RESEARCH ARTICLE

Electromagnetic Field Exposure and Male Breast Cancer Risk: A Meta-analysis of 18 Studies

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Abstract

Background: The possibility that electromagnetic fields (EMF) exposure may increase male breast cancer risk has been discussed for a long time. However, arguments have been presented that studies limited by poor quality could have led to statistically significant results by chance or bias. Moreover, data fo the last 10 years have not been systematically summarized. Methods and Results: To confirm any possible association, a meta-analysis was performed by a systematic search strategy. Totals of 7 case-control and 11 cohort studies was identified and pooled ORs with 95% CIs were used as the principal outcome measures. Data from these studies were extracted with a standard meta-analysis procedure and grouped in relation to study design, cut-off point, exposure assessment method, adjustment and exposure model. A statistical significant increased risk of male breast cancer with EMF exposure was defined (pooled ORs = 1.32, 95% CI = 1.14 -1.52, $P < 0.001$), and subgroup analyses also showed similar results. Conclusions: This meta-analysis suggests that EMF exposure may be associated with the increase risk of male breast cancer despite the arguments raised.

Keywords: Electromagnetic fields - male breast cancer - meta-analysis

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Introduction

Electromagnetic fields (EMF) are composed of electric fields and magnetic fields, and produced by a wide range of electric devices ranging from washing machines to electric power lines. Due to the ubiquity of EMF in residential, commercial and occupational settings, most of us are exposed to some levels of EMF, and those exposed in occupational settings may suffer from higher levels of exposure (Floderus et al., 1994; Nichols et al., 2005; Bellieni, 2012).

The potential carcinogenesis of EMF has been widely studied since 1979, and epidemiologic studies have shown the increased risk (Atzmon et al., 2012; Repacholi, 2012). However, its etiology remains elusive. Due, in part, to the associations found between higher level residential magnetic fields exposure and risk of childhood cancers (Wertheimer et al., 1979), the International Agency for Research on Cancer (IARC) concluded that even extremely low frequency (0-100Hz) EMF (ELF-EMF) exposure are possibly carcinogenic to humans.

Breast cancer is now the most common cancer in developed and developing regions, and the fifth cause of death from all cancers (458,000 deaths) worldwide (Ferlay et al., 2010). Of these breast cancer incidents, male breast cancer accounts for approximately 1%. But the incidence of male breast cancer has risen over the past few decades yet its etiology is not understood.

Epidemiologic studies, including both in vivo and vitro experimental studies have shown an association between EMF exposure and breast cancer (Feychting et al., 2006). However, some epidemiologic studies found no or weak association (Floderus et al., 1999; Johansen et al., 1998; Pollan et al., 2001; Nichols et al., 2005). In the recent years, some researchers argued that early studies were often limited by poor design, small numbers, crude information and underdeveloped exposure measuring methods, leading to statistical significant results by chance or bias (Feychting et al., 2006). It is important to reassess the association of EMF exposure and male breast cancer over the past 24 years.

This meta-analysis is to reassess the potential risk of male breast cancer associated with EMF exposure from all available sources, not only for contributing to the possible etiology of male breast cancer but also for ascertaining the potential risk factor of pubic health.

Materials and Methods

Search

The initial search for studies was performed using the following electronic databases: PubMed, Medline,

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Embase, Cochrane Library, Web of Science and the Chinese National Knowledge Infrastructure (CNKI). We employed a search strategy combined of Mesh term and text word, with the terms of "breast cancer", "breast neoplasm", and "electromagnetic fields", from 1979 to December 2012. Reference lists of included studies were also searched for relevant publications. Reviews, comments, and letters were also checked for studies missed.

Selection

Titles and abstracts of all citations and literatures were reviewed to identify eligible studies, according to the following criteria (Chen et al., 2010): (1) only published studies were included; (2) The publication was a population-based case-control or cohort study investigating the association between EMF and breast cancer risk in males, including studies that set multiple cancers as the endpoint; (3) all cases were first diagnosed as invasive or in situ breast cancer; (4) the study reported the sample size, number of cases and controls (or cases and cohort size), risk estimates and 95% CIs; (5) the most recent or largest population would be used if the publication used the same or overlapping data; and (6) language was restricted to English or Chinese.

