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Extremely low-frequency electromagnetic fields exposure and female breast cancer risk: a meta-analysis based on 24,338 cases and 60,628 controls

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Abstract Exposure to extremely low-frequency electromagnetic fields (ELF-EMF) has been suggested to increase female breast cancer risk; however, the data have been inconclusive. In order to derive a more precise estimation of the relationship, a meta-analysis was performed. Medline, PubMed, Embase, the Cochrane Library and Web of Science were searched. Crude ORs with 95% CIs were used to assess the strength of association between ELF-EMF exposure and female breast cancer risk. A total of 15 studies published over the period 2000 to 2009 including 24,338 cases and 60,628 controls were involved in this meta-analysis. The results showed no significant association between ELF-EMF exposure and female breast cancer risk in total analysis (OR = 0.988, 95% CI = 0.898–1.088) and in all the subgroup analyses by exposure modes, menopausal status, and estrogen receptor status. This result is in accordance with the previous meta-analysis carried out by Erren in 2000. In conclusion, this meta-analysis suggests that ELF-EMF exposure has no association with the susceptibility of female breast cancer.

Keywords Extremely low-frequency electromagnetic fields · Female breast cancer · Meta-analysis · Cancer risk

Introduction

Over the past three decades, potential health effects of exposure to electromagnetic fields have been extensively investigated in epidemiologic studies. These studies have suggested an association between occupational and residential exposure to extremely low-frequency electromagnetic fields (ELF-EMF) and cancer risk, and the International Agency for Research on Cancer evaluated the association in 2002 and concluded that ELF-EMF are possibly carcinogenic to humans, based on the association of higher level residential magnetic fields and increased risk for childhood leukaemia. The evidence for an association with breast cancer in women was, however, considered to be inadequate [1].

Breast cancer is the second most common cancer overall in the world and accounts for an estimated 16% of total cancer among women. However, the etiology of breast cancer remains poorly understood. The possible relation between ELF-EMF exposure and risk of breast cancer in women has received considerable attention and extensively studies. ELF-EMF are electric and magnetic fields with frequencies ranging between 3 and 3000 Hz. ELF-EMF exposures may occur at work, through residential proximity to electromagnetic field sources, or within homes, and the primary exposure frequency is power frequency. The ubiquity of ELF-EMF in houses, offices, and factories means that nearly everyone is likely to be exposed to some level of ELF-EMF. Even a modest EMF-attributable breast cancer risk could thus result in a considerable number of

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cases. Analysis of the evidence regarding a possible association between ELF-EMF and breast cancer is therefore of interest not only because it may contribute to a better understanding of the etiology of breast cancer, but also because of the public health implications if such an association really exists.

To date, epidemiologic studies of both residential and occupational exposures to ELF-EMF and the risk of breast cancer have led to conflicting results. The most underlying limitation relates to difficulties in quantifying EMF exposure, as studies have often relied on proxy measures such as occupational categories, wire codes, characteristics of power lines surrounding current and historical residences rather than direct measurements of current fields as markers of past exposure. In addition, details of the methods used to classify exposures within these broad categories differed widely. A meta-analysis of observational epidemiological studies has previously been carried out by Erren [2] in 2000 to examine the relationship between EMF exposure and breast cancer. The pooled RR from the study in women was 1.12 (95% CI = 1.09–1.15), and a fairly homogeneous increased risk was found for men (RR = 1.37, 95% CI = 1.11–1.71).

Over the period 2000–2009, still extensively epidemiological studies have been carried out to investigate the relationship between ELF-EMF and breast cancer, especially female breast cancer. Most of these studies are case–control studies and focused on both residential and occupational exposure. Several studies have investigated the use of electric bed-warming devices as a potential source of magnetic field exposure. Exposure levels for these different studies are usually measured according to the level of the magnetic field created in units of Gauss (mG; 1 Gauss = 1000 mG) or Tesla (mT; 0.1 mT = 1 mG). These epidemiologic literatures, as summarized previously, have yielded inconclusive results. It is still unclear whether exposure to ELF-EMF is associated with female breast cancer.

