Abstract

Nowadays, due to the extensive use of mobile phones and their portability, exposure to the electromagnetic non-ionizing waves is inevitable. Several research has studies the association between the malignant brain tumor of Glioma and the use of mobile phone, the results of which were contradictory. Therefore, the present study intended to conduct a systematic meta-analysis review on the association between the use of mobile phone and the risk of malignant brain tumor. Using the quality assessment scale of Newcastle-Ottawa Scale (NOS), it was realized that 7 out of 9 case-control studies and 2 out of 3 Cohort studies ranked high. In overall, 12 studies (9 case-control and 3 Cohort) were reviewed in the present meta-analysis. The heterogeneity of case-control and cohort studies was respectively 81% (P<0.001) and 47% (P=0.048) and in overall it was 79% (P<0.001). The mean odds ratio of case-control and cohort studies was estimated about REM=1.03 (P=0.762), FEM=0.91 (P=0.597) respectively and it was REM=1 (P=0.996) in overall. The results of the current study did not confirm the assumption that the increased risk of Glioma malignant brain tumor is associated with the use of mobile phones.

Keywords: Mobile Phone; Malignant Tumor; Brain; Glioma; Systematic Review; Meta-Analysis.
1. Introduction

Waves are divided into two ionizing and non-ionizing categories [1]. One of the non-ionizing waves is electromagnetic waves. Nowadays, exposure to electromagnetic waves emitted by mobile phones (low-energy electromagnetic waves in the range of 800 to 2000 MHz) is inevitable [2,3]. This exposure has caused many concerns in the field of health. Mobile phones have been used since 1983 and, Nowadays, a majority of people are using mobile throughout the world [4]. For instance, about 129.86 out of the 140-million Japanese population, 91% of Americans and 94% of British people used mobile phone in 2011 [5-7].

Furthermore, mobile phone ownership had increased from 12% in 1999 to 76% in 2009. According to Hardell et al. (2011) in Sweden and IARC Interphone, both the IARC1 and WHO classified the emitted waves of mobile phones into the class 2B (Possible Carcinogenic Class) [9,8]. Many research has reported that exposure to the electromagnetic waves of mobile phones causes headaches, poor concentration and memory, fatigue, drowsiness and nervousness in human [9,10], interface with the performance of cardiac batteries (at a distance of less than 5 cm) in people with heart disease [11], and adverse effects on reproductive system like male infertility [13]. One of the damaging effects of exposure to electromagnetic waves on health is brain damages especially malignant brain tumor [14]. Studies have shown that brain tumor is more prevalent in the side of the head that is more ipsilateral with mobile phone compared to the other parts of the brain [15,16].

On the contrary, several research has revealed that the emitted waves by mobile phones increase the temperature of brain tissues and its surrounding tissues to a slight extent [17]. Furthermore, there are inconclusive evidences about potential mechanisms of carcinogenesis of these waves [9]. Many investigations have been conducted into the effects of electromagnetic waves of mobile phones on the risks of brain tumor. The findings of these studies were contradictory. For instance, Frumkin et al. and Cardis et al. found that exposure to electromagnetic waves of mobile phone do not cause any damage to DNA cells [15,18] and do not increase the risk of brain tumor [19]. Conversely, according to several studies, exposure to electromagnetic waves of mobile phones can increase the risk of brain tumor significantly [20-24]. Consequently, the current study aimed at conducting a systematic meta-analysis review of the related literature and studies on the association between the use of mobile phone and the risk of malignant brain tumor (Glioma; 60% of all central nervous system tumors).
2. Materials and Methods

The purpose of the present study was a systematic meta-analysis review of the association between electromagnetic field of mobile phone and the risk of malignant brain tumor.

To this end, several databases including SID, Irandoc, Scopus, Pubmed and ISI Web of Science were used to collect related studies and data throughout Iran and the world.

1.2. Criteria and quality assessment of studies

First, a list of titles and abstracts of all the studies available in the aforesaid databases was compiled by three researchers (Ya, F., Ha, K. & Bi, M.) to avoid bias on the part of the researchers. The titles and abstracts of the studies conducted from 2000 to 2016 were examined independently.

The search took two weeks from 23 March 2016 to 09 April 2016 and the related studies were included in the present research independent of each other and based on blinding the initial assessment. The similar studies were excluded. The main inclusion criterion of different article into the present study was their reference to electromagnetic field of mobile phones and the risk of malignant brain tumor.

