EXPOSURE TO DDT AND RISK OF BREAST CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

Park J-H[1], Cha ES[2], Ko Y[2], Hwang M-S[1], Lee WJ[2]*

[1] Food Safety Risk Assessment Division, National Institute of Food & Drug Safety Evaluation, Ministry of Food and Drug Safety,Osong-eup, Cheongwon-gun, Chungcheongbuk-do 363-700, South Korea; [2]Department of Preventive Medicine, College of Medicine, Korea University, 73 Inchon-ro, Seongbuk-gu, Seoul 136-705, South Korea

Introduction

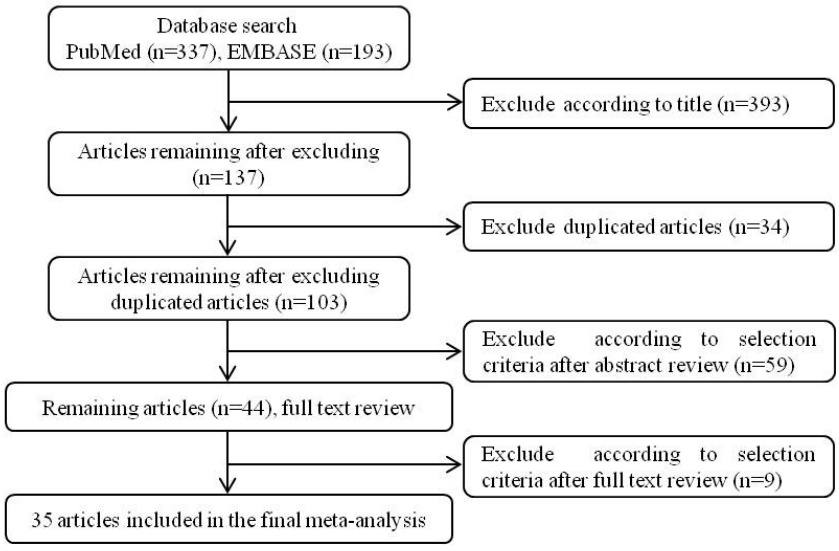
The insecticidebis[*p*-chlorophenyl]-1,1,1-trichloroethane (DDT) was widely used to prevent malaria and some agricultural pests worldwide. Since DDT and its main metabolite 2,2-bis[*p*-chlorophenyl]-1,1-dichloroethylene(DDE) were first reported to be related with breast cancer in 1993[1], there are increased attention between exposure to DDT and the risk of breast cancer. However, epidemiological evidence is far from conclusive. Although previous meta-analysis of 22 studies showed no evidence for an association between *p,p'*-DDE body burden levels and breast cancer risk[2],exposure to *p,p'*-DDT early in life was reported to increase breast cancer risk[3].

Therefore, we aimed to provide an update of a systematic review and meta-analysis to estimate the strength of the association between DDT exposure and the risk of breast cancer by different study characteristics.

Materials and methods

We searched and reviewed PubMed and EMBASE to identify eligible epidemiologic studies published in English up to August 2012, using selected common key words related to DDT exposure and risk of breast cancer. Reference lists of the identified articles and previous literature reviews were carefully examined for additional studies. The key words were as follows: 1) PubMed search key words(((DDT OR Dichlorodiphenyldichloroethylene) OR "Hydrocarbons, Chlorinated") OR (Organochlorines OR DDE) OR p,p'-DDE) AND "Breast Neoplasms" and 2) EMBASE key words ('chlorphenotane' OR '1,1dichloro 2,2 bis(4 chlorophenyl)ethylene' OR 'organochlorine pesticide' OR organochlorines OR dde OR 'pp, dde') AND 'breast cancer'. The subject of publication was limited to humans for all databases. We included epidemiologic studies that met the following criteria: (1) Studies that presented original data from case–control or cohort studies; (2) The outcome of interest was clearly defined as breast cancer; (3) The exposure of interest was DDT or DDT metabolites; and (4) Studies that provided measurement with standardized mortality ratio (SMR) and 95% confidence intervals (CI), adjusted relative risk (RR) estimatesand95% CIs, odds ratio (OR)and 95% CIs,or values in cells of a 2×2 table (e.g., number of cases and controls in exposure categories, from which OR could be calculated).If data were duplicated or shared in more than one study, only the most recent or more comprehensive study was included in the analysis.All studies from which a structured abstract was derived were reviewed and extracted independently by

