Funnel plot asymmetry was evaluated by Begger’s linear regression test, which is a linear regression approach to measure funnel plot asymmetry on the natural logarithm scale of the OR. The significance of the intercept was determined by t-test, as suggested by Begger’s test \( (p < 0.05 \) was considered as the presence of statistically significant publication bias). All statistical analyses were performed with STATA 12.0 statistical software (Stata Corporation, College Station, TX, U.S.A.). All \( p \)-values were two-sided, and \( p < 0.05 \) was considered statistically significant.

**Results**

**Search results**

The flow diagram and study selection process for the meta-analysis literature search are shown in Figure 1. Ten studies were included in this meta-analysis, in which one was a cohort and nine were case–control
studies [19–24,29–32]. Four studies were from Europe and six were from Canada/U.S.A. The search process is shown in Figure 1. Nine case–control studies were identified on the association of cigarette smoking exposure with risk of CML published between 1988 and 2015. A total of 1410 CML patients were included in this meta-analysis. Information on the relationship of cigarette smoking was obtained through interviews, self-administered questionnaires, or both. Study quality scores were assessed by the Newcastle-Ottawa Quality Assessment Scale [27], which ranged from 6 to 8 (with a mean of seven). The main characteristics of the included studies are shown in Table 1.

**Risk assessment**

As shown in Figure 2. There was little significant association between cigarette smoking and CML for individuals with history of tobacco consumption to never smoking (OR = 1.13, 95% CI: 0.99–1.29; Figure 2), as well as heterogeneity among studies with moderate heterogeneity (I² = 47.4%), were compared. Heterogeneity among studies was mild (I² = 24.7%) and without publication bias (p = 0.895, Egger’s test). Current smoking was also associated with increased risk for CML (OR = 0.99, 95% CI: 0.85–1.14) (Figure 3(a) and (b)). There was low heterogeneity among studies (I² = 12.9%). Egger’s test results revealed no evidence of publication bias (p = 0.709). A statistically significant heterogeneity was found among the nine studies (p = 0.047). Thus, a random-effects analysis was performed (I² = 47.4%). Sensitivity analyses were executed, and results demonstrated that our study would not considerably affect the summary of risk estimates in ever-smokers, including current or former smokers.

**Subgroup analyses**

As shown in Table 2, stratified group analyses were performed for the following subgroups: geographical region, gender, study design (case–control or cohort), patient source (population or hospital-based), smoking intensity, duration of smoking and number of pack-years in ever-smokers. Cigarette smoking has been shown to be consistently associated with increased incidence of CML via OR estimates. However, some results were not significant, although each subgroup was separately analyzed.

When subgroup analysis was conducted by gender, the effect of smoking on developing CML was observed in females (OR = 1.32, 95% CI: 1.02–1.69). However, a statistical significance was adverse in males (OR = 0.61, 95% CI: 0.21–1.75).

**Geographical regions**

Observed OR of ever-smokers in the analysis revealed a similar increase in risk of developing CML in Europe (OR = 1.22, 95% CI: 0.78–1.92) and Canada/United States (OR = 1.10, 95% CI: 0.88–1.38).

**Source of patients**

When subgroup analyses were conducted by study source of patients, a statistical significant adverse effect of smoking on developing CML (OR = 1.12, 95% CI: 0.94–1.34) was observed in population-based controls, compared to hospital-based controls (OR = 1.21, 95% CI: 0.71–2.06). There was high heterogeneity (I² = 73.2%) without publication bias in hospital-based subjects.

