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Review Paper

2,3,7,8-Tetrachlorodibezo-p-dioxin exposure and prostate cancer: a meta-analysis of cohort studies

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ABSTRACT

Objective: To perform a meta-analysis of cohort studies and evaluate the association between exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and prostate cancer quantitatively.

Study design: Publications before April 2012 about populations exposed to TCDD were searched in PubMed. Only cohort studies were included. Extraction and quality assessment of included articles was performed independently by two authors using the MOOSE guidelines.

Methods: A total of 17 cohort studies on prostate cancer with information about standardized mortality ratios (SMR), risk ratio (RR), standardized incidence ratios (SIR) and TCDD exposure were included. SMRs and RRs were pooled separately after weighing each study by calculating the inverse of the estimated variance.

Results: Based on the 13 reported SMRs or SIRs, the meta-analysis yielded a meta-SMR of 1.26 (95% confidence interval 1.00–1.57, $P = 0.046$). The meta-RR, based on four reported RR from four cohorts, was 1.04 (95% confidence interval 0.85–1.28). Begg's funnel plot showed little evidence of publication bias (Egger's test P-value = 0.817).

Conclusion: This meta-analysis suggests that exposure to TCDD is associated with increased risk of prostate cancer.

Introduction

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is a widespread environmental contaminant,[1] and it is the most toxic halogenated aromatic hydrocarbon.[2] TCDD is a multisite carcinogen.[3] Long-term TCDD exposure leads to the development of tumours of the liver, thyroid, lung, skin, oral cavity, ovary and other sites in animal experiments.[3,4] The last full-scale International Agency for Research on Cancer (IARC) Monographs review, completed in 1997, classified TCDD as a human carcinogen.[5] However, this claim has been challenged recently.[6,7] Therefore, it is still

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controversial whether TCDD could exhibit carcinogenic effect in humans.

The incidence of prostate cancer has increased over recent decades and it is now the most commonly diagnosed cancer among men in Europe and USA.[8,9] While the prostate cancer incidence remains lower in Asian countries than in North America, there is still a remarkable increase in the mortality in China, Japan, Korea and Singapore.[10,11] The current knowledge of the aetiology of prostate cancer is limited and the cause of prostate cancer remains speculative. Both in-vivo and in-vitro experiments suggest that TCDD, acting as an endocrine disruptor, may contribute to the development of certain cancers, including prostate cancer.[12,13] Because the epidemiological investigations are not conclusive, a meta-analysis was performed to evaluate the association between exposure to TCDD and prostate cancer quantitatively.

Methods

Data sources

Publications before April 2012 about populations exposed to TCDD were searched in PubMed. The search was conducted using several combinations of the following key words in the full text: prostatic neoplasm, prostate cancer, cancer of the prostate, prostate carcinoma, neoplasm, cancer, carcinoma, TCDD, cohort, standardized mortality ratio (SMR), risk ratio (RR), and standardized incidence ratio (SIR). References cited in the selected articles were also considered.

Study selection

The studies included in the meta-analysis should meet the following criteria:

(1) Cohort studies were published in English in peer reviewed journals. The publication date was before April, 2012;
(2) The cohort was a population with unequivocal evidence of exposure to TCDD (for example herbicide workers exposed to 2,4,5-trichlorophenol (TCP) and 2,4,5-Trichlorophenoxyacetic acid (2,4,5-T) and Veterans of the Vietnam War exposed to Agent Orange);[14]
(3) The cause-specific deaths were classified by the International Classification of Diseases (ICD) code;
(4) The SMR, SIR or RR was reported;
(5) The report provided sufficient data to determine the estimate and confidence intervals of SMR or RR.

Studies were excluded from the analysis if they:

(1) included subjects that were already included in another more complete or more recent study of a similar design, or these subjects were already included in a study with a longer follow-up time;
(2) did not report original results (reviews, comments, letters, and editorials);
(3) were population- or hospital-based case–control studies, or nested case–control studies that were with only limited documentation of TCDD exposure.

