EJGO European Journal of Gynaecological Oncology

Association between air pollution and female breast cancer: a meta-analysis

Y.Y. Yi, Y.B. Ling, X.F. Huang

[1]*Nanjing University of Posts and Telecommunications, Nanjing;* [2]*Nanjing Normal University of Special Education, Nanjing*
[3]*Affiliated Hospital of Nanjing University of TCM, Nanjing (China)*

Summary

Objective: To explore whether there is association between air pollution and female breast cancer by conducting a meta-analysis. *Materials and Methods:* Publications addressing the association between air pollution and female breast cancer risk were selected from PubMed, Medline-Ebsco, Web of Science, Google Scholar, CNKI, and other related research databases. Data were extracted from studies by two independent reviewers. The meta-analysis was performed by R 3.2.0 software, and odds ratio (OR) with a 95%-confidence interval (CI) were calculated. *Results:* Finally, nine case-control studies were retrieved with a total of independent 43 control groups. Significant association was identified between air pollution and female breast cancer (OR = 1.13, 95% CI: 1.07−1.20, $p < 0.0001$). Meanwhile, according to the nationality of the study population, stratified analysis found that people in America association between air pollution and breast cancer was statistically significant (OR = 1.13, 95% CI: 1.07−1.20, $p < 0.0001$); In European populations, the association between air pollution and breast cancer in women was not statistically significant (OR = 0.67, 95% CI: 0.36−1.24, $p = 0.2030$). In Asian populations, the association between air pollution and breast cancer was statistically significant (OR = 1.71, 95% CI: 1.06−2.76, $p = 0.0279$). Menopause stratified analysis showed that premenopausal women and the association between air pollution and breast cancer was statistically significant (OR = 1.23, 95% CI: 1.09−1.40, $p = 0.0009$). For postmenopausal women, association between air pollution and breast cancer was also statistically significant (OR = 1.11, 95% CI: 1.03−1.20, $p = 0.0093$). *Conclusion:* The present study confirms that there is association between air pollution and female breast cancer.

Key words: breast cancer, air pollution, meta-analysis.

Introduction

Breast cancer has become a major public health problem in the community. Since the late 1970s, the incidence of breast cancer on a global scale has been ranked first female malignancy. Overall, the incidence of the developed countries in Western Europe and North America is higher, and most parts of Asia, Latin America, and Africa are the low-incidence areas [1]. According to World Health Organization statistics, the incidence of breast cancer worldwide each year increases by 0.2−8%, which translates into 140 million people worldwide that are diagnosed with breast cancer. About 50 million people die of the disease and is the first cause of death in women aged 40 to 55 [2].

There are multiple factors that have been identified or suggested to be associated with the increased risk for breast cancer [3-5]. However, these factors do not fully explain the tendency of breast cancer to continue to grow each year. Some scholars believe that the first demographic characteristics such as childbearing age, high income, family genetic history, *etc.* can only explain 41% [6], and even some scholars believe that these factors may account for only 30% [7, 8]. Some studies show that active and passive smoking, high-fat foods [9-15], obesity [16-20], drink [21], age, early menarche, and late menopause [22] are the reasons leading to breast cancer risk, but they cannot be fully explained [23]. Studies have found that air pollution has a direct link with breast cancer [24-27]. The definition of the International Organization for Standardization (ISO) pointed out that the air pollution usually refers to the result of human activity or natural processes causing certain substances to enter into the atmosphere, showing a concentration sufficient to cause harm to body's comfort, health, and well-being. The main air pollutants include carbon monoxide (CO), nitrogen oxides (NOx), volatile organic compounds (VOC), sulfur dioxide (SO_2), and particulate matter up to 10/2.5 micrometers in diameter (PM10/PM2.5), and so on [28]. There are natural factors (such as forest fires, volcanic eruptions, *etc.*) and human factors (such as industrial waste, gas, coal, automobile exhaust, and others), especially caused by industrial production and transportation. Regarding the effect of outdoor air pollution on human carcinogenicity [29], World Health Organization's International Cancer Research in 2013 clearly states that PM2.5 air pollution sources are carcinogenic. World Health Organization also reported that at least 12.5% of annual global deaths are due to air pollution.