Fig 1. Flow diagram for study identification process



two evaluators (E.S.C and Y.K.), according to the meta-analysis of observational studies in epidemiology (MOOSE) guidelines[4]. Meta-analytic techniques that weight the logarithm of the OR of each study by a function of its variance were used to calculate a summary estimate. Meta-analyses were performed on the total data set and separately for the type of design (hospital based case-control, population based case-control and nested case-control), study years (2000s, 1990s, 1980s and 1970s), biologic specimen (serum, plasma, breast adipose tissue and other organic adipose tissue), and geographical region of the study (North America, Europe, Asia and South America). A random effect model was used to estimate pooled ORs regarding potential heterogeneity of the study populations. Statistical heterogeneity between studies was assessed with the Q-statistics and quantified by I^2. We assessed potential publication bias by examining funnel plots and using Egger's test.All the statistical analyses were performed using the software STATA11.

Results and discussion

The PubMed and EMBASE search yielded 530 articles, and 44 articles remained after screening based on the inclusion criteria. Upon reviewing of the full text of the remaining 44 articles, we identified 35 articles for DDT exposure and the risk of breast cancer.Two articles each consisted of two subpopulations, and we treated data of each subgroup as a separate study, therefore, yielding a total of 37 studies in final meta-analysis (Fig 1).

Table 1 shows the distribution of selected characteristics of studies included in the meta-analysis, which provided results for breast cancer. All were case-control studies, and of these ten were prospective (nested case-control) and 27 retrospective, which consist of 8,160 cases and 9,280controls.The five studies indicated a significant positive association with the risk of breast cancer, whereas no significant association was observed in 32 studies each.

Table 1. Summary of articles including in the meta-analysis for DDT exposure and breast cancer risk

