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Per- And Poly-Fluoroalkyl Substances (PFAS) Exposure and Risk of Breast, and Female Genital Cancers: A Systematic Review and Meta-Analysis

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Abstract

Background: *PFASs, synthetic chemicals, can be encountered by humans through occupational or environmental exposure, and some reports suggest that they can disrupt endocrine and hormonal activities. In this comprehensive review and meta-analysis, we explored the connection between exposure to PFASs and the risks of breast and female genital cancers.* **Methods:** *We systematically reviewed the literature from IARC Monographs, ATSDR documents, and PubMed (as of January 2024) for cohort, case-control, and ecological studies on PFAS exposure and breast or female genital cancers. Four reviewers independently screened studies, and data extraction included study design, patient characteristics, and effect size measures. The quality of studies was assessed using the modified version of the Newcastle-Ottawa Scale (NOS). Forest plots of relative risks (RR) were constructed for breast and female genital cancer. Meta-analyses were conducted using random-effects models, stratified analyses, dose-response assessments, and publication bias evaluation.* **Results:** *The meta-analysis included 24 studies, comprising 10 cohort, 13 case-control, and one ecological study. The summary relative risk (RR) of breast cancer for PFOA exposure was 1.08 (95% CI = 0.97-1.20; n=21), and for PFOS was 1.00 (95% CI = 0.85-1.18; n=12). The RR for ovarian cancer and PFAS was 1.07 (95% CI = 1.04-1.09; n=12). The stratification by quality score, year of publication, and exposure source did not reveal any differences. However, analysis by geographical region (p=0.01) and study design (p=0.03) did show differences, particularly in terms of incidence. Stratified analyses of the dose-response relationship did not reveal a trend in the risk of breast cancer or female genital cancers, and no publication bias was found for either cancer type. No results were available for cervical and endometrial cancers.* **Conclusion:** *In summary, our results suggest an association between PFAS exposure and ovarian cancer and a possible effect on breast cancer incidence in some specific groups. However, bias and confounding cannot be excluded and prevent conclusions regarding causality.*

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Abbreviations:

- Agency for Toxic Substances and Disease Registry; ATSDR
- The Environmental Protection Agency; EPA
- The European Chemicals Agency; ECHA
- Endocrine-disrupting chemicals; EDCs
- Human papillomavirus; HPV
- The International Agency for Research on Cancer; IARC
- Nitrogen dioxide; NO2
- Odds ratio; OR
- Risk ratio, rate ratio; RR
- Standardized mortality ratio; SMR
- Standardized incidence ratio; SIR
- Perfluorooctanoic Acid; PFOA
- Per- and poly-fluoroalkyl substances; PFAS
- Perfluorooctane sulfonic acid; PFOS
- Perfluorononanoic acid; PFNA
- Perfluorobutane sulfonate; PFBS
- Perfluorohexanesulfonic acid; PFHxS

1. Introduction

Breast cancer (BC) is the most commonly diagnosed cancer (ASR=46.8 per 100,000) and the leading cause of cancer death (ASMR=12.7 per 100,000) among females worldwide in 2022 [1]. Also, female genital organ cancers (vulva, vagina, cervix, endometrium, ovary) account for approximately 15% of all female cancer cases and fatalities worldwide [1]. Previous studies reported an association between several factors, including demographic, lifestyle, socioeconomic, and infection factors, with the incidence and mortality of these cancers [2, 3]. Furthermore, these studies have been associated with specific occupational and environmental agents, especially those that can impact endocrine glands. These factors include exposure to ionizing and non-ionizing radiation, working night shifts, being exposed to pesticides, asbestos, polycyclic aromatic hydrocarbons (PAH), per- and polyfluoroalkyl substances (PFASs), as well as other job exposure agents [4, 5, 14].