The studies which were not a part of seminal research and were associated with clinical decision-makings and investigations irrelevant to brain tumor all were excluded from the present study. Second, the abstract of the selected studies was reviewed by the researcher using the standard STROBE\(^1\) checklist.

STROBE consists of 43 various sections which evaluates diverse methodological aspects of a study including sampling methods, measurement of variable, data statistical analysis and research objectives [25]. The minimum and maximum attainable score was considered 40 and 45 respectively in this checklist. In finale, the top articles which attained the minimum score (40) of STROBE checklist entered the study and their data were collected for a meta-analysis. Furthermore, Funnel Plot and Egger’s test were used in order to determine Publication Bias.

2.2. Data Collection

The present study meta-analyzed 12 articles (9 case-control and 3 cohort), conducted from 2005 to 2014, all of which adhered to a quite similar methodology. The important information required for data analysis including the subject, title, methodology, type of research, period of investigation, score of each study in NOS\(^1\) system, RO\(^2\) of malignant brain tumor, sex of participants, sample size and confidence level were collected.
3.2. Quality of studies

The case-control and cohort studies were scored according to the quality assessment criteria of NOS including Exposure, Comparability and Selection. The score range in NOS system is 0 to 9. The current study divided the score of articles into low score (<7) and high score (≥7).

4.2. Data statistical analysis and synthesis

Data meta-analysis was performed by Comprehensive Meta-Analysis V. 2.2.064. To estimate the heterogeneity of studies, $I^2$ Higgins was used. Accordingly, Random Effect Model and Fixed Effect Model were used for the meta-analysis of the studies whose $I^2$ was greater and smaller than 50% respectively. The subgroups included the score of quality assessment i.e. qualitative score (low & high) and the type of study. Moreover, the significance level was $P<0.05$ in the present study.

3. Results

1.3. Identifying related studies

In overall, 376 articles were found searching Scopus, Ovid, Irandoc, PubMed, Embase and ISI Web of Science databases. About 207 articles were excluded at the stage of Eligibility due to irrelevant title, abstract and other reasons. About 157 out of the rest 169 articles were also excluded due to their reported correlation, hazard risk, mean missing key data for meta-analysis, letters, comments and correspondences. Ultimately, 12 articles (9 case-control & 3 cohort studies) were selected for the meta-analysis in the present study (Figure 1). Despite the investigation into the use of mobile phone, the studies of Hardell et al[26,23], Warren et al. [27] and Muscat [28] were also excluded from the present meta-analysis study due to the undistinguished malignant and benign brain tumors in their studies.

Figure 1. Flow diagram for identification of relevant case-control and cohort studies.
2.3. Characteristics of studies

Table 1 presents the overall characteristics of the studies including the year of publication, country, type of study, type of tumor, period of investigation, field of study and the results. The years of investigation ranged from 1990 to 2009 and they were published from 2005 to 2014.

An overall 27,694 individuals (119,84 patients & 15,710 control) participated in 18 articles. The mean age of the participants was 49.8 years. Out the overall participants, about 26.6% used digital phones, 29.6% used analog phones, 37.6% used cordless phones, and 18.6% used mobile phones. However, mobile phones were overall used by all the participants.

Table 1. Overall characteristics of the 16 case-control articles and 2 cohort articles included in the final analysis.

Based on the quality assessment criteria of NOS, 7 out of 9 case-control studies (Table 2) and all the 3 cohort studies (Table 3) scored ≥7.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year of Publication</th>
<th>Country</th>
<th>Study Design</th>
<th>Study Period</th>
<th>Study Length (years)</th>
<th>Type of Tumor</th>
<th>Type of Phone and Exposure</th>
<th>Outcome</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benson et al</td>
<td>2013</td>
<td>United Kingdom</td>
<td>Cohort</td>
<td>1999-2005</td>
<td>7</td>
<td>Glioma, meningioma or non-CNS cancers</td>
<td>Mobile phones; Non-subscribers and subscribers</td>
<td>Mobile phone use was not associated with increased incidence of glioma, meningioma or non-CNS cancers</td>
<td>[29]</td>
</tr>
<tr>
<td>Hardell et al</td>
<td>2010</td>
<td>Sweden</td>
<td>Case-Control</td>
<td>1997–2003</td>
<td>7</td>
<td>Malignant brain tumors (glioma)</td>
<td>Mobile phone, Cellular or cordless phone; use and not use</td>
<td>Confirmed our previous results of an association between mobile phone use and malignant brain tumors</td>
<td>[30]</td>
</tr>
<tr>
<td>Hardell et al</td>
<td>2013</td>
<td>Sweden</td>
<td>Case-Control</td>
<td>2007-2009</td>
<td>3</td>
<td>Malignant brain tumors (glioma)</td>
<td>Mobile phone, Cellular or cordless phone; use, not use</td>
<td>Provide support for the hypothesis that RF-EMFs play a role both in the initiation and promotion stages of carcinogenesis</td>
<td>[31]</td>
</tr>
</tbody>
</table>