Data extraction

Data were extracted from all eligible studies, including author names, year of publication, participant ages, number and sources of cases and controls, study period, confounding variables, EMF exposure assessment methods, occupation, cut-point, risk estimates and 95% CIs.

Validity assessment

The Ottawa-Newcastle Assessment Scale for case-control and cohort studies was used to assess the quality of eligible studies (Wells, 2003). Selection bias, comparability of the included studies, and assessment of exposure for case control studies and assessment of breast cancer for cohort studies were the three main factors considered in the quality assessment. The literature review, study identification, and data extraction were operated by two reviewers (J. Sun and X. Li) independently. Any conflicts were resolved by consensus.

Quantitative data synthesis

Pooled odds ratios and 95% CIs were calculated to assess the strength of association between EMF exposure and male breast cancer risk. The heterogeneity among studies contributing to the pooled Odds Ratios (ORs) was examined by Chi-square and the statistic of the inconsistency index (I^2). The I^2 statistic was defined as the percentage of variability among studies due to total heterogeneity with values >50% representing the possibility for substantial heterogeneity (Higgins et al., 2003). A fixed effects model was used to calculate pooled ORs if the heterogeneity among studies was acceptable, or a random effects model would be used. Subgroup analyses were performed by study design, cut-point, exposure assessment method, adjustment and exposure model. Possible publication bias was investigated by using funnel plots and Begg's test (Begg et al., 1994; Egger et al., 1997). If asymmetrical funnel plots presented, further assessment of the possible publication bias was performed using the Duval and Tweedie's nonparametric "trim-and-fill" procedure (Duval et al., 2000). All analyses and production of forest and funnel plots were conducted with STATA version 11.0 (Stata Corporation, college Station, Texas), and statistical significance for all tests and models was a two-sided P value of 0.05.

Ethics

This study needs no approval from Institutional Review Board because only anonymous published data were used.

Results

Identified studies

A total of 399 studies were identified using our search strategy. Of these 289 of them were eliminated for unrelated titles and 110 for unrelated abstracts (Figure 1). Upon further review for full-text articles, 19 of the remaining 37 studies were excluded for insufficient data, female breast cancer study, case-only study, duplicated data, and non-English or non-Chinese language. In the end 18 studies were eligible for the meta-analysis.

Characteristics of included studies

Seven of the 18 studies were case-control studies (57 cases and 223 controls combined) (Demers et al., 1991; Loomis, 1992; Rosenbaum et al., 1994; Stenlund et al., 1997; Cocco et al. ,1998; Feychting et al., 1998; Park et al., 2004) and the other 11 were cohort studies (299 cases and a total size of 7 486 643) (Matanoski et al., 1991; Tynes et al., 1992; Guenel et al., 1993; Floderus et al., 1994; Theriault et al., 1994; Savitz et al., 1995; Fear et al., 1996; Johansen et al., 1998; Floderus et al., 1999; Pollan et al., 2001; Nichols et al., 2005). Two studies involved residential exposure (Feychting et al., 1998; Park et al., 2004) and the remaining16 studies were occupational exposure. Nine studies provided quantitative exposure level (Guenel et al., 1993; Floderus et al., 1994; Theriault et al., 1994; Savitz et al., 1995; Stenlund et al., 1997; Feychting et al., 1998; Johansen et al., 1998; Floderus et

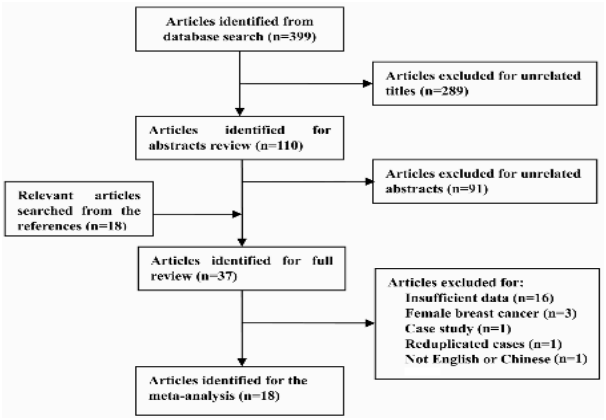

Figure 1. Flow Chart of Identification of Studies in the Meta-analysis

Table 1. General Characteristics of Studies Included in the Meta-analysis of Male Breast Cancer and Exposure to Electromagnetic Fields