The number of cigarettes smoked per day. The risk of developing CML in cigarette smokers was evaluated according to the number of cigarettes smoked per day.
| Study          | Study period | Country      | Sex | Age (years) | Study design          | Case source                                      | Control source      | No. of case/controls | CML assessment                  | Smoking assessment                   | Matching and adjustments | Quality score |
|---------------|--------------|--------------|-----|-------------|------------------------|--------------------------------------------------|--------------------|----------------------|--------------------------|-------------------------------------|-------------------------------|----------------|
| Richardson et al. [31] | 1986–1998    | Germany      | M/F | 15–75       | Case–control study     | Seven cities in Germany                           | Population-based    | 69/157               | Medical record review    | Personal interview            | Age, sex, birth year, region, household income, socioeconomic status | 7               |
| Musselman et al. [21] | 2005–2009    | United States | M/F | 20–79       | Case–control study     | Minnesota Cancer Surveillance System              | Population-based    | 185/692             | Pathological evaluation  | Self-administered questionnaire | Age, sex, race/ethnicity, education, alcohol, benzene/solvent exposure marital status residence, radiation exposure income, body mass index | 8               |
| Mele et al. [23] | 1986–1989    | Italy        | M/F | >15         | Case–control study     | Hospitals from Rome, Bologna and Pavia           | Hospitals-based     | 156/1161            | Medical record review by a hematologist | Personal interview          | Age, education, residence | 6               |
| Kasim et al. [22] | 1994–1997    | Canada       | M/F | 20–74       | Case–control study     | Canadian National Enhanced Cancer Surveillance SYSTEM | Population-based | 169/5093           | Pathological evaluation  | Malied-questionnaire          | Age, sex, race, education, residence, income, body mass index | 7               |
| Brownson et al. [29] | 1984–1990    | United States | M/F | >20         | Case–control study     | Hospitals from Missouri Cancer Registry          | Population-based    | 153/1899            | Medical record review    | Medical record review       | Age, sex, race                | 7               |
| Brown et al. [24] | 1981–1984    | United States | M   | >30         | Case–control study     | Local laboratories, physicians Regional Cancer Registry | Hospitals-based | 51/820              | Medical record review    | Personal interview          | Age, alcohol, region, family history, medical conditions, pesticides | 6               |
| Bjork et al. [19] | 1979–1993    | Sweden       | M/F | 31–72       | Case–control study     | The Swedish national bureau of statistics (Statistics Sweden) | Hospitals-based | 226/251            | Medical record review, cytogenetic evaluation | Structured telephone interview. | Age, sex, region, hair dye, occupational exposure | 8               |
| Strom et al. [30] | 1999–2006    | United States | M/F | 16–83       | Case–control study     | the University of Texas MD Anderson Cancer Center | Population-based    | 253/270             | Medical record review, cytogenetic evaluation | Self-administered validated questionnaire | Age, sex, alcohol consumption, BMI, family history, education, race, occupational solvent and ionizing radiation exposure | 8               |
| Fernberg et al. [32] | 1969–1992    | Sweden       | M/F | 14–82       | Cohort                 | Construction Industries Organization for Working Environment, Safety and Health | Population-based | 101/336381        | National Causes of Death Registry, Migration Registry, Cancer Registry | Personal interview          | Age, body mass index         | 7               |

M: male; F: female; NR: not report.
An association was found between ever-smokers who smoked fewer than 20 cigarettes per day and smoked more than 20 cigarettes per day and the risk of CML (OR = 1.72, 95% CI: 1.06–2.79; and OR = 1.24, 95% CI: 0.55–2.81; respectively). All this had an increased risk of CML in ever-smokers and a relationship with smoking intensity. There was no heterogeneity (I² = 0%) in the group that smoked fewer than 20 cigarettes per day. However, ever-smokers who smoked more than 20 cigarettes per day had moderate heterogeneity (I² = 59.7%) and both of these had no publication bias.

**Years of smoking**

According to our analysis, there was little significant change among those who smoked for less than 20 years (OR = 1.35, 95% CI: 0.96–1.89). The result of heterogeneity (I² = 0%) and publish bias were indicated as not found out. There was no heterogeneity (I² = 0%) without publication bias in individuals who smoked for more than 20 years, and pooled OR was 1.57 (95% CI: 1.13–2.17).

**Pack-years**

For individuals who smoked >0 and <15 pack-years, OR was 1.22 (95% CI: 0.97–1.53) with moderate heterogeneity (I² = 0%) without publication bias. Furthermore, a positive correlation of CML was found in individuals who smoked 15–30 pack-years and more than 20 pack-years (OR = 1.32, 95% CI: 0.97–1.81; and OR = 1.39, 95% CI: 0.99–1.98; respectively).

Complete results of the analysis are shown in Table 2. Our results would not change when adjustment for publication bias and heterogeneity was non-existing to moderate (Figure 4).

**Discussion**

Smoking is the main risk factor for the development of many types of cancer. Cigarette smoking was considered as a cofactor that raised this possibility and promoted its progression in the bone marrow (myeloid leukaemia) [33,34]. Some researchers suggest that cigarette smoking may impair bone marrow haematopoiesis *in vivo*, as well as induce inflammation; which are two processes that proceed malignant transformation as a potential increased risk factor of CML [35]. Nevertheless, previous literatures have not provided an overwhelming evidence link between cigarette smoking and risk of CML. Hence, we summarize the current data based on this potential relationship and illustrated several interesting points that are worth discussing.

