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A Meta-Analysis of Prenatal and Maternal Risk Factors for Childhood Leukemia in Iran, Case-Control Studies Approach

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Abstract

Context: Few possible risk factors for childhood leukemia including environmental, genetic, and infectious causes can be explained by epidemiologic studies but the etiology of most childhood leukemia is unknown.
Objectives: In this systematic review and meta-analysis, we aimed to find the relationship between prenatal and maternal risk factors with leukemia children in Iran.
Data Sources: Relevant studies published in English databases (PubMed, Scopus, and ISI) and Persian databases (Magiran, Medlib, SID, and Iran Medex)) were systematically searched.
Study Selection: The study included all case-control studies that estimated the effects of prenatal and maternal risk factors on leukemia children in Iran during years 2004 to 2016, and a standardized manner was used for the extraction of information.
Data Extraction: After reviewing all searched articles (title, abstract, and entire text), irrelevant studies were excluded and related ones were selected.
Results: We identified 10 case-control studies. The first relative history of leukemia was associated with four times raises of leukemia in children aged 15 > years (OR = 4.58, 95% CI = 1.16 - 7.99). Other significant risk factors were mothers with birth order 3 $\leq$ and maternal age > 35, ORs for these factors were respectively (OR = 2.39, 95% CI = 0.79 - 3.99) and OR = 2.25, 95% CI = 1.09 - 3.41).
Conclusions: Our results indicate that among maternal and prenatal risk factors, birth order $\geq$ 3, birth weight < 2,500 g, and first relative history of leukemia increased the risk of childhood leukemia; in contrast, breastfeeding was a protective factor.

Keywords: Child Leukemia, Leukemia, Leukemia, Risk Factors, Systematic Review

1. Context

Leukemia is the most common type of malignancy in children 15 $\geq$ years old (1), higher prevalence was reported in high social rank people and in developed countries (2). Leukemia occurred about 10 times higher in adults (3). 5-year survival rate in patients with childhood leukemia in Iran was reported 0.65 in a systematic review (4). Our knowledge about the etiology of childhood leukemia, currently, is limited. Some possible factors including environmental, genetic factors (5), past infections (6), birth order (7), status of immunization, Prenatal exposures of the parents to tobacco and alcohol residence (8), cigarette smoking of mothers, age > 35, exposure to ionizing radiation, and the educational level of mothers (9), have been shown by epidemiologic studies. However, strong reliable evidence towards tobacco smoke exposure in prenatal and postnatal outcomes is limited (10, 11).

Breast milk feeding is an important predictor in order to protect children from leukemia, by stimulating and improving the immune system in the early years of life (12). A possible explanation for this is related to the biological nature of the disease, personal characteristic, birth weight, and genetic alterations are possible to be determinative (13). Enhancing the knowledge about these potential risk factors can be helpful in deflecting exposures and reducing the risk of cancer.

2. Objectives

In this Meta-analysis, we evaluated current epidemiological studies that had assessed the relationship between prenatal and maternal risk factors and leukemia in childhood in Iran.

3. Data Sources

We carried out systematic review to determine the probable association between maternal and prenatal risk factors and leukemia in childhood in Iran: birth weight, maternal age, history of mother's radiography, breast feeding, history of the mother's OCP use, history of abortion, birth order, and paternal smoking father and mother. Relevant studies published in English databases (PubMed, Scopus, and ISI) and Persian databases (Magiran, Medlib, SID, and Iran Medex)) were systematically searched.

4. Study Selection

4.1. Inclusion and Exclusion Criteria

We identified all case-control studies that had assessed the association between maternal and prenatal risk factors and leukemia in childhood in Iran from 2004 to 2016, as well, articles that had focused on children (aged 0 -15 years) and duplicate articles (multiple publications of the same population) were excluded.