Currently there is sufficient evidence that exists between air pollution and breast cancer [30]. Number of data shows

Revised manuscript accepted for publication December 22, 2015

7847050 Canada Inc.
www.irog.net

that breast cancer incidence in industrialized countries is higher than in developed countries [31] and that the incidence of breast cancer is much higher in urban residents than in rural areas. Women 30 years ago if regular exposure to certain petroleum products, such as prolonged breathing of gasoline, and exhaust, menopausal problems and breast cancer will increase at least two-fold [32]. The cities in general include pollution. Benzopyrene air pollutants in the air have ubiquitously the strongest carcinogenic capacity, and is widely found in automobile exhaust pollutant and from factories that block solar radiation, resulting in a reduction synthesis of vitamin D [33]. Urban residents with breast cancer carcinogen cytochrome P4501A1 are significantly higher than among rural residents. In addition, studies also show that breast cancer may be associated with certain organic solvents, polycyclic aromatic hydrocarbons (PAN), and exposure to organochlorine compounds [33]. However, Mendez & Arab [34] and Lopez-Cervantes *et al.* [35] and other scholars believe that these organic chlorine compounds have no significant link to breast cancer. Because the sample size of different scholars in the study is limited, therefore, different scholars in the study of association between air pollution and breast cancer are likely to report conflicting results [36].

Materials and Methods

Search strategy

The authors performed a research of PubMed, Medline-Ebsco, Web of Science, Google Scholar, and CNKI (China National Knowledge Infrastructure) to retrieve articles linking air pollution and susceptibility to breast cancer, available up to September 2015. Search keyword included: “breast cancer”, “breast tumor”, “breast neoplasm”, “air pollution”, “gaseous pollutant”, “environmental pollution”, and “atmospheric pollution”. In addition, the authors searched the literature in references. Publications in English and Chinese were included for all the breast cancer and air pollution articles.

The study included met the following inclusion criteria: (1) cases related to air pollution associated with breast cancer control research, (2) study involved women, and (3) sufficient statistical data for estimating an OR with 95% CI. Exclusion criteria included: (1) sample was not accountable or with incomplete data; (2) only included a larger sample while the same author published repeated articles, and (3) abstracts, comments, reviews, and editorials.

Two researchers developed a unified form extracting all data included in the study, including the first author’s name, year of publication, the study sample nationality, for example, the number of cases and controls, source of cases and controls, as well as the OR and 95% CI values. In the process of extracting data, such as the case of difference, the experts discussed the arbitration, third-party-oriented research in the field through a third party.

Statistics

This study included R3.2.0 meta-analysis, the use of OR, and 95% CI to analyze the relationship between air pollution and breast cancer among women. To detect and remove sources of heterogeneity, this paper analyzed subgroups of differtent nationality and menopause. Q statistic was calculated by chi-square test I^2 and *p*-values. If p > 0.10 and I^2 > 50%, using a fixed effects model, statistical significance was indicated, otherwise random effects model merge statistics. Significant merger statistics take *Z* tests; $p < 0.05$ represents the difference which was statistically significant. If the data provided by the institutes included too much heterogeneity, only descriptive systemic reviews (SR) were included.

Sensitivity analysis was conducted to assess the stability and reliability of these results. By backspace included in the study to evaluate the impact of a single study of the overall results. Using Egger’s test and Begg’s test for publication, bias included in the study was used to assess and conduct visual display.

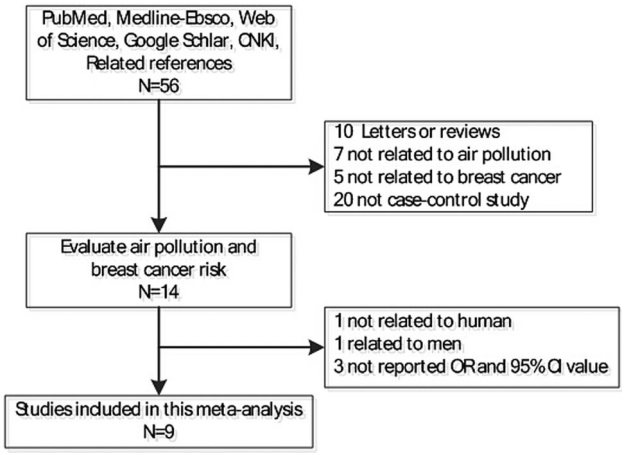

Figure 1. — Flow chart showing the study selection procedure.