Given that the recent studies may have a high quality, it might be important to reassess ELF-EMF exposure (both at home and at work) over the recent 10 years [3]. Our study is a response to this. The purpose of the present investigation was to reassess the risk of female breast cancer associated with ELF-EMF exposure in the light of these recent publications. Thirteen case–control reports focus on women are considered now. Subgroup analyses were carried out further with respect to the exposure modes, menopausal status and estrogen receptor (ER) status. This paper supplements an earlier meta-analysis on possible associations between exposures to ELF-EMF and female breast cancer. In so doing we hoped to be able to provide answers to the following questions: Could the association between ELF-EMF and female breast cancer be confirmed? What recommendations can we make for further studies, if warranted?

Methods

Search strategy and selection criteria

This study was performed according to the proposal of Meta-analysis of Observational Studies in Epidemiology group (MOOSE) [4]. A comprehensive search strategy was conducted towards the electronic databases including Medline, PubMed and Embase, the Cochrane Library and Web of Science using terms “breast cancer”, “breast neoplasm”, and “electromagnetic fields” over the period January 2000 to December 2009. Reference lists of the identified articles were also examined and the literature retrieval was performed in duplication by two independent reviewers (C.H. Chen and X.Y. Ma).

We reviewed titles and abstracts of all citations and retrieved literatures. The studies that met the following criteria were chosen: (1) the publication was a population-based case–control study referring to the association between ELF-EMF exposure and breast cancer in females; (2) all cases were first diagnosed as invasive or in situ breast cancer; (3) the papers must offer the size of the samples, number of exposed and non-exposed individuals in cases and controls or other information that can help us infer the results; (4) when multiple publications reported on the same or overlapping data, we used the most recent or largest population as recommended by Little et al. [5];and (5) publication language was confined to English.

Data extraction

A number of different methods were used to measure ELF-EMF exposure in the studies examined. Some expressed exposure simply as a binary variable, “exposed”/“not exposed”, other reports were stratified according to measured or assumed intensity or time-weighted average (TWA) of exposure to ELF-EMF. To aggregate exposure categories across studies, we dichotomized exposure strata using cut-off points. Although the specific cut-off points used for the epidemiologic analyses differed and the period over which the TWA was estimated varied. Generally, cut-off points closest to 0.2 μT, which were common to most of studies, were used in this meta-analysis.

Data was extracted from each study by two reviewers (C.H. Chen and X.Y. Ma) independently according to the pre-specified selection criteria. Decisions were compared and disagreements about study selection were resolved by consensus or by involving a third reviewer. The following information was extracted from the studies: first author, publishing year, studying population, time period, exposure assessment criteria and confounding variables.

Statistical analysis

Crude ORs with their 95% CIs were used to assess the strength of association between ELF-EMF exposure and breast cancer risk. Heterogeneity assumption was assessed by Chi-square based Q-test and I-squared test. The heterogeneity was not considered significant when $P < 0.10$. With lacking of heterogeneity among studies, the pooled OR estimate of the each study was calculated by the fixed effects model (Mantel–Haenszel) [6]. Otherwise, the random effects model (DerSimonian and Laird) was used [7, 8]. In order to obtain a more accurate and objective result, subgroup analyses were performed by exposure modes (occupational exposure, and residential exposure, which includes blanket exposure), menopausal status, and estrogen receptor (ER) status. Possible publication bias was tested by funnel plot and Egger's test. All statistical tests were conducted with STATA software package (version 11.0, College Station, TX). A P value of 0.05 for any test or model was considered to be statistically significant.

Results

Eligible studies

After examined carefully according to the inclusion criteria, our final pool of eligible studies included 15 case–control studies (published in 13 different papers, as two papers by Kabat et al. [9] and London et al. [10] both include two different series of cases and controls) with 24,338 cases and 60,628 controls [9–21]. Table 1 shows the characteristics of the studies included for this meta-analysis. Each row in the table describes a single study. Of the 15 studies, five studies were occupational exposure [11, 12, 16, 17, 19], and 10 studies were residential exposure [9, 10, 13–15, 18, 20, 21] including five electronic blanket exposure [9, 14, 20, 21]. Five studies provided data on ER status [9, 12, 13, 17, 19], seven on the premenopausal status [9, 11–14, 19] and eight on postmenopausal status [9, 11–14, 16, 19]. Subgroup analyses were based on these data above. Almost all of the cases were histologically confirmed, seven were based on cancer registry, and the rest were based on clinical examination. Controls were mainly healthy population-based individuals which were matched for age, ethnicity and years of resident. Exposure assessment was based mainly on measurement or assessment intensity, for which the cut-off points close to 0.2 μT were used in meta-analyses. Five studies focus on blanket exposure just simply base on exposed or not-exposed to electric blanket, for which meta-analyses were based on the author's decision in the original paper.