Data extraction

The articles and the extracted data were reviewed independently by two investigators (Ling Leng and Xiao-yan Luo), and any disagreement was resolved by consulting with a third reviewer (Chang-ping Li). The following information was recorded for each study: first author, year of publication, country, major chemicals exposed to, exposure setting, cohort size, observed deaths, average person-year, SMR/SIR/RR and 95% confidence interval (CI) for prostate cancer.

Statistical analysis

In recent publications, RR was calculated by comparing the mortality of two groups, while SMR was used more often in the past. Due to the differences between these two statistics, SMRs and RRs were pooled separately.[15] There was only one SIR included in this analysis, so it was pooled with SMR. Log-transformed 95% CIs were calculated for estimating the standard errors (SEs) for the ln(SMR) or ln(RR) by the formula: $SE = [\ln(\text{upper limit}) - \ln(\text{lower limit})] \div (2 \times Z_{1-\alpha/2})$, where for a 95% CI, $Z_{1-\alpha/2}$ equals 1.96.[16] For studies in which there was zero observed and expected events, 1 was added to both the observed and expected number of events so that an estimate of ln(SMR)/ln(SIR) and its associated standard error could be calculated.[17]

Overall pooled SMR estimates and their corresponding 95% CIs were obtained using fixed-effects (Mantel–Haenszel method) or random-effects (DerSimonian and Laird method) methods, weighing each study by measuring its precision as the inverse of the estimated variance.[18] When there is no detectable heterogeneity, the two estimates coincide. Heterogeneity of effects across studies was assessed by the Cochrane's Q statistic and was deemed significant when $P < 0.05$. In addition, the coefficient of inconsistency (I^2) as described by Higgins and Thompson was also computed to assess the heterogeneity.[19] I^2 is an estimate of the proportion of total variation that is due to heterogeneity. $I^2 > 25\%$ indicates significant heterogeneity.[16] Sensitivity analysis was conducted to determine whether the meta-SMR or meta-RR differed due to different study characteristics. Publication bias was evaluated by visual inspection of Begg's funnel plots and confirmed using Egger's regression asymmetry method.[20]

The meta-analysis was performed with Stata software (version 11; StataCorp LD, College Station, TX, USA) using a combination of available macros. A P-value <0.05 was considered statistically significant and would be indicated with an asterisk (*).

Results

Literature search

Overall, 319 citations were identified by using several combinations of key words, with 207 duplicate records. After removing duplicate citations, 112 citations were screened on basis of the title and abstract. 69 records were excluded for the following reasons: a, articles that were not population studies; b, articles did not report original results (reviews, comments,

Table 1 – Study characteristics.