4.2. Search Strategy

The search strategy for English databases was performed by the MeSH heading leukemia and/or keyword combinations in the title, keywords, affiliations (risk factors, smoking, maternal, paternal, birth weighing, maternal age, abortion, birth order, and Iran). We assessed articles that were focused on children (aged 0 - 15 years). After eliminating duplicated articles, relevancies were checked by title and abstract review. After we had been ensured about the relevance of articles, the full text was reviewed. In the full text review, articles that had reported at least one of the previously mentioned risk factors of leukemia in children were assessed. In order to increase the sensitivity of the arrival studies, all included studies were reviewed to identify more related articles through cross-referring publications. The search strategies in Pubmed were "((((((((((child leukemia[Title]) OR leukemia[Title]) AND risk factors) OR smoking) OR maternal) OR paternal) OR birth weight) OR weigh) OR abortion) OR birth order) AND Iran[Affiliation] AND ("case- control study"[Publication Type] OR "Case-Control Studies "[MeSH Terms] OR "Case-Control Studies "[All Fields])".

5. Data Extraction

After reviewing all searched articles (title, abstract, and entire text), irrelevant studies were excluded and related ones were selected. After key information was extracted from included articles: publications year, first author, study plan, subject's characteristic, subject's number, data gaining period, and assessed risk factors for childhood leukemia. Initial disagreements on the classification of study characteristics were resolved by discussion within the team of authors.

5.1. Statistical Analysis

At least two studies were necessary to perform Meta-analyses in relation to each risk factor. I^2 statistics was used to assess heterogeneity. We used the Fixed and random effects models which were calculated by the STATA by meta-analysis methods. For the meta-analysis of the variance of the odds ratio, fixed effects model was used in cases where heterogeneity was low ($I^2 \leq 25$), and when heterogeneity was moderate to high ($I^2 > 25$) the random effects model was used (11). Begg and Egger's test were used to assess the publication bias in included studies (14).

6. Results

6.1. Study Characteristics

We identified 573 article results from literature search strategy. 147 abstracts were recognized as potentially relevant for inclusion in the Meta analysis. 21 articles were reviewed in full text to identified final enrolled articles. Of these, 11 articles were excluded because of non-relevant and duplicated results. Finally 10 studies were included in the final Meta-analysis (Figure 1).

Table 1 shows details of 10 enrolled studies which were published from 2004 to June 2016. Published articles were in the English and Persian languages equally. The studies' reported results were from 4 different provinces. The majority of studies were conducted in Fars (n = 4). Others were conducted in Isfahan, Khorasan, Tehran, Arak, Guilan, and West Azarbaijan. Among the included studies, three of them evaluated the association of leukemia with mother and father's smoking, six articles the history of mother's radiography, three birth weight, two history of the mother's OCP use, four the history of abortion, six the high birth order 3 <, and three maternal age 35 <. All studies were case-control studies.

6.2. Meta-Analysis Results

Pooled analyses are shown in Table 2. Three studies reported the association between maternal age and leukemia in children. Results showed maternal age > 35 was not associated with leukemia in children (OR = 2.39, 95% CI = 0.79 - 3.99). The association of the history of mother's radiography with leukemia in children was not significant OR = 2.52, 95% CI = 0.65 - 4.39). The results of I^2 statistics showed a positive heterogeneity in articles (I^2