Quantitative synthesis

The main results of this meta-analysis and the heterogeneity test are shown in Table 2 and Fig. 1. Overall, no significant association was found for total comparison (OR = 0.988, 95% CI = 0.898–1.088) and subgroup comparisons (for residential exposure: OR = 1.017, 95% CI = 0.923–1.120; for occupational exposure: OR = 0.933, 95% CI = 0.790–1.101; for blanket expose: OR = 1.004, 95% CI = 0.925–1.089; for premenopausal: OR = 1.067, 95% CI = 0.811–1.402; for post menopausal: OR = 1.030, 95% CI = 0.862–1.230; for ER-positive: OR = 0.963, 95% CI = 0.754–1.230; for ER-negative: OR = 0.764, 95% CI = 0.567–1.029).

Sensitive analysis

Sensitivity analyses were conducted to determine whether modification of the inclusion criteria of the meta-analysis affected the final results. They were carried out by altering corresponding statistic variables and all the results were not materially altered, indicating that our results were statistically robust.

Bias diagnosis

Funnel plots and Egger's test were performed to access the publication bias of literatures. As shown in Fig. 2, the shape of the funnel plot revealed obvious asymmetry for total effect while symmetry for other subgroup comparisons. Then, the results were confirmed by Egger's test (for total effect: $P = 0.026$; for blanket exposure: $P = 0.501$; for premenopausal: $P = 0.398$; for postmenopausal: $P = 0.193$; for ER-positive: $P = 0.078$; for ER-negative: $P = 0.563$).

Discussion

We conducted a meta-analysis of 15 case–control studies published from 2000 to 2009 on the association of ELF-EMF exposure and female breast cancer. None of our analyses in overall and subgroup analysis showed statistically significant increases in female breast cancer risk in relation to the ELF-EMF exposure.

Of the previous meta-analyses in 2000, Erren [2] found some increase in male breast cancer risk associated with EMF exposure, albeit that the excess risk was small. However, the results from studies in female suggested that there was little evidence in support of an association between EMF and breast cancer risk. This study also found no

Table 1 Characteristics of epidemiological studies on exposure to ELF-EMF and female breast cancer