PFASs are a large, complex group of synthetic chemicals that are thermally and chemically stable in the environment [6]. The most commonly used PFAS are perfluorooctane sulfonic acid (PFOS), perfluorooctane sulfonic acid (PFOA), perfluorononanoic acid (PFNA), perfluorobutane sulfonate (PFBS), perfluorohexanesulfonic acid (PFHxS) [8]. These substances have been used in the aerospace, automotive, construction, and electronics industries since the 1940s. They also produce stain- and water-resistant fabrics, firefighting foams, cleaning products, and paints. Humans can be exposed to these substances through occupational and environmental sources such as water, air, and soil [7, 9].

The International Agency for Research on Cancer (IARC) classified PFOA as carcinogenic to humans (Group 1) and PFOS as possibly carcinogenic to humans (Group 2B), mainly based on an association with kidney and testicular cancers [10, 11]. In addition, there is some evidence that other types of cancer, such as breast and female genital cancer, are associated with PFAS exposure, but the evidence remains limited [12-14].

To better clarify the potential effects of PFAS on cancer incidence and mortality, we conducted a systematic review and meta-analysis of occupational and environmental exposures to PFAS and the risk of breast and female genital cancers.

2. Methods

2.1. Data Sources, Search Strategy, Selection Criteria

First, searches were undertaken on January 23, 2024, for English-language peer-reviewed publications in PubMed and Scopus with no limit according to year of publication to identify more recent studies. Our work included studies on incidence or mortality from all solid and non-solid cancer types other than liver, kidney, and testicular, which were included in a previous report (12), and exposure to different types of PFAS, including PFOA, PFOS, PFDA, and PFNA. Then, we searched the reference lists of the IARC Monograph on PFOA/PFOS (10) and the Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile of PFAS (15). Our study protocol was registered in the PROSPERO database (Registration No. CRD42024560837), and we followed the COSMOS-E and PRISMA-statements to conduct and report systematic reviews and meta-analyses (16,17) (Supplementary Tables 7a, b).

The search strategy utilized the following MeSH terms: (("PFOA" OR "Perfluorooctanoic Acid" OR "PFOS" OR "Perfluorooctane Sulfonic Acid" OR "PFAS" OR "per and poly-fluoroalkyl substances") AND ("cancer" OR "malignant" OR "carcinoma" OR "neoplasm" OR "tumor" OR "myeloid" OR "lymphoma" OR "Hematologic")). The complete search string is reported in Supplementary Table 1.

We only included cohort, case-control, cross-sectional, and ecological human studies of occupational and environmental exposure to PFAS, including studies based on serum level, drinking water, or workplace exposure to PFAS. Studies involving animals or other non-human experimental systems were excluded. Also, we excluded studies in which we needed help finding the full text of the relevant articles. Four reviewers independently screened the titles and abstracts. The final selection was made after thoroughly reviewing the full text of potentially relevant articles. If multiple reports utilized the same database, we only included the most informative article with the most recent update.

The data extraction file contained demographic characteristics of the original studies, such as the author's name, year of publication, country, study design type (cohort, case-control, ecological), patient characteristics (sex), cancer type, PFAS types, PFAS exposure source (occupational or environmental), duration and level of exposure. We also extracted the effect sizes measures, such as relative risks (RRs), odds ratios (ORs), risk ratios, rate ratio, standardized mortality ratio (SMR), or standardized incidence ratio (SIR), as well as their respective 95% confidence intervals (CI). If results were reported only for subgroups, we combined them using a fixed effect meta-analysis. When RRs or CIs were not reported, we calculated them from the raw data if possible. This strategy led to the identification of 39 independent studies related to different solid and non-solid cancer types other than liver, kidney, and testicular cancer (Figure 1). In this report, our analysis contained 24 studies that addressed breast cancer (24 studies) and also female genital cancer only (6 studies) (Figure 1).

2.2 Quality Assessment

Four independent reviewers critically appraised the eligible studies using a modified version of the Newcastle-Ottawa Scale (NOS) (Supplementary Table 2) [18] for case-control, ecological, and cohort studies.

The scores were divided into two categories: low quality if the study scored less than 8 and high quality if it scored 8 or higher (Table 1).