**Table 1.** Overall characteristics of the 16 case-control articles and 2 cohort articles included in the final analysis.
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Study Location</th>
<th>Study Type</th>
<th>Period</th>
<th>Outcome</th>
<th>Mobile Phone Use</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lahkola et al</td>
<td>2005</td>
<td>5 North European countries: Denmark, Finland, Norway, Sweden, and United Kingdom; followed a protocol of the interphone Study</td>
<td>Case-Control</td>
<td>2000-2004</td>
<td>4</td>
<td>Malignant brain tumors (glioma)</td>
<td>Mobile phone (analog and digital); regular use and never or no regular use</td>
</tr>
<tr>
<td>Aydin et al</td>
<td>2011</td>
<td>Denmark, Sweden, Norway, and Switzerland</td>
<td>Case-Control</td>
<td>2004-2008</td>
<td>4</td>
<td>Malignant brain tumors (glioma)</td>
<td>Mobile phone, Cellular or cordless phone; use or not use</td>
</tr>
<tr>
<td>Coureau et al</td>
<td>2014</td>
<td>France</td>
<td>Case-Control</td>
<td>2004-2006</td>
<td>2</td>
<td>Malignant and benign brain tumors</td>
<td>Mobile phone, analog and digital and cordless phones; ever regular use and never use</td>
</tr>
<tr>
<td>Linet et al</td>
<td>2006</td>
<td>United States</td>
<td>Case-Control</td>
<td>1998-2000</td>
<td>2</td>
<td>Non-Hodgkin's lymphomas</td>
<td>Mobile phone, Cellular phone; lifetime ever use and never use</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Year</td>
<td>Country</td>
<td>Study Design</td>
<td>Time Period</td>
<td>Case</td>
<td>Control</td>
<td>Risk Factor</td>
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</tr>
<tr>
<td>Mild et al 2007</td>
<td>Sweden</td>
<td>Case-Control</td>
<td>1997-2003</td>
<td>Malignant and benign brain tumors</td>
<td>Mobile phone (analog and digital); regular use and never or no regular use</td>
<td>Malignant brain tumors, increased with latency period, especially for astrocytoma grade III–IV</td>
<td></td>
</tr>
<tr>
<td>Cardis et al 2011</td>
<td>Australian, Canadian, French, New Zealand</td>
<td>Case-Control</td>
<td>2000-2004</td>
<td>Malignant and benign brain tumors</td>
<td>Mobile phone, Cellular or cordless phone (analog and digital); use and no use</td>
<td>Increased risk of glioma in long-term mobile phone users with high RF exposure and of similar, but apparently much smaller, increases in meningioma rise</td>
<td></td>
</tr>
<tr>
<td>Hardell et al 2014</td>
<td>Sweden</td>
<td>Case-Control</td>
<td>1997–2003 and 2007–2009</td>
<td>Malignant brain tumors</td>
<td>Mobile phone (analog and digital); regular use and never or no regular use</td>
<td>The OR increased statistically significant both per 100 h of cumulative use, and per year of latency for mobile and cordless phone use.</td>
<td></td>
</tr>
<tr>
<td>Frei et al 2011</td>
<td>Denmark</td>
<td>Cohort</td>
<td>1990-2007</td>
<td>Malignant and benign brain tumors</td>
<td>Mobile phone (analog and digital); regular use and never or no regular use, Cellular phone</td>
<td>There were no increased risks of tumors of the central nervous system, providing little evidence for a causal association</td>
<td></td>
</tr>
</tbody>
</table>
There were no evidence for an association between tumor risk and cellular telephone use among either short-term or long-term users [39].