Results

Characteristics of eligible studies

According to the literature of inclusion and exclusion criteria, a total of nine case-control studies were included. Among them, there were seven literatures that distinguished premenopausal women and postmenopausal women. The flow chart of the study selection is summarized in Figure 1 and the selected study characteristics are summarized in Table 1 [8, 17,18, 20, 21, 37-40]. Nine document control studies were included: six from the Americas, two from the Europe, and one from the Asian. All included studies were conducted using logistic regression method.

Meta-analysis results

This research divided women in premenopausal and postmenopausal. Analyzing various conditions, such as age, different pollutants, and breast cancer, the present can be considered as an independent research. The main results of this meta-analysis and the heterogeneity test are shown in Figure 2. Heterogeneity test results showed that there was no heterogeneity between studies, therefore, the fixed-effect model (I^2 = 0.00%, p = 0.1896) was utilized. Meta-analysis showed an association between air pollution and breast cancer which statistically significant (OR = 1.13, 95% CI: 1.07−1.20, p < 0.0001). Meanwhile, according to the nationality of the study

Table 1. — *Characteristics of eligible case-control studies included in the meta-analysis.*

First author	Year	Country	Pre-and post-Menopausal	Case/control	Research method	OR	95%CI
Elizabeth L.L-M.	1996	USA	Premenopausal	33/28	Logistic regression	1.12	0.60-2.08
				8/6		1.24	0.41-3.73
				15/15		0.95	0.42-2.12
				2/2		0.96	0.13-7.00
			Postmenopausal	127/149		1.11	0.84-1.48
				33/32		1.33	0.80-2.21
				44/54		1.12	0.72-1.74
				11/16		0.92	0.42-2.03
Petralia S.A.	1999	USA	Premenopausal	43/27	Unconditional	1.95	1.14-3.33
				14/8	logistic regression	2.40	0.96-6.01A
Gammon M.D.	2002	USA	Premenopausal	30/23	Unconditional	0.86	0.44-1.71
				36/27	logistic regression	0.94	0.51-1.74
				32/22		1.11	0.56-2.17
			Postmenopausal	99/112		1.10	0.70-1.74
				174/109		0.73	0.47-1.12
				79/101		1.09	0.70-1.69
Bonner M.R.	2005	USA	Premenopausal	164/283	Unconditional	1.78	0.62-5.10
				204/386	logistic regression	0.66	0.38-1.16
				181/371		0.52	0.22-1.20
			Postmenopausal	357/521		2.42	0.97-6.09
				469/757		1.45	0.74-2.87
				435/782		1.33	0.87-2.06
Nie J.	2007	USA	Premenopausal	56/83	Unconditional	2.07	0.91-4.72
				39/92	logistic regression	1.22	0.44-3.36
				35/100		1.29	0.59-2.82
				22/124		1.49	0.65-3.43
			Postmenopausal	62/75		2.58	1.15-5.83
				119/292		0.82	0.58-1.18
				81/310		0.80	0.55-1.17
Viel J.F.	2008	France	Total	11/67	Conditional	0.88	0.43-1.79
				4/60	logistic regression	0.31	0.08-0.89
Crouse D.L.	2010	Canada	Postmenopausal	383/416	Unconditional	1.31	1.00-1.71
				383/416	logistic regression	1.35	0.94-1.94
Huo Q.	2013	China	Total	–	Logistic regression	1.71	1.06-2.76
Perry H.	2015	Canada	Premenopausal	30/23	Unconditional	0.86	0.44-1.71
				36/27	logistic regression	0.94	0.51-1.74
				32/22		1.11	0.56-2.17
			Postmenopausal	99/102		1.10	0.70-1.74
				174/109		0.73	0.47-1.12
				79/101		1.09	0.70-1.69