Author (year)	Study years	Country	Design	Case/Control	Biologic specimen	OR (95% CI)
Aronson (2000)[5]	1995-1997	Canada	hospital CC	217/213	adipose tissue	1.10 (0.78, 1.55)
Charlier (2004)[6]	2001-2002	Belgium	population CC	231/290	serum	2.21 (1.41, 3.48)
Cohn (2007)[3]	1959-1967	USA	hospital CC	129/129	serum	1.29 (0.85, 1.96)
Dello Iacovo (1999)[7]	1997-1998	Italy	population CC	170/195	serum	1.02 (0.68, 1.54)
Demers (2000)[8]	1994-1997	Canada	population CC	315/307	plasma	0.91 (0.70, 1.17)
Demers (2000)[8]	1994-1997	Canada	hospital CC	315/219	plasma	1.01 (0.74, 1.39)
Dorgan (1999)[9]	1977-1987	USA	nested CC	105/207	serum	0.70 (0.47, 0.99)
Gammon (2002)[10]	1996-1997	USA	population CC	643/427	serum	1.20 (0.76, 1.90)
Gatto (2007)[11]	1995-1998	USA	population CC	355/327	serum	1.05 (0.82, 1.35)
Helzlsouer (1999)[12]	1974	USA	nested CC	235/235	serum	0.94 (0.71, 1.25)
Helzlsouer (1999)[12]	1989	USA	nested CC	105/105	serum	0.88 (0.56, 1.38)
Hoyer (1998)[13]	1976	Denmark	nested CC	237/469	serum	0.88 (0.56, 1.37)
Hoyer (2000)[14]	1976-1978/1981-1983	Denmark	nested CC	240/477	serum	1.04 (0.70, 1.55)
Ibarluzea (2004)[15]	1996-1998	Spain	hospital CC	198/260	adipose tissue	1.16 (0.83, 1.62)
Itoh (2009)[16]	2001-2005	Japan	population CC	349/349	serum	0.74 (0.48, 1.13)
Iwasaki (2008)[17]	1990-1995	Japan	nested CC	139/278	plasma	1.23 (0.80, 1.90)
Krieger (1994)[18]	1964-1969	USA	nested CC	150/150	serum	1.31 (0.82, 2.09)
Laden (2001)[19]	1989-1990	USA	nested CC	372/372	plasma	0.79 (0.61, 1.01)
Liljegren (1998)[20]	1993-1995	Sweden	hospital CC	43/35	adipose tissue	0.40 (0.10, 1.20)
Lopez-Carrillo (1997)[2]	1994-1996	Mexico	hospital CC	141/141	serum	0.68 (0.43, 1.07)
McCready (2004)[21]	1995-1997	Canada	hospital CC	68/52	adipose tissue	2.48 (1.08, 5.71)
Mendonca (1999)[22]	1995-1996	Brazil	hospital CC	162/331	serum	1.05 (0.75, 1.46)
Millikan (2000)[23]	1993-1996	USA	population CC	748/659	plasma	1.07 (0.86, 1.32)
Moysich (1998)[24]	1986-1991	USA	population CC	154/192	serum	1.15 (0.74, 1.79)
Olaya-Contreras (1998)[25]	1995-1996	Colombia	hospital CC	153/153	serum	1.56 (1.02, 2.39)
Pavuk (2003)[26]	1997-1999	USA	hospital CC	24/85	serum	1.49 (0.45, 4.87)
Raaschou-Nielsen (2005)[27]	1993-1997	Denmark	nested CC	363/363	adipose tissue	0.87 (0.69, 1.10)

Romieu (2000)[28]	1990-1995	Mexico	population CC	120/126	serum	2.02 (1.14, 3.57)
Rubin (2005)[29]	1981-1987	USA	population CC	63/63	serum	0.97 (0.41, 2.32)
Schecter (1997)[30]	1994	Veitnam	hospital CC	21/21	serum	0.69 (0.23, 2.07)
Stellman (2000)[31]	1994-1996	USA	hospital CC	232/323	adipose tissue	0.94 (0.66, 1.33)
van't Veer (1997)[32]	1991-1992	Five European counties	hospital CC	265/341	adipose tissue	0.75 (0.52, 1.08)
Wolff (1993)[1]	1985-1991	USA	population CC	58/171	serum	2.30 (1.31, 4.04)
Wolff (2000)[33]	1994-1996	USA	hospital CC	151/317	serum	0.86 (0.61, 1.22)
Wolff (2000)[34]	1987-1992	USA	nested CC	110/213	serum	0.83 (0.50, 1.37)
Zheng (1999)[35]	1994-1997	USA	hospital CC	304/304	adipose tissue	1.02 (0.73, 1.41)
Zheng (2000)[36]	1995-1997	USA	hospital CC	475/502	serum	1.01 (0.79, 1.28)

hospital CC, hospital-based case-control; population CC, population-based case-control; nested CC, cohort-based case-control; OR, odds ratio; CI, confidence interval

As shown in Table 2, therewas no significantly associationbetween exposure to DDT and the risk of breast cancer in a random-effect model meta-analysis of all 37 case-control studies (OR=1.03; 95% CI, 0.94-1.13).Inthe subgroup meta-analyses by the type of study design, study years, type of biologic specimen and country, no significant association was observed between exposure to DDT and the risk of breast cancer. In meta-regression, the type of study design, study years, type of biologic specimen and country were not significant predictors of heterogeneity among the study populations (data not shown).