Ref.	Cohort name	Country	Population	Exposure compounds	Outcome	Exposed persons	Average person-year (y)	Observed prostate cancer	SMR or RR (95% CI)
21	Pavuk (2006)	US	Air Force veterans of the Vietnam war	Agent Orange	RR	1019	21.0	59	1.07[a] (0.76–1.51)
22	Consonni (1) (2008)	Italy	Seveso accident exposed citizens in zone A	TCDD	RR	390	25.0	1	0.87 (0.12–6.17)
	Consonni (2) (2008)	Italy	Seveso accident exposed citizens in zone B	TCDD	RR	3017	25.0	8	0.88 (0.44–1.77)
	Consonni (3) (2008)	Italy	Seveso accident exposed citizens in zone R	TCDD	RR	19,199	25.0	65	1.06 (0.81–1.38)
23	McBride (2009)	New Zealand	Dow AgroSciences plant workers	2,4,5-T and TCP	SMR	1754	21.7	3	0.54 (0.11–1.56)
24	t Mannetje (2005)	New Zealand	Phenoxy herbicides sprayers	2,4,5-T	SMR	699	28.7	2	0.60 (0.07–2.16)
25	Collins (2009)[c]	US	Dow Chemical Company workers	2,4,5-T and TCP	SMR	1419	36.6	20	1.50 (0.90–2.40)
26	Steenland (1999)	US	12 plants workers	TCDD-conta-minated products	SMR	5132	–	28	1.17 (0.78–1.69)
6	Hooiveld (1998)	Nether-lands	Workers exposed to phenoxy herbicides	TCP	SMR	549	24.8	4	2.20 (0.60–5.70)
27	Becher (1) (1996)	Germany	Workers exposed to phenoxy herbicides and dioxins (Boehringer Ingelheim)	2,4,5-T and TCP	SMR	1144	24.0	7	1.47 (0.59–3.02)
	Becher (2) (1996)	Germany	Workers exposed to phenoxy herbicides and dioxins (Bayer Uerdingen)	2,4,5-T and TCP	SMR	135	29.4	1	1.53 (0.04–8.53)
	Becher (3) (1996)	Germany	Workers exposed to phenoxy herbicides and dioxins (Bayer Dormagen)	2,4,8-T and TCP	SMR	520	15.0	0	0.83[b] (0.02–4.64)
	Becher (4) (1996)	Germany	Workers exposed to phenoxy herbicides and dioxins (BASF Ludwigshafen)	2,4,8-T and TCP	SMR	680	21.9	1	0.67 (0.02–3.73)
28	Collins (1993)	US	Workers exposed by Monsanto accident	TCP	SMR	754	30.7	9	1.60 (0.70–3.00)
29	Cypel (2010)[c]	US	Army Chemical Corps Veterans	Agent Orange	SMR	2872	32.5	5	1.05 (0.34–2.45)
30	Ruder (2011)	US	PCP production workers exposed to TCP as well	PCP and TCP	SMR	720	–	8	1.08 (0.47–2.12)
31	Ott (1996)	Germany	Workers dealing with BASF AG accident	TCP	SIR	243	–	4	1.10 (0.30–2.80)

Not available.

[a] RR was calculated using the data from the article.

[b] 1 was added to both the observed and the expected number of events.

[c] These article were from relevant references. Average person-year (y) was calculated through dividing the total person-years of observation by exposed persons.

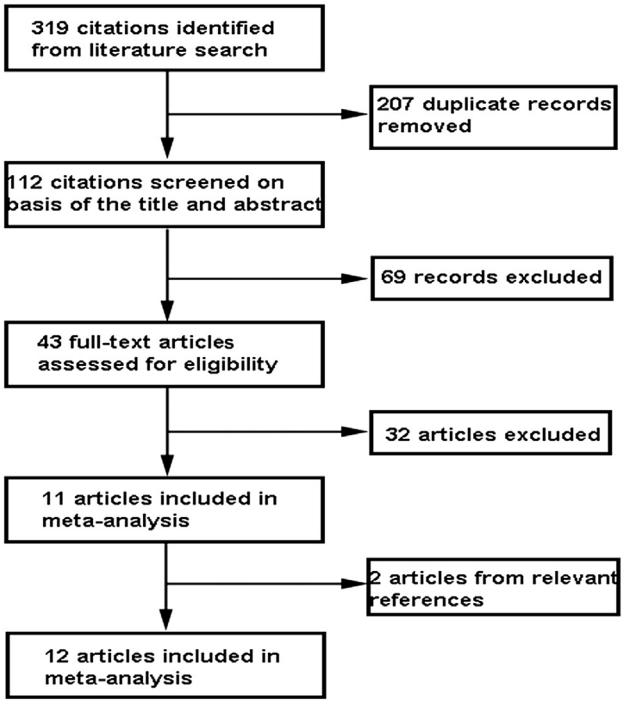

Fig. 1 – Flow chart of the meta-analysis.