population, stratified analysis found an association between air pollution and breast cancer in America which was statistically significant (OR = 1.13, 95% CI: 1.07−1.20, $p < 0.0001$). In European populations, the association between air pollution and breast cancer in women was not statistically significant (OR = 0.67, 95% CI: 0.36−1.24, $p = 0.2030$). In Asian populations, the association between air pollution and breast cancer was statistically significant (OR = 1.71, 95% CI: 1.06 −2.76, $p = 0.0279$). Stratified analysis showed that in premenopausal women, the association between air pollution and breast cancer was statistically significant (OR = 1.23, 95% CI: 1.09−1.40, $p = 0.0009$). In postmenopausal women, air pollution was associated with breast cancer with statistical significance (OR = 1.11, 95% CI: 1.03−1.20, $p = 0.0093$).

Publication bias and sensitivity analysis

The authors also performed a sensitivity analysis to explore the influence of individual studies on the overall result of influence by backspace included in the study, were included in the study results show that a single no significant effect on the overall results. Publication bias was assessed by Begg's funnel plot and Egger's test. Begg's funnel plot in each point represents a separate study for the indicated association; as can be seen the graph symmetrical to the funnel-shaped distribution, indicates no clear publication bias (Figure 3). Egger linear regression analysis included studies which further con-

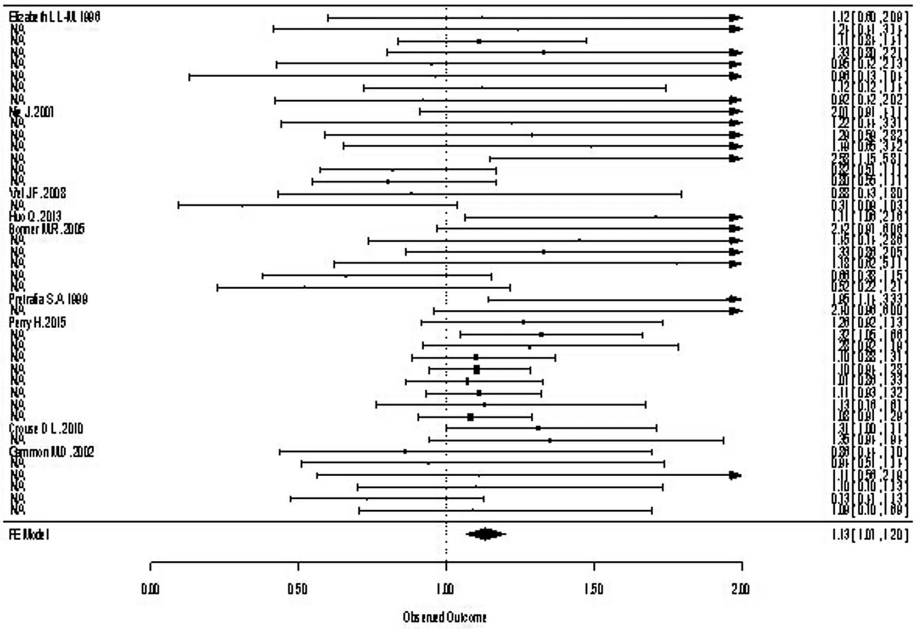

Figure 2. — Forest plot of meta-analysis between air pollution and female breast cancer.