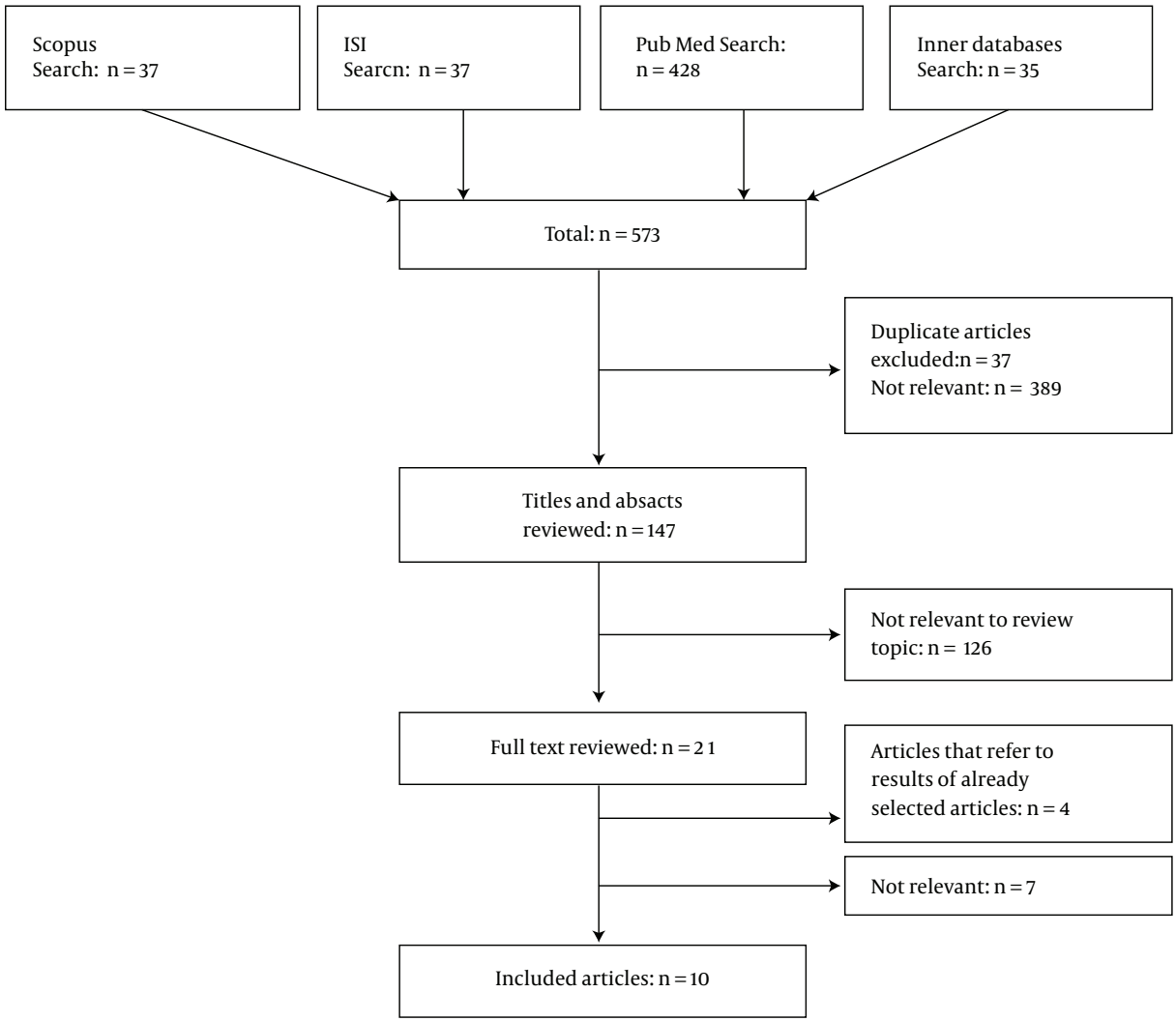

Figure 1. Flow Diagram of the Literature Search Process

= 94.0%; P = < 0.01). The two studies reported the potential role of mother's OCP use and probably of leukemia in children. The pooled OR showed the association was statistically significant for mother's OCP use and leukemia in children (OR = 2.46, 95% CI = 1.32 - 3.60).

Among all potential risk factors, breast feeding had an inverse association with childhood leukemia and (OR = 0.67, 95% CI = 0.13 - 1.48). The strongest significant association was found between the first relative history of leukemia and leukemia in children. The first relative history of leukemia was associated with four times enhancing the risk of leukemia in children aged 15 > years old (OR = 4.58, 95% CI = 1.16 - 7.99).