In this meta-analysis, further analysis revealed that current smokers had 0.99% lower risk of developing CML than never smokers, suggesting that current smokers were under a small risk of CML. Similar studies have been reported in some previous epidemiological investigations [9,36]. The reason for the higher risk of ever-smokers than current smokers might be due to the higher total cumulative dose and longer exposure time. A previous study [37] demonstrated that those who had quit smoking may not have excess risk of AML, perhaps similar with CML. Such observation suggests that certain smoking-related damage may be reversible upon smoking cessation, but the effect of cessation may be
only partially beneficial [38]. The subgroup analyses also failed to demonstrate any significant correlations, except with a number of smoking (0–20/day). Those individuals exhibited a 72% increased risk of CML. When we conducted a subgroup analysis, our study revealed that male individuals who ever smoked faced an added 32% risk of CML; however, women have no such risk.

When a subgroup analysis on geographical region was conducted, we noticed a low relationship on risk of CML in the United States (10%); while no such association was found in Europe (25%).

There was a high risk of CML in individuals who smoked less than 20 cigarettes per day (OR = 1.72, 95% CI: 1.06–2.79); and there was a non-significant 13% risk of CML, indicating that smoking may play a weak role in the incidence of CML. An insignificant risk of smoking on CML was detected in individuals who smoked for less than 20 years, whereas a higher correlation was detected if smoking was more than 20 years (OR = 1.57, 95% CI: 1.13–2.17). A direct relationship existed between higher numbers of cigarettes smoked per day/pack-years and increased risk of developing CML. In assessing the number of pack-years, our data shows a slow increasing risk of CML with gradually increasing smoking pack-years. In particular, smoking more than 20 pack-years increased the risk of CML to 39%. Totally, our data shows that the duration and intensity of smoking appears to play critical roles in the development of CML. There was a positive correlation between cigarette smoking and the incidence of CML, which was in a dose-dependent manner.

Our meta-analysis confirms the complicated nature of the mechanisms by which tobacco consumption may be involved in the pathogenesis of CML. Several potential mechanisms could support smoking as a risk factor for CML. First, smoking may exert a direct toxic effect by causing bone marrow failure. Commonly, benzene, chromium and formaldehyde contained in cigarettes might contribute to direct carcinogenicity [39,40]. In addition, previous studies

**Table 2.** Odds ratios estimates of CML for ever smoking compared with never smoking in subgroups.

| Subgroup          | Number of studies | Pooled OR (95% CI) | Q-test for heterogeneity p value (I2 score, %) | Beggar’s test p value | Egger’s p value |
|-------------------|-------------------|--------------------|-----------------------------------------------|-----------------------|----------------|
| Total             | 1.13 (0.99–1.29)  | 0.047 (47.4%)      | 0.592                                         | 0.709                 |                |
| Geographical region |                  |                    |                                               |                       |                |
| Canada/U.S.A.     | 6                 | 1.10 (0.88–1.38)   | 0.107 (44.7%)                                 | 0.851                 | 0.779          |
| Europe            | 4                 | 1.22 (0.78–1.92)   | 0.047 (62.2%)                                 | 0.497                 | 0.77           |
| Source of patients |                  |                    |                                               |                       |                |
| PB                | 6                 | 1.12 (0.94–1.34)   | 0.315 (15.4%)                                 | 0.869                 | 0.975          |
| HB                | 4                 | 1.21 (0.71–2.06)   | 0.011 (73.2%)                                 | 0.497                 | 0.63           |
| Gender            |                  |                    |                                               |                       |                |
| Male              | 3                 | 1.32 (1.02–1.69)   | 0.602 (0.0)                                  | 0.602                 | 0.346          |
| Female            | 2                 | 0.61 (0.21–1.75)   | 0.045 (75.1%)                                 | 0.317                 | –              |
| Study design      |                  |                    |                                               |                       |                |
| Cohort            | 1                 | 0.87 (0.43–1.76)   | 0.042 (47.4%)                                 | 0.009                 | 0.372          |
| Case–control      | 9                 | 1.16 (0.94–1.43)   | 0.035 (51.8%)                                 | 0.009                 | 0.372          |
| No. of cigarettes |                  |                    |                                               |                       |                |
| 0–20              | 2                 | 1.72 (1.06–2.79)   | 0.63 (0)                                      | 0                     | –              |
| >20               | 2                 | 1.24 (0.55–2.81)   | 0.115 (56.9%)                                 | 0                     | –              |
| Duration          |                  |                    |                                               |                       |                |
| 0–20              | 2                 | 1.35 (0.96–1.89)   | 0.465 (0)                                     | 0                     | –              |
| >20               | 2                 | 1.57 (1.13–2.17)   | 0.83 (0)                                      | 0                     | –              |
| Pack-years        |                  |                    |                                               |                       |                |
| 0–15              | 4                 | 1.22 (0.97–1.53)   | 0.68 (0)                                      | 0.073                 | –              |
| 15–30             | 4                 | 1.32 (0.97–1.81)   | 0.81 (0)                                      | 0.66                  | –              |
| >30               | 4                 | 1.39 (0.99–1.98)   | 0.56 (0)                                      | 0.459                 | –              |
have revealed a positive relationship between benzene exposure duration, level and frequency and CML development [41]. In smoking, a number of circulating CD34+ progenitor cells in healthy individuals decreased [42], suggesting that smoking may directly affect the central and peripheral haematopoietic system. Furthermore, the reduction in the number of erythrocyte and granulocyte colony-forming units, upregulation of toll-like receptor expression, and increase in NF-kb, AKT and ERK expression to induce IL-8 and TGF-β1 production in the bone marrow was attributed to cigarette smoking exposure [37]. In addition, previous studies have pointed out that these might induce chromosomal defects in hematological malignancies due to smoking exposure. The prognostic impact of cytogenetic abnormalities also influences CML survival [25,43].