letters, and editorials); c, articles that showed little information about TCDD exposure; d, articles that were not relevant to prostate cancer such as female populations. Among the remained 43 articles, full-text articles were assessed. According to the eligible criteria and/or the excluding criteria, 32 articles were excluded. Two articles came from cited references, of which Collins' (2009)[25] study took the place of Bodner's result[32] with the most updated data. Finally, 12 publications that included 17 cohorts and 40,286 TCDD exposed persons meeting the criteria for inclusion in the meta-analysis were identified (Table 1).[6,21–31] Fig. 1 shows the flow chart. One of these articles reported findings from three distinct cohorts,[22] and another one reported findings from four district cohorts.[27] Therefore data from 17 distinct populations were analysed. The mortalities of four cohorts were compared by RR. The prostate cancer incidence ratio of one cohort was calculated by SIR. SMR was used as the final statistic for the remaining 12 cohorts. As there was only one SIR, it was pooled with SMR.

All data of included cohorts were from the most recent publications. Subgroups of chloracne workers and high exposure groups were not considered as independent cohort because their information had already been included in their original cohort. A study[33] that included 13,144 men with or without exposure to Agent Orange was excluded because what the authors needed was the number of prostate cancer patients rather than the number of people who were likely to develop prostate cancer. The studies by Kogevina[34] and Saracci[35] were also excluded because most of the cohorts in their studies were updated and already included in this analysis. Table 1 summarizes the main characteristics of the selected studies.

Quantitative synthesis

Fig. 2 shows the SMR and 95% CI from the individual studies, as well as the pooled SMR. Due to the lack of detectable heterogeneity, the authors pooled them by fixed-effect model. An excess risk for prostate cancer with TCDD exposure was observed for the 13 pooled cohorts with SMRs, which is statistically significant (meta-SMRs = 1.26, 95% CI, 1.00, 1.57, *$P = 0.046$). The heterogeneity was not statistically significant ($Q = 5.09$, $I^2 = 0\%$, $P = 0.955$).

The precision of the meta-RRs for the prostate cancer incidence outcomes was lower than that of the corresponding mortality outcomes because of the smaller number of studies. The pooled RR for TCDD exposure and prostate cancer was 1.04 (95% CI, 0.85, 1.28, $P = 0.667$), with no statistically significant heterogeneity ($Q = 0.30$, $I^2 = 0\%$, $P = 0.961$).

Sensitivity analysis

The sensitivity analysis was conducted via systematic 'leave one out' exclusion method. The result for prostate cancer mortality and TCDD exposure was so robust that the exclusion of any one study did not change the conclusion of the meta-analysis (Fig. 3). The magnitude of the excess mortality observed for prostate cancer in the meta-analysis varied, with Consonni's cohort (3) and Collins cohort (2009) having the largest excess and being the most influential in reducing the point estimate for the pooled outcome. However the inference remains unchanged. The pooled SMR changed more or less when excluding any single study from the overall meta-analysis, but the change was no more than 10% (data was not shown).

Assessment of publication bias

Fig. 4 shows the Begg's funnel plot and results of Egger's corresponding asymmetry test for all 17 populations. All of the studies fall within the guidelines for a homogeneous funnel supplied on the graph. Egger's test produced a P-value of 0.817, indicating that this meta-analytic finding is robust to publication bias.

Discussion

This is the first meta-analytic review of cohort studies that evaluates the association between exposure to TCDD and prostate cancer. By combining results from 17 large observational cohort studies representing 40,286 participants followed for an average of >2 decades, the authors found that TCDD exposure is associated with a meta-SMR of 1.26 for prostate cancer. Therefore, it might be meaningful to include TCDD exposure as a risk factor for prostate cancer. Traditionally, hormonal imbalance associated with old age is considered to contribute to the development of prostate cancer.[36] Genetic predisposition may also be important because a higher prostate cancer incidence is observed in several ethnic groups.[37] Recently, attention has been paid to metabolic factors and androgens, which may promote prostate carcinogenesis via multiple mechanisms including inflammation,