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Denmark</th>
<th>Cohort</th>
<th>1982 - 1995 to 2002</th>
<th>13</th>
<th>Malignant and benign brain tumors</th>
<th>Mobile phone (analog and digital); regular use and never or no regular use, Cellular phone; ever regular use and never use</th>
<th>Non-subscribers and subscribers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schuz et al</td>
<td>2006</td>
<td></td>
<td></td>
<td></td>
<td>13</td>
<td></td>
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<tr>
<td>Schuz et al 2006</td>
<td>Denmark</td>
<td>Cohort</td>
<td>1982 - 1995 to 2002</td>
<td>13</td>
<td>Malignant and benign brain tumors</td>
<td>Mobile phone (analog and digital); regular use and never or no regular use, Cellular phone; ever regular use and never use</td>
<td>There were no evidence for an association between tumor risk and cellular telephone use among either short-term or long-term users</td>
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</tbody>
</table>

Table-2. Methodological quality of studies included in the final analysis based on the Newcastle-Ottawa scale for assessing the quality of case-control studies.

<table>
<thead>
<tr>
<th>Year</th>
<th>Selection (Score)</th>
<th>Compatrability (Score)</th>
<th>Exposure (Score)</th>
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<tbody>
<tr>
<td></td>
<td>Adequate definition of patient cases</td>
<td>Representativeness of patient cases</td>
<td>Selection of controls</td>
</tr>
<tr>
<td>Study</td>
<td>Adequate definition of patient cases</td>
<td>Representativeness of patient cases</td>
<td>Selection of controls</td>
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<td></td>
<td>Adequate definition of patient cases</td>
<td>Representativeness of patient cases</td>
<td>Selection of controls</td>
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<td>Adequate definition of patient cases</td>
<td>Representativeness of patient cases</td>
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<td>Adequate definition of patient cases</td>
<td>Representativeness of patient cases</td>
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<td>Adequate definition of patient cases</td>
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<td>Adequate definition of patient cases</td>
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<td>Selection of controls</td>
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<td>Adequate definition of patient cases</td>
<td>Representativeness of patient cases</td>
<td>Selection of controls</td>
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<td>Adequate definition of patient cases</td>
<td>Representativeness of patient cases</td>
<td>Selection of controls</td>
</tr>
<tr>
<td></td>
<td>Adequate definition of patient cases</td>
<td>Representativeness of patient cases</td>
<td>Selection of controls</td>
</tr>
</tbody>
</table>

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Before excluding the studies with a higher CI\(^1\) than other studies, the heterogeneity of case-control and cohort studies was respectively 87% (<0.001) and 67% (P=0.048) and it was 85% (P<0.001) in overall (Figure 2). After excluding the studies of Hardell (2010), Frei et al. and Mild et al., the heterogeneity of case-control and cohort studies was estimated respectively 81% (P<0.001), 47% (P=0.048) and it was 79% (P<0.001) in overall. Therefore, Random Effect Model and Fixed Effect Model were used for case-control and cohort studies respectively, and the Random Effect model was used for all studies in overall in order to calculate the mean odds ratio.

### 3.3. Use of Mobile Phone and Risk of Brain Tumor

The confidence interval obtained from Egger’s test before and after the exclusion of the aforesaid studies was respectively 95% CI (0.8 to 3.8) (Figure 4A) and 95% CI (-0.15 to 3.61) (Figure 4B). Thus, the erratum\(^1\) reached to an acceptable level after excluding the studies. Before excluding the aforementioned three studies with a low weight percentage, the REM\(^2\) was 1.22 (P=0.117), 1.05 (P=0.809) respectively for case-control and cohort studies and 1.18 (P=0.138) in overall (Figure 2). After excluding the studies with low weight percentage, the mean odds ratio (OR) of case-control and cohort studies was estimated about REM=1.03 (P=0.762), FEM=0.91 (P=0.597) respectively and it was REM=1 (P=0.996) in overall.
(Figure 3) indicating that the use of mobile phone is not associated with any increase or decrease in the risk of brain tumor.

4. Discussion

The results of the present meta-analysis showed that according to the high quality studies, there is not any significant association between the use of mobile phone and the risk of malignant brain tumor. In overall, using mobile phones cannot increase the risk of brain tumor (P-value>0.05).