Prenatal exposure to smoking father was not indicated to enhance the risk of leukemia in children, the pooled OR was 1.33, 95% CI = 0.69 - 1.96. This result repeated in passive mothers' smoking with having a childhood leukemia child (OR = 6.54, 95% CI = -4.54 - 17.26). But prenatal exposure to smoking mother was indicated to enhance the risk of leukemia in children, the pooled OR was 2.59, 95% CI = 1.21 - 3.96. When we included all studies that had evaluated the effect of smoking on childhood leukemia (Prenatal exposure to smoking mother and father and passive mothers' smoking), we found an increased risk in the risk of childhood leukemia related to smoking (OR = 1.87, 95% CI = 1.01 - 2.73) (Figure 2).

In this study, birth order 3 $\leq$ increased the risk of leukemia in children significantly, (OR = 2.25, 95% CI = 1.09 -

Table 1. The Specifications of Case-Control Studies that Had Reported an Association Between Prenatal and Maternal Risk Factors and Leukemia

Ref.	First Author, Publish Date	Province	No. Participants		Age Range	Setting, Control Type	Assessed Risk Factor (s)
			Case	Control			
(15)	Hassanzadeh 2011	Fars	163	163	< 15	hospital-based, matched	Maternal age, Birth order, History of mother's radiography, History of abortion, birth weight
(16)	Hashemizadeh 2013	Mashhad	100	400	< 15	hospital-based, no matched	Paternal smoking mother
(17)	Hadi 2004	Fars	107	2014	< 15	hospital-based, matched	History of mother's radiography, Birth order, Brest feeding, Paternal smoking mother, Paternal smoking father,
(18)	Gholami 2011	West Azarbaijan	130	260	<15	hospital-based, matched	Maternal age, Birth order, Breastfeeding, Paternal smoking mother, Paternal smoking father
(19)	Zolala 2004	Fars	93	186	< 15	hospital-based, matched	Birth order, Brest feeding, Paternal smoking father, birth weight
(20)	Tabrizi 2015	Isfahan	22	100	< 15	hospital-based, no matched	History of mother's radiography
(21)	Damirchi 2013	Guilan	106	110	< 15	hospital-based, no matched	History of the father's smoking, Passivesmoking
(22)	Hassanzade 2012	Fars	141	141	< 15	hospital-based, matched	Maternal age, Birth order, History of mother's radiography, History of abortion, birth weight
(23)	Nikpour 2012	Tehran	300	300	< 15	hospital-based, no matched	birth order
(24)	Mobarak-Abadi, 2014	Arak	34	78	< 15	hospital-based, no matched	Brest feeding

Table 2. Pooled OR (Odds Ratio) of Related Risk Factors for Childhood Leukemia

Exposure	No. of Studies	Pooled OR	95% CIs	Heterogeneity	
				I^2, %	P Value
birth order 3 ≤	6	2.25	1.09 - 3.41	79.9	0.054
Maternal age > 35	3	2.39	0.79 - 3.99	0.00	0.919
Paternal smoking mother	3	6.94	0.84 - 15.73	71.8	0.029
Paternal smoking father	4	1.47	0.02 - 2.06	0.00	0.566
History of mother's radiography	6	2.52	0.65 - 4.39	0.00	0.940
Breast feeding	4	0.67	0.13 - 1.48	59.0	0.553
History of the mother's OCP use	2	2.46	1.32 - 3.60	46.0	0.584
History of abortion	4	1.19	0.63 - 1.76	62.0	0.048
Birth weight < 2500 g	3	1.75	1.75 - 2.42	0.00	0.673
Mothers with prenatal passive smoking	2	6.54	0.54 - 17.26	88.9	0.003
History of stillbirth	2	3.99	0.83 - 7.15	55.0	0.454
history of leukemia	3	4.58	1.16 -7.99	57.6	0.095

3.41, I^2 = 79.9%, 6 articles). The significant heterogeneity between the studies was not related to the date of publication (P = 0.76) and sample size (P = 0.86).