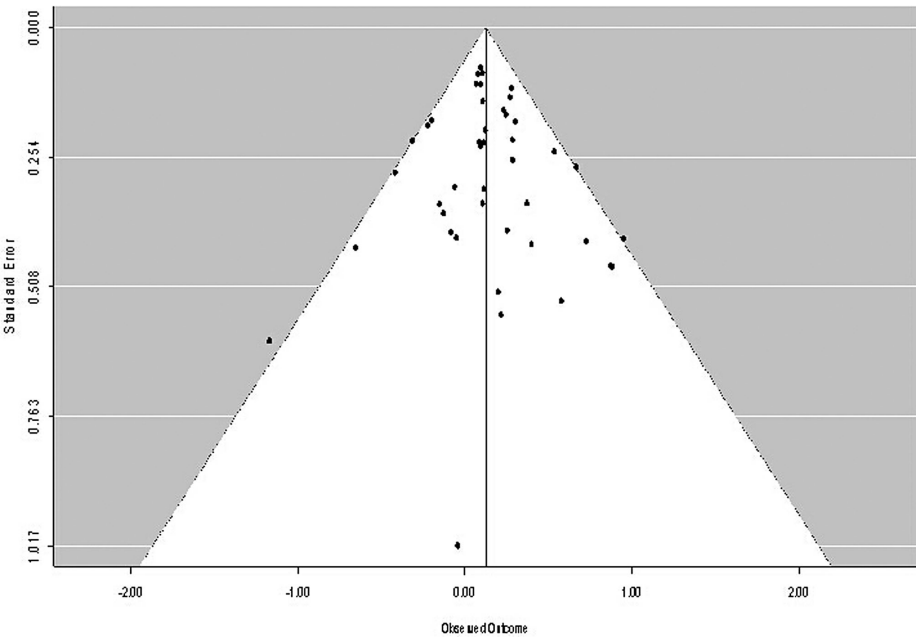

Figure 3. — Begg's funnel plot for pubblication bias test.

firmed that no publication bias existed (t = 0.5779, p = 0.5665).

Discussion

In recent years, air pollution has become increasingly serious. World Health Organization in an attempt to monitor the cities in 2014, most air pollution indexes exceeded the WHO standards for air quality. Among them, the Asian countries were the most severe, followed by South America, and European countries which generally had better air quality. Air pollution has become the world's largest killer, and can lead to heart disease, stroke, lung disease, acute respiratory infections, diabetes, and cardiovascular, and other major diseases [37]. With the rising incidence of breast cancer each year, more and more scholars are examining its association with air pollution. However, despite the growing number of studies, all regions have varying air qualities, even in the same area and at different times, air

pollutant concentrations will be different. The incidence of breast cancer also shows large differences according to region, in the number of samples, and in various study groups; consequently there is conflicting data in the researches conducted.

Meta-analysis can be integrated and systematic study of multiple quantitative analyses can improve statistical power. The main idea of this method is to combine multiple research results, thus increasing the sample size to improve results' credibility and accuracy. Thus, meta-analysis requires strict inclusion and exclusion criteria. The present study met the inclusion criteria's nine literature meta-analyses.

Although the present authors performed a comprehensive research of all available studies and provided an overview of the association between air pollution and female breast cancer, there are however, some deficiencies and limitations. First, because a small number of them met the inclusion criteria, each article in the control groups was treated individually, which may lead to homogeneity between studies. Secondly, most of the included studies where conducted in the Americas, United States, Canada, from Europe, only in France, from Asia, only in China, while Africa and Oceania have no reported literature, hence this might caused inconspicuousness. Third, most of the included studies only divided women into premenopausal and postmenopausal women, which may not represent the general population. Lastly, OR values reported in the literature were adjusted, however various factors in the studies may not have been used for the same.

Conclusion

In summary, the present meta-analysis successfully indicated that there are some associations between air pollution and female breast cancer. Because there were several limitations to this meta-analysis, in particular, research especially from Africa and Oceania, is required to further assess the association of air pollution and female breast cancer in order to refine the study on this interesting issue.

Acknowledgements

The authors acknowledge the General Project of National Natural Science Foundation of China (71473117 and 71173099)

References

[1] Topal F., Van R.S., Van H.G., Jacquemyn Y.: "Factors contributing to the low participation rate of Turkish women to a breast cancer screening program in Antwerp, Belgium". *Eur. J. Gynaecol. Oncol.*, 2015, *36*, 520.

[2] Liang Y., Chu P.H., Wang X.K.: "Health-related quality of life of Chinese earthquake survivors: a case study of five hard-hit disaster counties in Sichuan". *Soc. Indic. Res.*, 2014, *119*, 943.

[3] Zhu D. M., Xue, W.L., Tao W., Li J.C.: "Effects of cyclopamine on the biological characteristics of human breast cancer MCF-7 cell line and its mechanism". *Eur. J. Gynaecol. Oncol.*, 2015, *36*, 469.