1st author, year	NO. of cases/Total NO. of population , nationality	Exposure assessment method	Cut- Point (μT)	Confounding variables	Study Quality Score	Risk estimate (95%CI)
Case-control studies						
Demers, 1991	33/59, American	Job title	—	Jewish religion, education, diagnostic X-rays, serious head injuries, Quetelet index	7	OR=1.8 (1.0, 3.7)
Loomis, 1992	3/33, American	Job title	—	—	4	MOR=2.2 (0.6, 7.8)
Rosenbaum, 1994	6/39, American	Job title	—	Age, county, race	5	OR=0.6 (0.2, 1.6)
Stenlund, 1997	3/71, Swedish	Job title linked to job exposure matrix based on measurements	0.15	Age, education, solvents, family history of breast cancer	7	OR=1.5 (0.3, 8.3)
Cocco, 1998	9/63, American	Job exposure matrix including estimates of intensity and probability of exposure	—	Age, marital status, socioeconomic status, BMI, alcohol use, cigarette smoking	6	OR=1.0 (0.5, 2.1)
Feychting, 1998	2/11, Swedish	Real calculations of magnetic fields in homes	0.1	Age, socioeconomic status	9	RR=2.1 (0.3, 14.1)
Park, 2004	1/4, Korean	Electric power output	—	Age	5	MRR=1.09 (0.03, 34.7)
Cohort studies						
Matanoski, 1991	2/50 582, American	Job title, personal monitoring of a sample of workers	—	—	5	SIR=6.5 (0.8, 23.5)
Tynes, 1992	12/37 945, Norwegian	Job title, type of exposure	—	—	6	SIR=2.07 (1.07, 3.61)
Guenel, 1993	2/1 401 967, Dane	Job title, potential exposure	0.3	—	5	SIR =1.36 (0.16, 4.91)
Theriault, 1994	7/223 292, Canadian and French	Job-exposure matrix based on job title, current magnetic field measurements, estimation of past levels	0.16*	Occupational carcinogens, socioeconomic status, smoking (HQ)	7	SIR=0.85 (0.34, 1.75)
Floderus, 1994	3/36 207 540 (person-years) Swedish	Job title, magnetic field measurements	0.18	Age	6	RR=4.9 (1.6, 11.8)
Savitz, 1995	6/138 905, American	Job-exposure matrix based on job title, magnetic field assessment, chemical exposure assessment	0.60**	Age, calendar time, race, social class, work status, PCB and solvent exposure	8	SMR=0.80 (0.29, 1.74)
Fear, 1996	14/252 663, British	Job title	—	Age, social class, cancer registry of origin	6	PRR=1.29 (0.71, 2.17)
Johansen, 1998	2/26 135, Dane	Job exposure matrix based on job title, ELF-EMF measurements in 1993 partly judgments, asbestos at work	0.09	Age, calendar time	6	SIR=0.50 (0.1, 1.8)
Floderus,1999	37/1 596 959, Swedish	Job exposure matrix	0.116	Age	6	RR=1.2 (0.7, 1.9)
Pollen, 2001	203/1 779 646, Swedish	Job exposure matrix based on job title, magnetic field assessment	0.12	age, period, geographical category	7	RR=1.31 (0.94, 1.81)
Nichols, 2005	11/72 889, British	Job title, work location	—	Age, calendar time	8	SMR=1.44 (0.72, 2.58)

MOR, mortality odds ratio; MRR, mortality relative risk; NO, number; OR, odds ratio; PMA, proportional mortality analysis; PRR, proportional registration ratio; RR, relative risk; SMR, standardized mortality ratio; SIR, standardized incidence ratio; *median value; **μT-years is used as an unit here