Our meta-analysis collected a number of review and analysis studies. Therefore, we have enough data to perform multiple subgroup analyses. Nevertheless, our study also has limitations. First, the studies included in our meta-analysis were the source of retrospective dates, and included studies were mainly from Europe/U.S.A. and did not cover Asian regional studies; thus, possibly introducing substantial heterogeneity. In addition, combining data from different study designs may also be a source of bias. Second, our meta-analysis included articles that may be a source of publication bias and contributed to those only published in the English language, even though Begg’s or Egger’s test did not reveal evidence of publication bias. Third, there were a limited number of studies in our meta-analysis, and there were few original articles that concluded the potential existence of the relationship between cigarette smoking exposure and CML. In addition, our results were affected by methodological differences through cohort and case-control studies, which might also influence the outcomes obtained and obviously bring publication bias. Lastly, the majority of studies included in our analysis that record smoking habits used variety questionnaires, which may reach an inaccurate conclusion.

Additionally, self-reporting of cigarette smoking in some studies may have been affected by statistical multiplicity difference.

To summarize, our meta-analysis shows that cigarette smoking may be related to increased risk of developing CML in a dose-dependent manner. However, heavy tobacco consumption is associated with a weak risk of CML, compared with those who smoked fewer than 20 cigarettes per day; owing to the limited number of studies. The risk for male individuals appears to be higher and associated with increasing pack-years. This suggests that smoking cessation should be advised for a positive impact on public health.

**Acknowledgements**

Ling Qin was involved in conception and design; Hui-Yang Deng provided the administrative support; Sheng-Jiang Chen contributed to the provision of study materials or patients; Wei Wei did the collection and assembly of data, as well as data analysis and interpretation.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

**Notes on contributors**

**Ling Qin**, the author of the article, is an associate professor, a PhD holder in medicine, master tutor, and is the chief physician of Department of Haematology.

**Hui-Yang Deng** is a postgraduate and a resident physician.

**Sheng-Jiang Chen** is a postgraduate, and an associate clinical professor.

**Wei Wei** is a postgraduate.

**References**

[1] Ren R. Mechanisms of BCR-ABL in the pathogenesis of chronic myelogenous leukaemia. Nat Rev Cancer. 2005;5:172–183.

[2] Hagemeijer A. Chromosome abnormalities in CML. Baillieres Clin Haematol. 1987;1:963–981.

[3] Faderl S, Talpaz M, Estrov Z, et al. Chronic myelogenous leukemia: biology and therapy. Ann Intern Med. 1999;131:207–219.

[4] Hehlmann R, Hochhaus A, Baccarani M. Chronic myeloid leukaemia. Lancet. 2007;370:342–350.

[5] Yin SN, Li GL, Tain FD, et al. A retrospective cohort study of leukemia and other cancers in benzene workers. Environ Health Perspect. 1989;82:207–213.

[6] 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.

[7] McLean D, Mannetje A, Dryson E, et al. Leukaemia and occupation: a New Zealand Cancer Registry-based case-control Study. Int J Epidemiol. 2009;38:594–606.
[8] Gentile G, Mele A, Monaco B, et al. Hepatitis B and C viruses, human T-cell lymphotropic virus types I and II, and leukemias: a case-control study. The Italian Leukemia Study Group. Cancer Epidemiol Biomarkers Prev. 1996;5:227–230.

[9] Winters N, Goldberg MS, Hystad P, et al. Exposure to ambient air pollution in Canada and the risk of adult leukemia. Sci Total Environ. 2015;526:153–176.