The possibility of publication bias was explored by different exposure assessment methods, but our results did not indicate any publication bias (Bias: 2.13, 95% CI = -12.75 - 17.01; P = 0.60), so we tried to consider the most of the published articles in this subject (Figure 3).

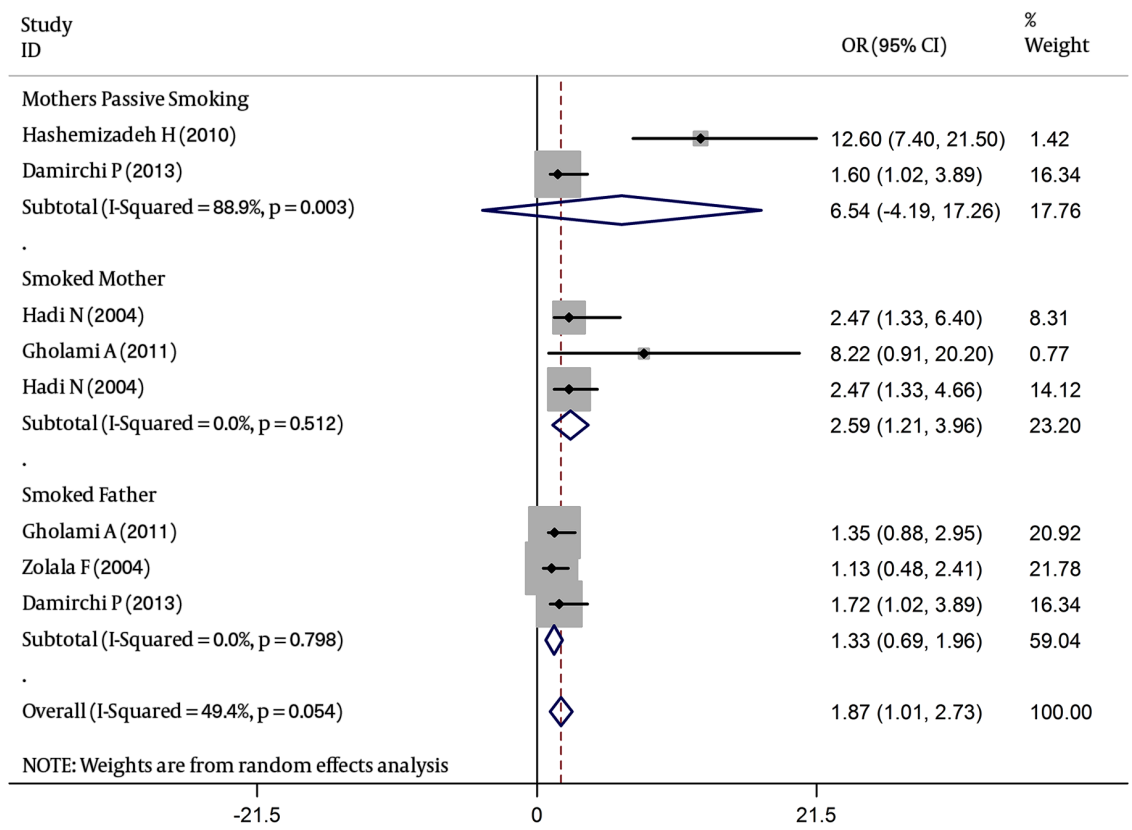

Figure 2. Forest Plot for the Effect of Smoking on Childhood Leukemia, Pooled and by Prenatal Exposure to Smoking (Mother and Father) and Passive Smoking Mothers by Statistical Methods in Iran