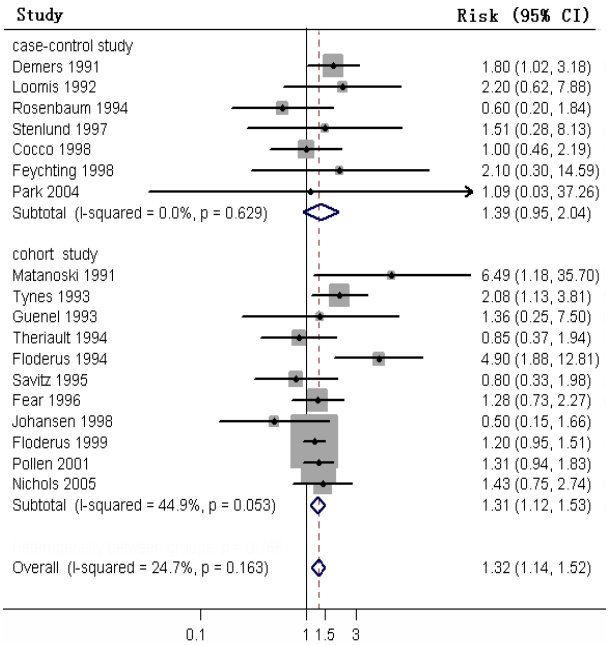

Figure 2. The Forest Plot for RRs and ORs with Regard to the Risk of Male Breast Cancer According to EMF Exposure

al., 1999; Pollan et al., 2001), while 2 studies set a cut-point no less than 0.2μT (Guenel et al., 1993; Savitz et al., 1995). Nearly half of the studies used multiple exposure assessment methods and included: job title (n=14), an exposure matrix (n=7), EMF measurement (n=10), and other methods (n=4). Six studies did not adjust results for age. Subgroup analyses were based on the data above. Quality assessment was performed for all 18 studies with Ottawa-Newcastle Assessment Scale, and the quality of the studies was modest, as shown in Table 1.

Quantitative data synthesis

Of the 18 studies only three studies found statistical

Table 2. Pooled Risk Estimate and 95% CI by Study Design, Exposure Dose, Exposure Assessment Method, Adjustment for Age, IARC Exposure Classification and Quality Score

Stratification Variables	No. of Studies	OR (95%CI)
Study Design		
Case and Control Study	7	1.39 (0.95, 2.04)
Cohort Study	11	1.31 (1.12, 1.53)
Cut-Point (μT)		
<0.2	7	1.26 (1.05, 1.50)
≥0.2	2*	0.90 (0.41, 2.00)
Not provided	9	1.52 (1.17, 1.97)
Exposure Assessment Method		
Job Title (including job - matrix)	7	1.32 (1.10, 1.59)
Others	11	1.31 (1.04, 1.65)
Adjustment for Age		
Yes	12	1.24 (1.05, 1.45)
No	6	1.75 (1.24, 2.46)
IARC Exposure Model		
Occupational	16	1.33 (1.15, 1.54)
Residential	2	1.80 (0.33, 9.87)

*One of the studies used μT-year as unit

significant associations: one was a case-control study and the other two were cohort studies, and all of them were published at least 17 years ago. However in the pooled analysis, there was a significant increase in male breast cancer risk and EMF exposure (Figure 2, pooled OR = 1.32, 95% CI = 1.14 -1.52, $P < 0.001$), and heterogeneity among studies was not obvious (I^2 =24.7%, P=0.163). In a subgroup analysis, the results indicated an increased risk for: a cohort study design (OR=1.31, 95%CI=1.12-1.53), cut-point less than 0.2μT (OR=1.26, 95%CI = 1.05-1.50), exposure assessments by job title (including job-matrix, OR = 1.42, 95% CI = 1.17-1.72), EMF measurement (OR = 1.31, 95% CI = 1.04-1.66), occupational exposure (OR = 1.33, 95% CI = 1.15-1.54), and results adjusted for age showed a significant increase (Table 2).