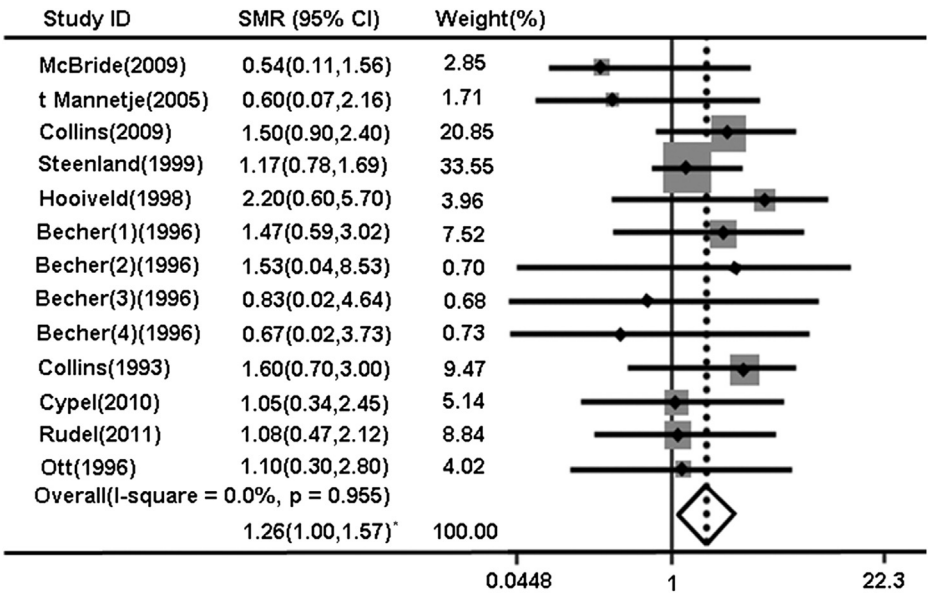

Fig. 2 – SMR and 95% CIs of prostate cancer associated with TCDD exposure. Weights are from fixed-effects analysis. Boxes show the study-specific SMR's proportional weight. Horizontal lines represent 95% CIs for the study-specific SMRs. The pooled SMR, which was shown as a diamond, was 1.26 (1.00, 1.57)*. The middle of the diamond corresponds to the SMR, and the width of the diamond represents the 95% CI.

adipokine action, fatty acid metabolism and insulin growth factor signalling.[38] Furthermore, there is increasing evidence suggesting that endocrine disruption plays a significant role in the induction and development of prostate cancer.[39–41]

The mechanism through which TCDD is linked to prostate cancer is probably multifactorial. Some animal studies indicated that TCDD acts directly on Aryl hydrocarbon Receptor (AhR), Aryl hydrocarbon Receptor Nuclear Translocator (ARNT), and AhR-induced transcripts in the periprostatic mesenchyme, and disrupts the dorsoventral patterning of the urogenital sinus. As a result, the prostatic bud areas are reprogrammed, and the formation of the prostate lobes is disrupted.[12,42,43] In addition, TCDD has been shown to induce cytochrome P450, family 1, subfamily A, polypeptide 1 (CYP1A1) activity and to a lesser extent cytochrome P450, family 1, subfamily B (CYP1B) activity in the hormone-independent human prostate cancer cell lines.[13] It also dramatically induces cytochrome P450, family 1, subfamily A, polypeptide 2 (CYP1A2) mRNA expression.[44] Moreover, TCDD exposure induces matrix metalloproteinase 9 (MMP-9) expression in human prostate cancer cells, suggesting that TCDD may regulate the expression of genes involved in tumour invasion.[45]