First author, year of publication	Study population	Time period	Exposure assessment, criteria	Confounding variables	Main results
Zheng, 2000	608 cases and 609 controls in Connecticut, USA, 31–85 years old	1994–1997	Frequency and mode of use of electric blankets; exposed or not exposed	Age, race, annual income, body mass index, fat intake, age at menarche, age at first full pregnancy, lifetime lactation, family breast cancer history	OR = 0.9 (0.7–1.1)
McElroy, 2001	1,949 cases and 2,498 controls in Wisconsin, Massachusetts, and New Hampshire, USA, 50–79 years old	1994–1995	Frequency and duration of use of electric blankets; exposed or not exposed	Age at first full-term pregnancy, body mass index, family history of breast cancer, education, menopausal status, age at menopausal	OR = 0.93 (0.82–1.06)
Wijngaarden, 2001	843 cases and 773 controls in North Carolina, USA, 20–74 years old	1993–1995	Magnetic field measurements, estimated time-weighted average; 0.2 μT (conversion)[a]	Menopausal status, ER status	OR = 1.5 (1.1–2.0)
Davis, 2002	813 cases and 793 controls in Seattle, Washington, USA, aged 20–74 years	1992–1995	Magnetic field measurements; 0.2 μT	Age, menopausal status, ER status, no. of full-term pregnancies, age at first pregnancy, family history of breast cancer, hormone replacement therapy, alcohol intake, cigarette smoking	OR = 1.0 (0.8–1.3)
Kabat, 2003a	1,354 cases and 1,426 controls in USA	1996–1997	Duration and mode of use of electric blankets; exposed or not exposed	Menopausal status, ER status	OR = 0.97 (0.76–1.23)
Kabat, 2003b	576 cases and 585 controls in USA, under 75 years old	1996–1997	Duration and mode of use of electric blankets; exposed or not exposed	Menopausal status, ER status	OR = 1.11 (0.94–1.30)
Schoenfeld, 2003	576 cases and 585 controls in USA, under 75 years old	1996–1997	Magnetic field measurements, estimated personal exposure measure; 0.2 μT	Age, race, cigarette smoking, annual income, education, alcohol use, hormone replacement therapy, age at menarche, age at first birth	OR = 1.08 (0.77–1.51)
Kliukiene, 2003	99 cases and 396 controls in Norwegian	–	Employment years + magnetic field measurements; exposed or not exposed	Age, ER status	OR = 1.43 (0.74–2.74)
Labreche, 2003	608 cases and 667 controls in Montreal, Canada, aged 50–75 years	1996–1997	Job history + magnetic field measurements; 0.2 μT	Family history, age at menarche, age at 1st full-term pregnancy, number of full-term pregnancies, hormone replacement therapy, body mass index, ER and PR status	OR = 1.06 (0.75–1.49)
London, 2003a	743 cases and 699 controls in Los Angeles, USA, aged 45–74 years	1993–1999	Magnetic field measurements; 0.2 μT	Ethnicity, menopausal status, hormone replacement therapy, age at menopausal, no. of children, ER status, breast cancer in a mother or sister, alcohol consumption	OR = 1.12 (0.64–1.97)
London, 2003b	347 cases and 286 controls in Los Angeles, USA, aged 45–74 years	1993–1999	Magnetic field measurements; 0.2 μT	Ethnicity, menopausal status, hormone replacement therapy, age at menopausal, no. of children, ER status, breast cancer in a mother or sister, alcohol consumption	OR = 0.78 (0.61–1.00)

Table 1 continued

First author, year of publication	Study population	Time period	Exposure assessment, criteria	Confounding variables	Main results
Zhu, 2003	304 cases and 305 controls in Tennessee, USA, aged 20–64 years	1995–1998	Duration and mode of use of electric bedding devices; exposed or not exposed	Age, educational level, annual income, marital status, employment status, menopausal status	OR = 1.4 (0.9–2.2)
Kliukiene, 2004	1,380 cases and 2,760 controls in Norwegian, older than 16 years old	1980–1996	Magnetic field measurements, estimated time-weighted average; 0.2 μT	Age, type of dwelling, age at birth of first child, education, ER status	OR = 1.38 (1.04–1.83)
Forssen, 2005	20,400 cases and 116,227 controls in Sweden, older than 15 years old	1976–1999	Job exposure matrix, magnetic field measurements; 0.2 μT	Nulliparous, age at first birth, socioeconomic status, ER status	OR = 1.03 (0.94–1.134)
McElroy, 2007	6,213 cases and 7,390 controls in Massachusetts, New Hampshire, and Wisconsin, USA, aged 20–69 years	1997–2001	Job title + occupational history, TWA; 0.2 μT(conversion)[a]	Family history, recent alcohol consumption, age at birth of first child, menopausal status, age at menopause, hormone use, education, age at menarche, race	OR = 0.95 (0.89–1.02)

[a] Cut-off point were converted by the formula the author provided in the paper

Table 2 Summary ORs and 95% CI of ELF-EMF exposure and female breast cancer risk

Subgroup analysis	Study number	OR	95% CI	P[a]
Exposure modes				
RE[b]	10	1.017	0.923–1.120	0.092
RE(Blanket expose)	5	1.004	0.925–1.089	0.129
OE[b]	5	0.933	0.790–1.101	0.000
Total effect[b]	15	0.988	0.898–1.088	0.000
Menopausal status				
Premenopausal[b]	7	1.067	0.811–1.402	0.000
Postmenopausal[b]	8	1.030	0.862–1.230	0.000
ER status				
ER+[b]	5	0.963	0.754–1.230	0.004
ER−[b]	5	0.764	0.567–1.029	0.035