Table 2.Meta-analysis of the effect of the exposure to DDT on the risk of breast cancer according to subgroup

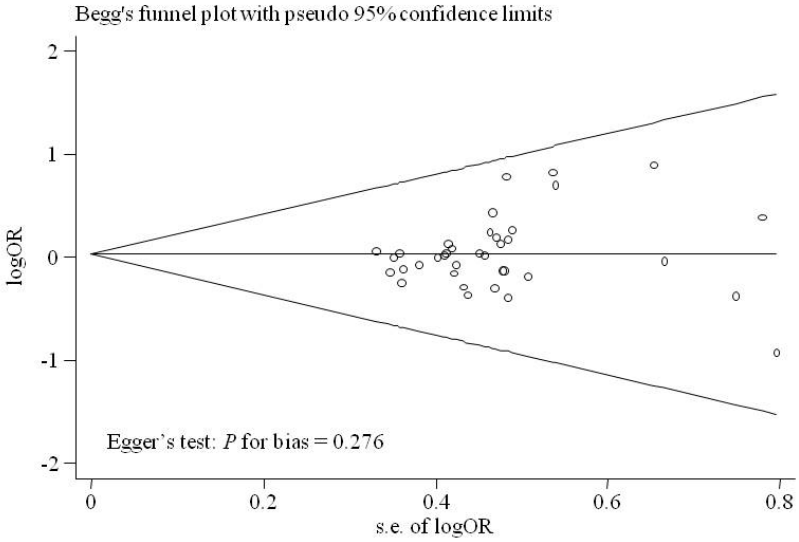
Studies included	**No. of Studies**	**Summary OR**	**95% CI**	**Heterogeneity, I^2(%)**
All	37	1.03	0.94 to 1.13	27.7
Type of study design				
hospital CC	15	1.09	0.95 to 1.25	20.5
population CC	11	1.07	0.91 to 1.26	42.2
nested CC	7	0.89	0.75 to 1.05	0
Study years				
2000s	2	0.99	0.59 to 1.66	75.2
1990s	22	1.09	0.98 to 1.21	22.7
1980s	6	0.97	0.74 to 1.27	34.2
1970s	3	0.84	0.66 to 1.08	0
Type of biologic specimen				
Serum	21	1.04	0.93 to 1.17	22.3
Plasma	5	0.92	0.78 to 1.08	9.8
Breast adipose tissue	4	1.20	0.79 to 1.84	52.7
Other organic adipose tissue	3	1.08	0.79 to 1.46	46.7
Country				
North America	20	1.03	0.92 to 1.15	25.2
Europe	6	0.99	0.82 to 1.18	8.4
Asia	3	0.98	0.58 to 1.65	59.6
South America	4	1.03	0.94 to 1.13	44.6

Funnel plots of all studiesrevealed a symmetrical distribution, suggesting no publication bias in this meta-analysis (Begg's funnel plot was symmetric; Egger's test, *P* for bias=0.276; Fig 2).Although these results showed no evidence for an association between exposure to DDT and the risk of breast cancer, there are a few limitations of these epidemiologic studies. The major concern is that most of thesestudies were undertaken after 1990s and in developed countries, where use of DDT had been banned before 20 years. There is a possibility that it may dilute or reduce an association between exposure to DDT metabolites and the risk of breast cancer. The other limitation is that most studies neglected the age of exposure to DDT metabolites. Based on the Cohn's study, however, high levels of serum *p,p'*-DDT predicted a statistically significant 5-fold increased risk of breast cancer among women who were born after 1931. These women were under 14 years of age in 1945 when DDT came into widespread use, and mostly under 20 years as DDT use peaked[3].

Despite of limitations, our overall summary estimates strongly demonstrated that exposure to DDT was not increase the risk of breast cancer. Considering low heterogeneity and no significant publication bias in this study, the findings would have high level of evidence.

Acknowledgements
This study was supported by a grant (12161KFDA767) from Korea Food & Drug Administration in 2012.

Fig 2. Begg's funnel plots and Egger's test for identifying publication bias in a meta-analysis of overall case-control studies (n = 37).