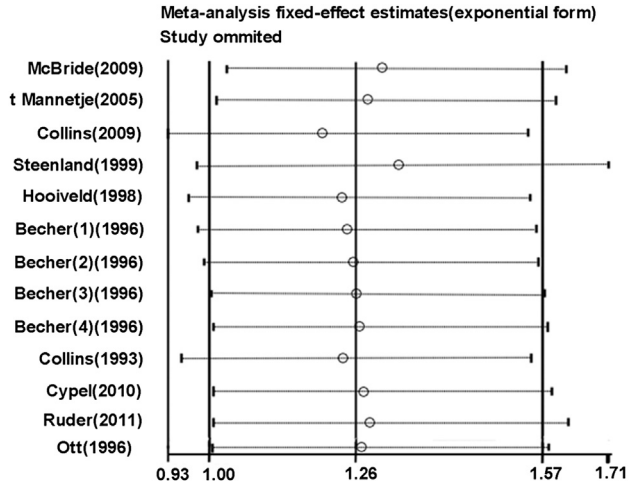

Fig. 3 – Plot shows the influence of excluding each individual study on the pooled estimate of prostate cancer mortality. Solid line on the left and right, the 95% CI of pooled SMR obtained using all studies; solid line in the middle, pooled SMR obtained using all studies; dotted lines, 95% confidence interval for the pooled SMR.

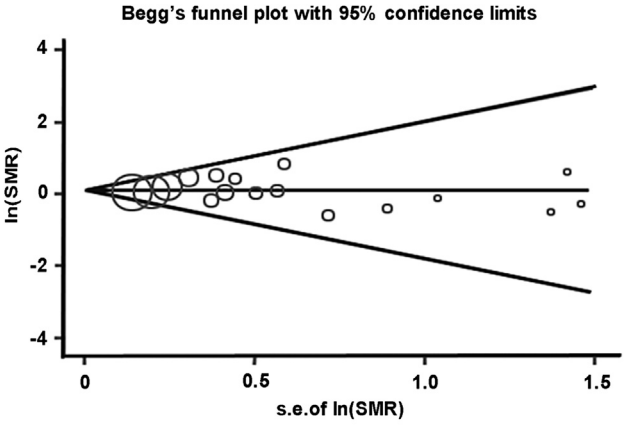

Fig. 4 – Begg's funnel plot with pseudo-95% CIs for prostate cancer mortality associated with TCDD exposure. Shown in the figure is [natural log (ln)] of pooled effect size of 17 cohorts. $P = 0.817$. s.e., standard error.

There are some limitations in this analysis. Firstly, the absence of known differences in TCDD exposure levels and exposure times among different studies weaken the association between exposure to TCDD and prostate cancer. Secondly, the statistics (such as SMR, SIR, RR and OR) were different among studies, which make it difficult to summarize the aggregate effect of TCDD exposure. This meta-analysis incorporated 17 cohorts, and used meta-SMR and meta-RR independently as final outcomes, since it is not appropriate to transform any one to the other.[15] Another limitation of this analysis is its inability to account for dose–response effect. Differences in the definitions of duration and latency of TCDD exposure measures prevented a proper evaluation of a dose–response relationship. Although there were limitations, this meta-analysis focused on men exposed to TCDD, and determined the SMR of prostate cancer. The results provide evidence for a potential role of TCDD exposure in prostate cancer. Further investigations, including larger and more precise epidemiological studies, are warranted to further understand the dose–response effect of TCDD exposure on prostate cancer.

Conclusion

The increased meta-standardized mortality ratio of prostate cancer in TCDD exposed subjects suggests that TCDD exposure is a contributing risk factor for prostate cancer. Future epidemiological studies should focus more on the relationship between dose–response effect of TCDD exposure and prostate cancer.

Author statements

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Ethical approval

Not required.

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Authors' contributions

Nai-jun Tang, Ling Leng and Xi Chen were involved in the conception and design, data search and analysis, interpretation of the results, and write-up of the first draft of the manuscript. Ling Leng and Xiao-yan Luo contributed to literature search and data extraction. Chang-Ping Li resolved the disagreement between Ling Leng and Xiao-yan Luo during data extraction. Besides, she gave advice on the design of the study, the analysis and interpretation of the results. All authors were involved in the preparation of the manuscript and approved the submitted manuscript.

Supporting statement

MOOSE guidelines have been used in preparation of this meta-analysis.

Competing interests

The authors declare that they have no competing interests.

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