RE residential exposure, *OE* occupational exposure, *ER+* ER positive, *ER−* ER negative

[a] *P*-value for heterogeneity

[b] Estimates for random effects model

significant association between ELF-EMF exposure and female breast cancer risk. For the ubiquitous sources of ELF-EMF, we made subgroup analyses by occupational exposure and residential exposure. For the extensive focus on electronic blanket in bedroom, we made subgroup analyses by blanket exposure specially. In 1987, Stevens proposed a biologic hypothesis in which ELF-EMF may suppress production of melatonin, which can suppress production of estrogen, and directly inhibit breast cancer cell growth [22]. On the basis of Stevens' hypothesis, we would expect that women can be affected differentially by ELF-EMF depending on their ER status or menopausal status. Thus, we also made subgroup analyses by premenopausal status and postmenopausal status, by ER-positive status and ER-negative status. The pooled ORs in all our subgroup analyses were close to 1.0 with relatively narrow confidence intervals. The great majority of the studies reported risk estimates with *P* values greater than 0.05, suggesting that non-significant results are readily publishable.

We attempted to identify all published materials by means of a MEDLINE search, supplemented by searching on PubMed, Embase, the Cochrane Library and Web of Science. Bibliographic references in all retrieved papers and reports were reviewed, and, as far as we can assess this point, we are quite confident on the exhaustivity of our searching strategy of published research. Most of the studies published during the years 2000–2009 are case–control studies except two cohort studies [23, 24]. Thus, we just focus our analysis on case–control studies.

Heterogeneity is a potential problem when interpreting the results of all meta-analyses. However, there was evidence of statistical heterogeneity in our analyses. Epidemiological research of breast cancer and exposure to ELF-EMF has to face several threats to validity, mostly in relation to case ascertainment, control selection, exposure assessment and control of confounding. These points are next briefly discussed in relation to included studies in this review.

Incomplete ascertainment of cases will contribute to decreased statistical power in the studies. Of the 15 studies,