[4] Liang Y., Wu W.: "Exploratory analysis of health-related quality of life among the empty-nest elderly in rural China: An empirical study in three economically developed cities in eastern China". *Health Qual. Life Out.*, 2014, *12*, 1.

[5] Lafaille A., Tjalma W.A.A.: "Guide wire surgery in breast cancer and why to avoid scissors". *Eur. J. Gynaecol. Oncol.*, 2015, *36*, 477.

[6] Liang Y., Lu W.Y., Wu W.: "Are social security policies for Chinese landless farmers really effective on health in the process of Chinese rapid urbanization? a study on the effect of social security policies for Chinese landless farmers on their health-related quality of life". *Int. J. Equity Health*, 2014, *13*, 1.

[7] Madadi M., Zhang S.F., Henderson L.M.: "Evaluation of breast cancer mammography screening policies considering adherence behavior". *Eur. J. Oper. Res.*, 2015, *247*, 630.

[8] Liang Y., Cao R.X.: "Employment assistance policies of Chinese government play positive roles! The impact of post-earthquake employment assistance policies on the health-related quality of life of Chinese earthquake populations". *Soc. Indic. Res.*, 2015, *120*, 835.

[9] Zhang X.X., Wang T., Wang W., Ding Y.B., Zhou L.X., Chen Q.Y., *et al.*: "Does familial breast cancer and thymoma suggest a cancer syndrome? A family perspective". *Gene*, 2015, *573*, 333.

[10] Liang Y., Guo M.L.: "Utilization of Health Services and Health-Related Quality of Life Research of Rural-to-Urban Migrants in China: A Cross-Sectional Analysis". *Soc. Indic. Res.*, 2015, *120*, 277.

[11] Liang Y., Cao R.X.: "Is the health status of female victims poorer than males in the post-disaster reconstruction in China: a comparative study of data on male victims in the first survey and double tracking survey data". *BMC Womens Health*, 2014, *14*, 1.

[12] Nagari A., Franco H.L.: "Interplay between inflammatory and estrogen signaling in breast cancer". *Cytokine*, 2015, *76*, 588.

[13] Liang Y.: "Satisfaction with economic and social rights and quality of life in a post-disaster zone in China: evidence from earthquake-prone Sichuan". *Disaster Med. Public Health Prep.*, 2015, *9*, 111.

[14] Liang Y., Lu P.Y.: "Medical insurance policy organized by Chinese government and the health inequity of the elderly: longitudinal comparison based on effect of New Cooperative Medical Scheme on health of rural elderly in 22 provinces and cities". *Int. J. Equity Health*, 2014, *13*, 1.

[15] Alonso-González C., González A., Martínez-Campa C., Menéndez-Menéndez J., Gómez-Arozamena J., García-Vidal A., Cos S.: "Melatonin enhancement of the radiosensitivity of human breast cancer cells is associated with the modulation of proteins involved in estrogen biosynthesis". *Cancer Lett.*, 2016, *370*, 145.

[16] Liang Y., Wang X.K.: "Developing a new perspective to study the health of survivors of Sichuan earthquakes in China: a study on the effect of post-earthquake rescue policies on survivors' health-related quality of life". *Health Res. Policy Syst.*, 2013, *11*, 1.

[17] Vriend J., Reiter R.J.: "Breast cancer cells: Modulation by melatonin and the ubiquitin-proteasome system – A review". *Mol. Cell. Endocrinol.*, 2015, *417*, 1.

[18] Liang Y., Wu W.: "Exploratory analysis of health-related quality of life among the empty-nest elderly in rural China: An empirical study in three economically developed cities in eastern China". *Health Qual. Life Out.*, 2014, *12*, 1.

[19] Eissa S., Matboli M., Sharawy A., El-Sharkawi F.: "Prognostic and biological significance of microRNA-221 in breast cancer". *Gene*, 2015, *574*, 163.

[20] Liang Y., Lu P.Y.: "Health-related quality of life and the adaptation of residents to harsh post-earthquake conditions in China". *Disaster Med. Public Health Prep.*, 2014, *8*, 390.

[21] Liang Y., Wang P.G.: "Influence of Prudential Value on the Subjective Well-Being of Chinese Urban–Rural Residents". *Soc. Indic. Res.*, 2014, *118*, 1249.