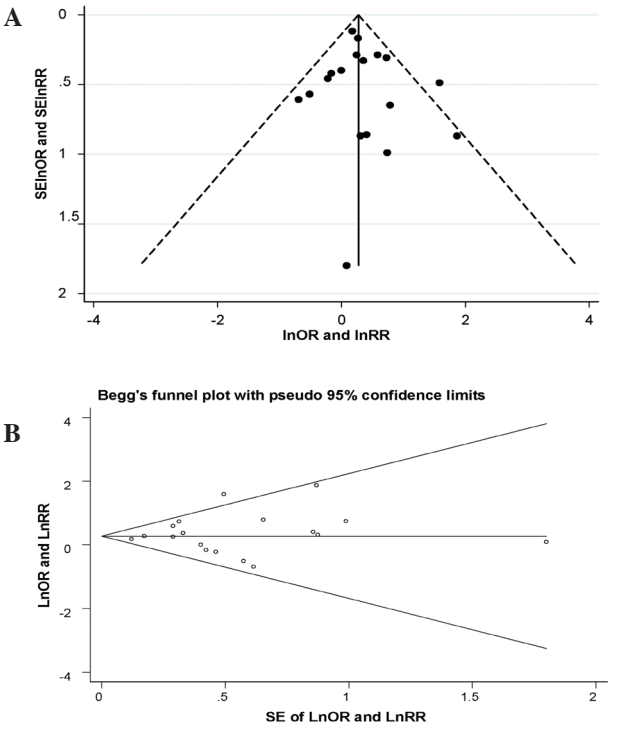

Figure 3. A: Funnel Plot with 95% Confidence Limits for All the Identified Studies; B: Begg's Funnel Plot for All the Identified Studies

The funnel plot and Begg's test (Z = 0.00, *P* = 1.000) both indicated little publication bias in the 18 studies (Figure 3). Because moderate heterogeneity might exist in the cohort studies (I^2 = 44.90%), along with overlapping of CIs in the forest plot, we conducted further analysis using the trim-and-fill method. And the result continued to show a significant association between EMF and male breast cancer risk, even though the true OR estimate might be lower than the premier one (OR = 1.30, 95% CI = 1.17-1.51). Moreover, no significant difference was found in sensitivity analyses to determine whether the inclusion criteria affected the results. Thus our results were deemed statistically acceptable.

Discussion

The possibility that EMF exposure may increase male breast cancer risk has been inconclusive for decades, and there was no systematical summary for the conflicting results of the last 10 years. Given our search parameters we identified 18 epidemiologic studies published from 1991 until December 2012, investigating the association between EMF exposure and risk of male breast cancer. Pooled risk estimates showed a significant increase with EMF exposure overall and in some subgroups (pooled OR =1.32, 95% CI = 1.14-1.52).

However, the etiology remains elusive due to inadequate available evidence (Kluttig et al., 2009). In 1987, it was firstly hypothesized that exposure to ELF-EMF could increase the long term risk of breast cancer based on the assumption that EMF exposure inhibited melatonin production (Stevens, 1987; Feychting et al., 2006). Melatonin, which is secreted by the pineal gland, has been considered to be protective against breast cancer. Some tentative studies proposed that EMF affected melatonin production in the same way as light in the evening. A suppressive effect of melatonin on estrogen receptor positive breast cancer was found and supported by recent experiments in vitro (Hill et al., 1988; Girgert et al., 2008; Girgert et al., 2010), and researchers indicated that melatonin acted as a potent antioxidant or a protective factor in the immune system (Guerrero et al., 1992; Reiter et al., 1995). Though the relationship between melatonin and breast cancer development had been confirmed in vivo and in vitro experiments, it failed in prospective epidemiological studies (Travis et al., 2004). Besides the effect on melatonin, EMF damage in genetic and other research level has been discussed also. It has been proposed that EMF theoretically is not able to produce sufficient energy to break DNA molecules or other chemical bonds, but may have a direct genotoxic effect in exposed persons, or disturb the concentration of intracellular calcium ion and the 6-hydroxy melatonin sulfate (Davis et al., 2001; Nordenson et al., 2001; Pessina et al., 2001; Zhang et al., 2010). But these hypotheses have not gained firm support from experimental researches because of conflicting results (Forssen et al., 2000; Christoffer, 2004; Chen et al., 2010).

At the same time, epidemiologic researches, even those focused only on the potential relationship between EMF and male breast cancer have not led to a firm conclusion yet. Many studies had indicated little or no effect of EMF exposure, while some early studies showed statistical significant results (Demers et al., 1991; Tynes et al., 1992; Floderus et al., 1994). Erren (2001) conducted a meta-analysis of epidemiologic studies on male breast cancer, which included 13 studies (Demers et al., 1991; Matanoski et al., 1991; Loomis, 1992; Tynes et al., 1992; Guenel et al., 1993; Floderus et al., 1994; Rosenbaum et al., 1994; Theriault et al., 1994; Savitz et al., 1995; Fear et al., 1996; Stenlund et al., 1997; Cocco et al., 1998; Floderus et al., 1999), and found a pooled RR of 1.37 (CI = 1.11-1.71). However, some researchers argued that early studies were often limited by poor design, small numbers, crude information and underdeveloped exposure measuring methods, leading to statistical significant results by chance or bias (Feychting et al., 2006).