[10] Gudzenko N, Hatch M, Bazyka D, et al. Non-radiation risk factors for leukemia: a case-control study among chromium cleanup workers in Ukraine. Environ Res. 2015;142:72–76.

[11] Moura MA, Bergmann A, Aguiar SS, et al. The magnitude and temporal patterns of association between smoking and the risk of developing cancer in Brazil: a multicenter study. BMJ Open. 2014:e003736.

[12] Brownson RC, Reif JS. A cancer registry-based study of occupational risk for lymphoma, multiple myeloma, and leukaemia. Int J Epidemiol. 1988;17:27–32.

[13] 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.

[14] Vineis P, Veglia F, Garte S, et al. Genetic susceptibility according to three metabolic pathways in cancers of the lung and bladder and in myeloid leukemias in nonsmokers. Ann Oncol. 2007;18:1230–1242.

[15] Lichtman MA. Cigarette smoking, cytogenetic abnormalities, and acute myelogenous leukemia. Leukemia. 2007;21:1137–1140.

[16] Khalidyanidi S, Sikora L, Orlovskaya I, et al. Correlation between nicotine-induced inhibition of hematopoiesis and decreased CD44 expression on bone marrow stromal cells. Blood. 2001;98:303–312.

[17] Williams RR, Horn JW. Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients. Interview study from the Third National Cancer Survey. J Natl Cancer Inst. 1977;58:525–547.

[18] Severson RK. Cigarette smoking and leukemia. Cancer. 1987;60:141–144.

[19] Bjork J, Albin M, Welinder H, et al. Are occupational, hobby, or lifestyle exposures associated with Philadelphia chromosome positive chronic myeloid leukemia?. Occup Environ Med. 2001;58:722–727.

[20] Kabat GC, Augustine A, Hebert JR. Smoking and adult leukemia: a case-control study. J Clin Epidemiol. 1988;41:907–914.

[21] 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.

[22] 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.

[23] Mele A, Szko 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.

[24] Brown LM, Gibson R, Blair A, et al. Smoking and risk of leukemia. Am J Epidemiol. 1992;135:763–768.

[25] Herr R, Ferguson J, Myers N, et al. Cigarette smoking, blast crisis, and survival in chronic myeloid leukemia. Am J Hematol. 1990;34:1–4.

[26] Severson RK, Linet MS. Does cigarette smoking lead to the subsequent development of leukemia? Arch Intern Med. 1993;153:425–427.

[27] Wells GA, Shea B, O’Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. 2015 [website]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

[28] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177–188.

[29] Brownson RC, Chang JC, Davis JR. Cigarette smoking and risk of adult leukemia. Am J Epidemiol. 1991;134:938–941.

[30] Strom SS, Yamamura Y, Kantarijian HM, et al. Obesity, weight gain, and risk of chronic myeloid leukemia. Cancer Epidemiol Biomarkers Prev. 2009;18:1501–1506.

[31] Richardson DB, Terschüren C, Pohlabeln H, et al. Temporal patterns of association between cigarette smoking and leukemia risk. Cancer Causes Control. 2008;19:43–50.

[32] 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.

[33] Secretan B, Straif K, Baan R, et al. A review of human carcinogens – Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet Oncol. 2009;10:1033–1034.

[34] Pisanii P, Parkin DM, Bray F, et al. Erratum: Estimates of the worldwide mortality from 25 cancers in 1990. Int. J. Cancer. 1999;83:18–29. Int J Cancer. 1999;83:870–873.

[35] 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.

[36] Kaufman DW, Anderson TE, Issarragis S. Risk factors for leukemia in Thailand. Ann Hematol. 2009;88:1079–1088.

[37] Kane EV, Roman E, Cartwright R, et al. Tobacco and the risk of acute leukemia in adults. Br J Cancer. 1999;81:2065–2070.

[38] Blakely T, Barendregt JJ, Foster RH, et al. The association of active smoking with multiple cancers: national census-cancer registry cohorts with quantitative bias analysis. Cancer Causes Control. 2013;24:1243–1255.

[39] Vigliani EC, Saita G. Benzene and Leukemia. N Engl J Med. 1964;271:872–876.

[40] Brugnone F, Perbellini L, Maranelli G, et al. Effects of cigarette smoking on blood and alveolar air levels of benzene. Med Lav. 1990;81:101–106.

[41] Vines P, Alavanja M, Buffer P, et al. Tobacco and cancer: recent epidemiological evidence. J Natl Cancer Inst. 2004;96:99–106.

[42] 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;10:964.

[43] Archimbaud E, Maupas J, Lecluze-Palazzolo C, et al. Influence of cigarette smoking on the presentation and course of chronic myelogenous leukemia. Cancer. 1989;63:2060–2065.