Although several studies addressing vivo animal models and vitro cancer cell lines indicated that exposure to low frequencies of electromagnetic waves emitted by mobile phones causes biological changes in cytoplasm membrane, nucleus of cell and gene and eventually makes the brain cells become cancerous [43-40], the results of the present meta-analytical study revealed that there is not any significant association between the use of mobile phone and the risk of malignant brain tumor. These differences in the findings may contribute to the presence of confounders such as age [44], nutrition [45], other radiations [46] and errors in studies. Like the present study, Regina et al., who studied 480 rats exposed to microwaves with a frequency of 835.62 MHz, did not observe any significant increase in the risk of malignant brain tumor of Glioma. Nevertheless, it should be noted that the power statistics of the current study was low due to the low number of control (n=160) [47].

Before excluding the studies of Hardell et al. (2010), Mild et al. and Frei et al. with low weight percentage (wt%), the results indicated that the risk of malignant brain tumor increases in an insignificant manner (Table 2). Whereas, after excluding the aforesaid studies, the Publication Bias reached to an acceptable level and the risk of malignant brain tumor decreased (Figure 3).

Figure 2. Forest plot of meta-analysis on EMF of mobile phones with malignant brain tumors before exclude low score studies.
Figure 3. Forest plot of meta-analysis on EMF of mobile phones with malignant brain tumors after exclude low score studies.

Since the CI exceed 0 in Egger’s test, there is not any significant erratum in overall [Egger’s Test; Intercept = 1.72 CI (-0.15 to 3.61)]. As displayed in Figure 4, the reverse funnel plot indicated the absence of overall publication error (erratum) amongst the studies.

![Funnel plot of the studies included in the meta analysis](https://via.placeholder.com/150)

Figure: Funnel plot of the studies included in the meta analysis (A; before exclude high CI studies, B; after exclude high CI studies).
Exposure to ionizing waves causes brain tumor [48]. Due to the high energy level of these radiations, the breakage and rearrangement of DNA appears predominantly. Therefore, the diagnosis of latency period will be simpler and more precise than the exposure to non-ionizing radiations such as the waves emitted by mobile phones[49].

Considering the fact that non-ionizing radiations, like radiations emitted by mobile phones, are not potent enough to directly damage DNA, they are considered the second risk factor after ionizing radiation in terms of carcinogenetic risk. The latency period of brain tumor due to the exposure to mobile phone’s radiations (non-ionizing) is less than ionizing radiations (<5 years)[50]. Since the causes of brain tumor have not yet been identified completely, one cannot define the latency period conclusively; hence, the range of 1 to 10 years is considered as the minimum latency period[53-51].

Like the other four meta-analyses, the overall results of the present study showed that the use of mobile phone cannot significantly increase the risk of brain tumor[57-54]. Unlike the present study, Myung et al. found that according to the studies with high score, there is a significant positive association between the use of mobile phone and the risk of malignant brain tumor[57]. The current study did not consider the blinding experiments whereas Myung et al. used blinding experiments. On the other hand, Myung et al. studied different types of phones including analog, digital and cordless phones as well. Like Hardell et al. which used blinding experiments, the results of the present study showed that according to almost 5 reviewed studies, there is not any significant difference between the case (patient) and control groups in terms of exposure to electromagnetic waves emitted by mobile phones[59,58,31,30,24]. On the contrary, other studies which did not use blinding experiments, except for Song et al., indicated a significant increase in the risk of brain tumor due to the use of mobile phones[60].

The limitations of the current study included language (except for English and Persian), undistinguishing blinding from un-blinding experiments, and not considering the effect of passage of time on the incidence of malignant brain tumor. It is recommended to determine the effects of confounders such as age, sex, type of study, period of study, electrical and magnetic fields on the heterogeneity of studies in the prospective meta-analyses.

5. Conclusions

The results of the this systematic meta-analysis showed that there is not ant significant association between exposure to electromagnetic waves of mobile phones and the risk of brain tumor. Despite the disassociation between the use of mobile phone and the risk of malignant brain tumor, more and newer investigations are required to draw upon more precise
conclusion in this regard due to the few number of studies reviewed in the current meta-analysis. To conclude, the results of the this study did not confirm the assumption that the increased risk of brain tumor is associated with the use of mobile phones.

7. References


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