In our research, among case-control studies, the only statistical significant result was given by the earliest study (Demers et al., 1991). The latest statistical significant result was reported in 1994, in a cohort study (RR=4.9, CI=1.6-11.8), while a recent large cohort study on mortality of UK electricity generation and transmission workers, with longer study period, found no significant excesses of deaths (SMR=1.44, CI=0.72-2.58) (Floderus et al., 1994; Nichols et al., 2005). Considering the recent studies may have higher quality, and a larger study size may attribute to a more solid conclusion, it is necessary to summarize these conflicting results of the studies over 24 years and ensure if the relationship between EMF exposure and male breast cancer is significant.

Our meta-analysis was a response to the demand. 18 studies were eligible in the study: 7 case-control studies (57 cases and 223 controls combined) and 11 cohort studies (299 cases and a total size of 7 486 643). And the study

size was much larger than the earlier one (5 case-control studies and 8 cohort studies eligible). Pooled risk estimates (OR=1.32, 95%CI=1.14-1.52) showed an increase with EMF exposure in overall and some subgroups.

More analyses were done to insure the quality of this research. The assessment of the quality of individual studies helped determine study quality and sources of heterogeneity, which bolstered our finding. The Ottawa-Newcastle Assessment Scale for case-control and cohort studies was used effectively for all 18 studies. Though most of the cohort studies (9 of 11) did not demonstrate that outcome of interest was not present at start of study, or state the adequacy of follow up of the cohorts, the quality of the studies could be defined as fair, as the studies contented most of options. Therefore we believed the results were acceptable and most selection bias had been avoided.

Publication bias, which is derived from exclusion of "no case" reports or results that are not published but may contribute to incomplete coverage for the meta-analysis and risk the pooled ORs value, was assessed in our study. Although the Begg's test showed no publication bias exist, we conducted a further analysis with the trim-and-fill method for a more certain conclusion. The association remained statistically significant with a little depressed risk; however a possible publication bias did not affect the main results.

Heterogeneity is a potential problem when interpreting the results of all meta-analyses (Chen et al., 2010). It was said that the I^2 statistic value less than 50% represents acceptable quantity of heterogeneity. And in this meta-analysis, little evidence of the heterogeneity among 18 studies was observed as the I^2 was lower than 25%. Even so, the potential heterogeneity might impact the result because of the low sensitivity of the heterogeneity test. So subgroup analyses were performed by factors that might contribute to heterogeneity, such as study design, cut-point, exposure assessment method, adjustment and exposure model. And no obvious different result was found. Moreover, the sensitive analyses found little significant difference in the visual inspection. Therefore the heterogeneity among these studies was acceptable.

In the subgroup analysis we were not able to determine a dose-response due to complicated exposure conditions and various exposure assessment methods. The ubiquity of EMF in houses, offices, and factories determines that almost everyone is likely to be exposed to some level of EMF (Christoffer, 2004; Chen et al., 2010). Moreover, considering cancer latencies of 20 to 30 years, it is important to assess total exposures both at home and at work, and over decades of time. However, most of the studies only focused on either occupational or residential exposure (only 2 on residential exposure), or a simply job-title-reference (used in 14 of the 18 identified studies), rather than an improved comprehensive exposure assessment methods. Although no distinct difference appeared in the exposure assessment method subgroup, we could not determine a dose-response relationship or less than cut-point identification. Limited sample size would not allow us to lower the level than 0.2μT (Chen et al., 2010).

In conclusion, to our knowledge, this meta-analysis investigated the association between EMF exposure and male breast cancer risk, and it is the most recent meta-analysis in the last 10 years. The results suggest that EMF exposure may be associated with the increase risk of male breast cancer despite the arguments. However, further epidemiology studies with higher quality may lead to more solid conclusions.

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