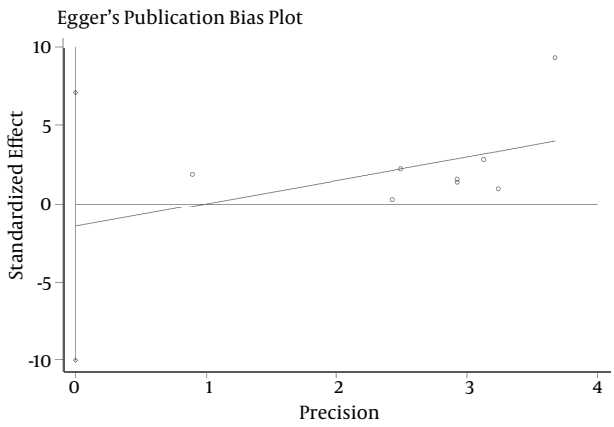

Figure 3. Beggs and Eggers Plot, Results for Selected (Birth Order) Risk Factor, Publication Bias

7. Discussion

In this review, we drew data systematically from over 10 studies on the association between maternal and prenatal risk factors and childhood leukemia reported between 2004 and 2016. Three of the studies were conducted in Fars province. The number of the cases ranged from 22 childhood leukemia in Tabrizi et al.'s study (20), to 300 childhood leukemia subjects in Nikpour et al.'s.(23). At least two studies were necessary to perform Meta-analyses relation for each risk factor. Age, birth order, history of mother's radiography, history of abortion, Brest feeding, paternal smoking mother and father, history of stillbirth, History of the mother's OCP use, history of leukemia and prenatal passive smoking in mothers. The increased risks were observed for the history of leukemia, birth order 3 $\leq$, birth weight < 2500 g, and history of the mother's OCP, but not for maternal age, history of mother's radiography, history of abortion, breast-feeding and paternal smoking father and mother.

In our results, the strong negative relationship was observed between breast-feeding and childhood leukemia. In the study by van Martin et al. (25) it is suggested that 50% to 100% of increasing the rate of breast-feeding would re-

duce 5% of cases of acute leukemia in children. The only protective factor for childhood leukemia in this study was breast-feeding.

Results, also, acknowledged previous findings towards the increased risk of childhood leukemia in prenatal cigarette smoking. The other available recent systematic review by lee et al. (3), revealed that paternal smoking and smoking before the pregnancy increased the risk of leukemia in children and suggested that smoking before birth is a potential risk for childhood leukemia. A plausible biological mechanism for the association could be cigarette DNA damage in human semen, which causes the breaking down of DNA strands and ultimately leads to childhood development of leukemia (12). Another article that evaluated the level of DNA damage supports this view (3), male smoker sperms being higher compared with non-smoking males.

Also, we observed a significant relationship between birth order 3 $\leq$ and the risk of leukemia in children. Inconsistency in our results with previous reports about birth order and leukemia childhood is existent (26), but a similar result taking into account 2,000 children in a register-based case-control study with age from 1 to 5 years has recently been reported (27).

About birth order position, this comes to our mind that children with a higher birth order position are more likely to be exposed to common infections early in life than children having a low birth order position (28), Birth order can be an indirect indicator that order position is significant with using more of vaccination programs and the use of day care.

Our systematic review has a number of limitations. At first, this meta-analysis was limited by studies based on the individual data, and population based study is limited.

Supplementary analysis to adjust potential confounders was not preformed, these include maternal age, education, parity, smoking and folic acid intake, or maternal age. Second, some studies (5 studies) allocated not randomized control groups. Third, most sample sizes were small (50% > of studies less than 100 subjects), so the statistical power reduced in pooled estimates. Fourth, despite no significant publication bias in this study, it empirically enrolled all related studies.

8. Conclusions

Our results indicate that among maternal and prenatal risk factors, the strongest significant effect was the first relative history of leukemia, other associated risk factors were birth order 3 $\leq$, and Birth weight < 2500 g.

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