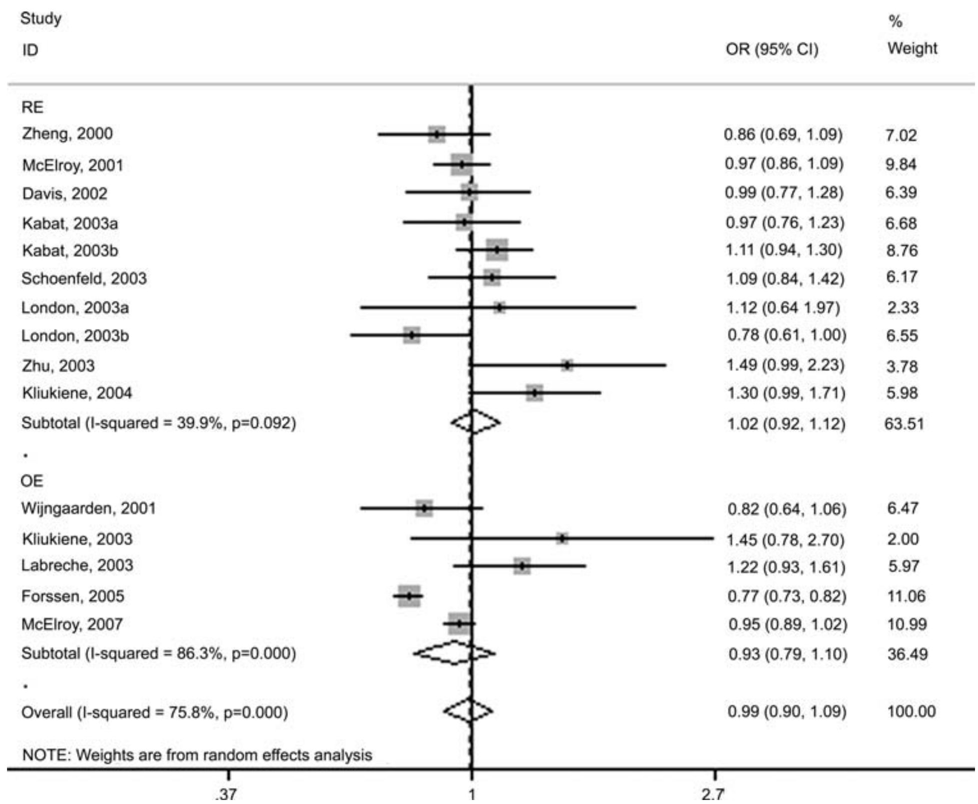

Fig. 1 Forest plot of female breast cancer risk associated with ELF-EMF exposure

seven were based on cancer registry and the rest were based on clinical examination. Only five provided data on estrogen receptor status, seven on the premenopausal status and eight on postmenopausal status. Possible misclassification of the disease warrants more detailed consideration. Other sources of variability include case-finding period and time from first exposure (to allow for adequate time lags between exposure to EMF and clinical manifestation of breast cancer). Different strategies were applied for the selection of controls, including controls selected from hospitals, health care financing administration files and population. In general, potential for selection bias (i.e. selection of controls somehow related with their potential for exposure) arriving from these different sources for controls selection could be low. Criteria for inclusion and exclusion of controls also substantially differ between studies. These sources of variation may contribute to the observed heterogeneity affecting pooled analysis.

Different investigators studying the possible association between exposure to ELF-EMF and female breast cancer defined a variety of methods of exposure classification, as do cut-off points of exposure. Since there appears to be no “gold standard” at present for EMF measurement, we did not evaluate the operational definition of exposure (e.g. all EMF measurements methods were assumed to be equally valid). After careful review, cut-off points closest to 0.2 μT were used in this meta-analysis, as previously used in many other meta-analyses [3, 25, 26]. Given cancer latencies of 20–30 years and the ubiquitous sources of ELF-EMF, it may be important to assess total exposures both at home and at work, and over decades of time. However, most of the studies considered either residential or occupational exposure, and the reliability of retrospective estimates of exposures is problematic. When possibly relevant exposures to ELF-EMF in the whole environment are assessed only partially, errors in the categorization of exposure status are likely to occur. For instance, studies that focused on power frequencies may have ignored relevant exposure to electromagnetic spectra at other wavelengths. If such misclassification is random and thus similar in subgroups being compared (non-differential), then the error will tend to introduce a bias towards the null. Substantial random misclassification of exposures would thus tend to generate spurious reports of “little or no effect”.

The original studies are not suggestive of strong confounding effects derived from variables controlled for analysis as potential confounders. However, confounding effects derived from unknown and unmeasured variables are still possible, but it is not likely that strong risk factors for female breast cancer remain unnoticed. More importantly, the study of interaction effects between ELF-EMF exposure and established risk factors is still unexplored. This should be a mostly interesting focus for future research in this area.