2.3 Statistical Analysis

In this report, we examined the exposure to total and different types of PFAS and incidence or mortality from breast and female genital (ovarian, cervix, and uterus, the latter comprising endometrium and uterus not otherwise specified) cancers based on the RR and the respective 95% CIs. Heterogeneity among studies was assessed using the Q test, which evaluated variation across studies rather than within them, and the I^2 statistic, which indicates the percentage of variance in a meta-analysis attributable to study heterogeneity [19]. Random-effect models were used for the meta-analysis to

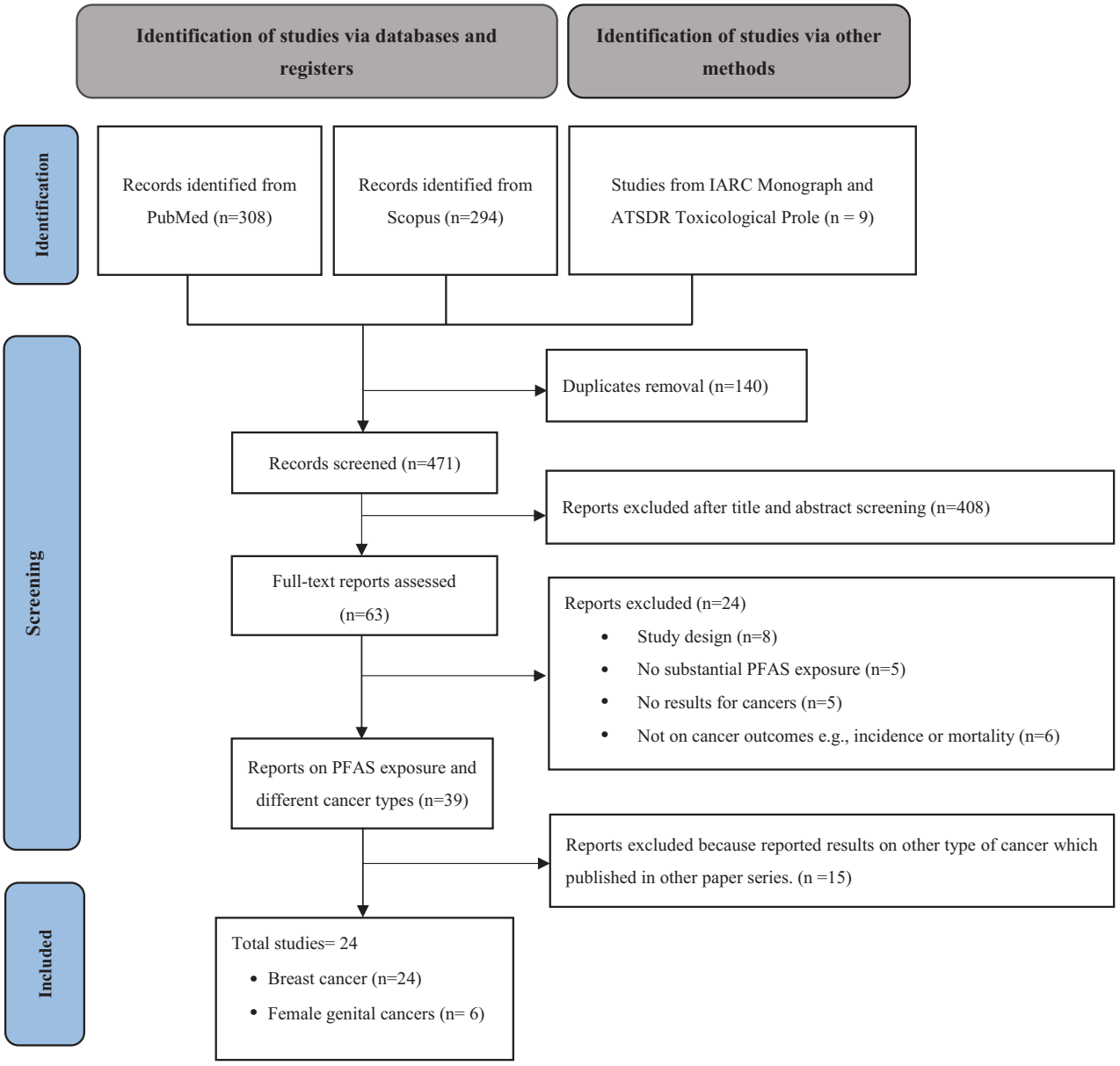


Figure 1. Selection of studies for inclusion in the review and meta-analysis.