References

1. Wolff, M. S., *et al.* (1993); *J Natl Cancer Inst*. 85: 648-52
2. Lopez-Carrillo, L., *et al.* (1997); *Cancer Res*. 57: 3728-32
3. Cohn, B. A., *et al.* (2007); *Environ Health Perspect*. 115: 1406-14
4. Stroup, D. F., *et al.* (2000); *JAMA*. 283(15): 2008-12
5. Aronson, K. J., *et al.* (2000); *Cancer Epidemiol Biomarkers Prev*. 9: 55-63
6. Charlier, C., *et al.* (2004); *Clin Chem Lab Med*. 42: 222-7
7. Dello Iacovo, R., *et al.* (1999); *Adv Exp Med Biol*. 472: 57-66
8. Demers, A., *et al.* (2000); *Cancer Epidemiol Biomarkers Prev*. 9: 161-6
9. Dorgan, J. F., *et al.* (1999); *Cancer Causes Control*. 10: 1-11
10. Gammon, M. D., *et al.* (2002); *Cancer Epidemiol Biomarkers Prev*. 11: 686-97
11. Gatto, N. M., *et al.* (2007); *Cancer Causes Control*. 18: 29-39
12. Helzlsouer, K. J., *et al.* (1999); *Cancer Epidemiol Biomarkers Prev*. 8: 525-35
13. Hoyer, A. P., *et al.* (1998); *Lancet*. 352: 1816-20
14. Hoyer, A. P., *et al.* (2000); *Cancer Causes Control*. 11: 177-84
15. Ibarluzea, J. J., *et al.* (2004); *Cancer Causes Control*. 15: 591-600
16. Itoh, H., *et al.* (2009); *Cancer Causes Control*. 20: 567-80
17. Iwasaki, M., *et al.* (2008); *Sci Total Environ*. 402: 176-83
18. Krieger, N., *et al.* (1994); *J Natl Cancer Inst*. 86: 589-99
19. Laden, F., *et al.* (2001); *Int J Cancer*. 91: 568-74
20. Liljegren, G., *et al.* (1998); *Eur J Cancer Prev*. 7: 135-40
21. McCready, D., *et al.* (2004); *Cancer Causes Control*. 15: 399-418
22. Mendonca, G. A., *et al.* (1999); *Int J Cancer*. 83: 596-600
23. Millikan, R., *et al.* (2000); *Cancer Epidemiol Biomarkers Prev*. 9: 1233-40
24. Moysich, K. B., *et al.* (1998); *Cancer Epidemiol Biomarkers Prev.* 7: 181-8
25. Olaya-Contreras, P., *et al.* (1998); *Cad Saude Publica*. 14: 125-32
26. Pavuk, M., *et al.* (2003); *J Expo Anal Environ Epidemiol*. 13: 267-75
27. Raaschou-Nielsen, O., *et al.* (2005); *Cancer Epidemiol Biomarkers Prev*. 14: 67-74
28. Romieu, I., *et al.* (2000); *Am J Epidemiol*. 152: 363-70
29. Rubin, C. H., *et al.* (2006); *Int J Circumpolar Health*. 65: 18-27
30. Schecter, A., *et al.* (1997); *Arch Environ Contam Toxicol*. 33: 453-6
31. Stellman, S. D., *et al.* (2000); *Cancer Epidemiol Biomarkers Prev*. 9: 1241-9
32. van't Veer, P., *et al.* (1997); *BMJ*. 315: 81-5
33. Wolff, M. S., *et al.* (2000); *Environ Res*. 84: 151-61
34. Wolff, M. S., *et al.* (2000); *Cancer Epidemiol Biomarkers Prev*. 9: 271-7
35. Zheng, T., *et al.* (1999); *Am J Epidemiol*. 150: 453-8
36. Zheng, T., *et al.* (2000); *Cancer Epidemiol Biomarkers Prev*. 9: 167-74