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Environmental Endocrine Disruptors and Endometrial Cancer Risk: A Comprehensive Systematic Review

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ADMINISTRATIVE INFORMATION

Support - This review received no external funding.

Review Stage at time of this submission - Data extraction.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202560030

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 7 June 2025 and was last updated on 7 June 2025.

INTRODUCTION

Review question / Objective Population: Women at risk for or diagnosed with endometrial cancer
Intervention/Exposure: Exposure to endocrine-disrupting chemicals (EDCs) such as BPA, cadmium, phthalates
Comparator: Women not exposed or with lower levels of EDCs
Outcome: Association with increased risk of endometrial cancer
Study design: Observational studies and RCTs
Objective: To systematically evaluate the association between exposure to environmental EDCs and the risk of developing endometrial cancer in women.

Rationale Endometrial cancer (EC) is one of the most common gynecological malignancies, with increasing incidence globally. While traditional risk factors such as obesity, unopposed estrogen exposure, and age are well-established, growing evidence suggests that exposure to environmental endocrine-disrupting chemicals (EDCs) may play a role in endometrial carcinogenesis. EDCs are exogenous compounds that interfere with hormonal regulation and can mimic or block natural hormone actions. Substances such as bisphenol A (BPA), cadmium, phthalates, alkylphenols, and phytoestrogens have shown potential estrogenic effects in both in vitro and in vivo studies. However, epidemiological data remain inconsistent and fragmented. This systematic review aims to synthesize current evidence on the association between EDC exposure and EC risk in human populations, contributing to the identification of environmental risk factors and supporting preventive strategies in public health.

Condition being studied The condition of interest is endometrial cancer (EC), a hormone-sensitive malignancy originating in the lining of the uterus. EC predominantly affects postmenopausal women and is classified into estrogen-dependent (Type I) and non-estrogen-dependent (Type II) forms. The review focuses on how exposure to environmental endocrine disruptors may influence the risk of

developing EC through estrogenic or oxidative stress-mediated pathways.

METHODS

Search strategy A comprehensive literature search was conducted in the following electronic databases: Medline (via PubMed), Embase, Scopus, the Cochrane Database of Systematic Reviews, and ClinicalTrials.gov. The search covered all records from inception to April 2025. Search terms included MeSH terms and keywords related to the condition and exposures of interest: ("endometrial cancer" OR "endometrial neoplasms") AND ("endocrine disruptors" OR "endocrine-disrupting chemicals" OR "bisphenol A" OR "cadmium" OR "phthalates" OR "alkylphenols" OR "isoflavones"). The search was limited to human studies published in English. Additional articles were identified through manual screening of reference lists from eligible studies. Duplicates were removed, and records were screened using the Rayyan QCRI platform.

Participant or population Adult women, particularly those in postmenopausal status, who were evaluated in observational or interventional studies for exposure to EDCs in relation to endometrial cancer incidence.

Intervention Exposure to specific endocrine-disrupting chemicals (EDCs), including but not limited to bisphenol A (BPA), cadmium, phthalates (such as DBP, MnBP), lead, nonylphenol, octylphenol, and phytoestrogens (e.g., soy isoflavones), assessed through biomonitoring (urine, blood, dietary intake) or environmental measures.

Comparator Women with no documented exposure to EDCs or with lower levels of exposure.

Study designs to be included Observational studies (case-control and cohort) and randomized controlled trials.

Eligibility criteria Studies in humans; published in English; quantitative assessment of EDC exposure; outcome measured as risk/incidence of endometrial cancer. Exclusion: Reviews, editorials, commentaries, conference abstracts, in vitro or animal studies, insufficient data.

Information sources MEDLINE (PubMed), Embase, Scopus, Cochrane Library, ClinicalTrials.gov.
Manual screening of reference lists was also performed.

Main outcome(s) Association between exposure to EDCs and endometrial cancer risk, reported as odds ratios, relative risks, or hazard ratios.

Additional outcome(s) Subgroup effects based on menopausal status, BMI, or smoking history when reported.

Data management References were imported and managed using Rayyan QCRI. Data extraction was performed using standardized Excel forms. Discrepancies were resolved through consensus or by consulting a third reviewer.

Quality assessment / Risk of bias analysis The risk of bias for observational studies was assessed using the Newcastle-Ottawa Scale (NOS). The RCT was evaluated using the Cochrane RoB-2 tool. Two reviewers assessed quality independently.

Strategy of data synthesis A narrative synthesis was conducted due to heterogeneity in study designs, populations, and exposure assessment methods. Summary tables were used to report characteristics and outcomes of included studies.

Subgroup analysis When data allowed, subgroup analysis was considered by BMI categories (<25 vs ≥25 kg/m^2), menopausal status, and smoking history.

Sensitivity analysis Sensitivity analyses were planned by excluding studies at high risk of bias or those with insufficient exposure measurement details.

Language restriction Yes, English only.

Country(ies) involved Italy.

Other relevant information This protocol refers to a systematic review that includes both case-control and cohort studies assessing the relationship between exposure to endocrine-disrupting chemicals and endometrial cancer. The review follows PRISMA 2020 guidelines.

Keywords endometrial cancer; endocrine disruptors chemicals; BPA; cadmium; phthalates.

Dissemination plans Results will be submitted for peer-reviewed publication and presented at relevant scientific conferences.

Contributions of each author
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