[22] Wei Z. X., Song X.L., Shaikh Z.A.: "Cadmium promotes the proliferation of triple-negative breast cancer cells through EGFR-mediated

cell cycle regulation". T*oxicol. Appl. Pharmacol.*, 2015, *289*, 98.
[23] LIANG Y., LI S.Q.: "Landless female peasants living in resettlement residential areas in China have poorer quality of life than males: results from a household study in the Yangtze River Delta region". *Health Qual. Life Out.*, 2014, *12*, 1.
[24] Liang Y., Yi Y.Y., Sun Q.F.: "The Impact of Migration on Fertility under China's Underlying Restrictions: A Comparative Study Between Permanent and Temporary Migrants". *Soc. Indic. Res.*, 2014, *116*, 307.
[25] Hystad P., Villeneuve P.J., Goldberg M.S., Crouse D.L., Johnson K.: "Exposure to traffic-related air pollution and the risk of developing breast cancer among women in eight Canadian provinces: A case–control study". *Environ. Int.*, 2015, *74*, 240.
[26] LiangY.: "Correlations Between Health-Related Quality of Life and Interpersonal Trust: Comparisons Between Two Generations of Chinese Rural-to-Urban Migrants". *Soc. Indic. Res.*, 2015, *123*, 677.
[27] Forman M.R., Winn D.M., Collman G.W., Rizzo J., Birnbaum L.S.: "Environmental exposures, breast development and cancer risk: Through the looking glass of breast cancer prevention". *Reprod. Toxicol.*, 2015, *54*, 6.
[28] Liang Y., Zhu D.M.: "Subjective well-being of Chinese landless peasants in relatively developed regions: measurement using PANAS and SWLS". *Soc. Indic. Res.*, 2015, *123*, 817.
[29] Bidgoli S.A., Ahmadi R., Zavarhei M.D.: "Role of hormonal and environmental factors on early incidence of breast cancer in Iran". *Sci. Total. Environ.*, 2010, *408*, 4056.
[30] Liang Y.: "Trust in Chinese Government and Quality of Life (QOL) of Sichuan Earthquake Survivors: Does Trust in Government Help to Promote QOL". *Soc. Indic. Res.*, 2016, *172*, 541.
[31] Tang M.L., Zhao M.R., Zhou S.S., Chen K., Zhang C.L., Liu W.P.: "Assessing the underlying breast cancer risk of Chinese females contributed by dietary intake of residual DDT from agricultural soils". *Environ. Int.*, 2014, *73*, 208.
[32] Liang Y., Wang H.W., Tao X.J.: "Quality of life of young clinical doctors in public hospitals in China's developed cities as measured by the Nottingham Health Profile (NHP)". *Int. J. Equity Health*, 2015, *14*, 1.
[33] Mohamed M.M., Al-Raawi D., Sabet S.F., El-Shinawi M.: "Inflammatory breast cancer: New factors contribute to disease etiology: A review". *J. Adv. Res.*, 2014, *5*, 525.
[34] Zhou W.Q., Wang G.D., Guo S.C.: "Regulation of angiogenesis via Notch signaling in breast cancer and cancer stem cells". *BBA-Rev. Cancer*, 2013, *1836*, 304.
[35] Lee J.S., Oh M.: "Reproductive factors and subtypes of breast cancer defined by estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2: a register-based study from Korea". *Clin. Breast Cancer*, 2014, *14*, 426.
[36] He B.S., Pan Y.Q., Lin K., Ying H.Q., Wang F., Deng Q.W., *et al.*: "Evaluation the susceptibility of five polymorphisms in microRNA-binding sites to female breast cancer risk in Chinese population". *Gene*, 2015, *573*, 160.
[37] Fortune M.L.: "The impact of the national breast and cervical cancer early detection program on breast cancer outcomes for women in Mississippi". *J. Cancer Policy*, 2015, *6*, 25.

Corresponding Author:
Y.B. LING, M.D.
Nanjing Normal University of Special Education
Shennong Road 1, Qixia District
Nanjing, Jiangsu (China)
e-mail: lingyingbing2010@163.com