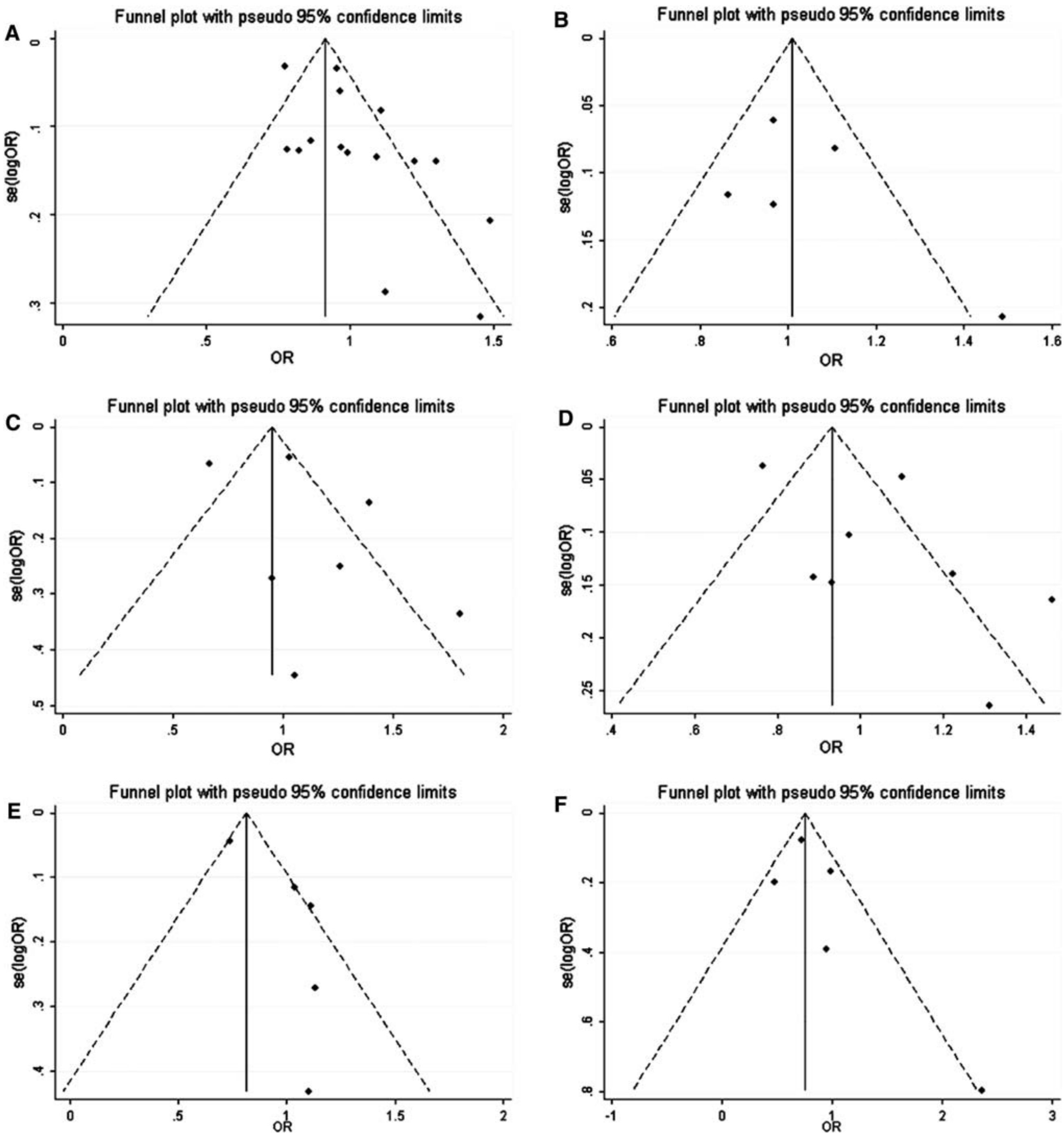

Fig. 2 Funnel plot analysis to detect publication bias. Each point represents a separate study for the indicated association. **a** Funnel plot for total comparison; **b** funnel plot for blanket expose; **c** funnel plot for premenopausal; **d** funnel plot for postmenopausal; **e** funnel plot for ER+; **f** funnel plot for ER−

Some limitations of this meta-analysis should be acknowledged. First, we had to rely on results and figures as presented in the papers, and our analyses were restricted by choices and decisions (e.g., about cut-off points, analytical techniques) made by the original authors. The samples in some subgroup analyses were restricted for some of the authors did not provide full information of ER status and menopausal status. Second, the controls were not uniformly defined. Although most of the controls were selected mainly from healthy populations, some had benign disease. Therefore, non-differential misclassification bias was possible because these studies may have included the control groups who have different risks of developing breast cancer.

This review includes 15 case–control studies on the association between female breast cancer and ELF-EMF exposure. Most of the studies put marked efforts into disease and exposure measurements. Despite the limitations, assessment of the quality of the individual studies used in our meta-analysis allowed us to draw the following conclusions: First, pooled estimates for all studies suggest no risk of female breast cancer for exposure to ELF-EMF. However, given the possibility of selection bias, exposure misclassification, and the existence of confounding variables in the individual studies, it is premature to conclude that the observations reflect a real, rather than artifactual, association. Second, the publication of new state-of-the-art epidemiological studies that incorporated comparable measures for both exposure and outcomes is required to facilitate future meta-analyses. If this excess risk of breast cancer is confirmed, we should thoroughly investigate, also from a cost-effectiveness point of view, possible options for minimizing exposure in order to provide definitive answers for policy-makers.

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