account for heterogeneity in the design characteristics of the included studies [20]. We initially performed a meta-analysis including non-overlapping studies for each cancer type (breast and female genitals) separately. We then conducted stratified analyses by region (North America, Europe, and other areas), study design (case-control or cohort), quality score (low quality or high quality), outcome (incidence or mortality), exposure source (environmental, occupational), gender (male/female/both), and year of publication (<2019, >= 2019).

In addition, we performed a meta-regression of the RR on the quality scores. We also extracted dose-response results, including analyses by level of low, medium, or high exposure (Table 2 and Supplementary Tables 5, and 6). We conducted a meta-analysis

Table 1. Selected characteristics of the studies included in the review and meta-analysis.

Ref.	First Author, Year	Country	Study Type	Measure Source	Gender	Exposure Source	Pfas Type	Cancer Type	Outcome	Quality S.
22	Gilliland FD (1993)	US-MN	cohort	Job history	Female	Occupational	PFOA	Breast	Mortality	8
23	Alexander BH (2003)	US-AL	cohort	Serum sample	Both	Occupational	PFOS	Breast	Mortality	6
24	Leonard RC (2008)	US-WV	cohort	Serum sample	Both	Occupational	PFOA	Breast	Mortality	6.5
25	Bonefeld-Jorgensen EC (2011)	GL & CA	case-control	N/A	Female	Environmental	PFOS, PFOA	Breast	Incidence	7.5
26	Steenland K (2012)	US-WV	cohort	Serum sample	Both	Occupational	PFOA	Breast	Mortality	7
27	Barry V (2013)	US-WV	cohort	Serum sample	Both, Female	Occupational & Environmental	PFOA	Breast, Cervix, Ovarian, Uterus	Incidence	8.5
28	Vieira VM (2013)	US-OH & US-WV	case-control	Serum sample	Female	Environmental	PFOA	Breast, Cervix, Ovarian, Uterus	Incidence	7
29	Raleigh KK (2014)	US-MN	cohort	Work records	Both	Occupational	PFOA	Breast	Mortality	8
30	Bonefeld-Jørgensen EC (2014)	DK	case-control	Serum sample	Female	Environmental	PFOS, PFOA, PFNA	Breast	Incidence	8.5
31	Wielsøe M (2017)	GL	case-control	Serum sample	Female	Environmental	PFOS, PFOA, PFNA, PFDA	Breast	Incidence	7
32	Mastrantonio M (2018)	IT	ecological	Drinking water	Both	Environmental	PFAS	Breast	Incidence	6.5
33	Hurley S (2018)	US-CA	case-control	Serum sample	Female	Environmental	PFOA, PFNA, PFOS	Breast	Incidence	8.5
34	Mancini FR (2020)	FR	case-control	Serum sample	Female	Environmental	PFOA	Breast	Incidence	9
35	Tsai MS (2020)	TW	case-control	Serum sample	Female	Environmental	PFOS, PFOA, PFNA, PFDA	Breast	Incidence	7.5
36	Itoh H (2021)	JP	case-control	Serum sample	Female	Environmental	PFOS, PFNA, PFDA, PFOA	Breast	Incidence	7.5
37	Omoike OE (2021)	USA	case-control	Serum sample	Female	Environmental	PFOA, PFOS, PFNA	Breast, Ovarian, Uterus	Incidence	6.5

(*Continued*)

Ref.	First Author, Year	Country	Study Type	Measure Source	Gender	Exposure Source	Pfas Type	Cancer Type	Outcome	Quality S.
38	Velarde MC (2022)	PH	case control	Serum sample	Female	Environmental	PFOS, PFOA, PFNA, PFDA	Breast	Incidence	7
39	Li X (2022)	CN	case control	Serum sample	Female	Environmental	PFOA, PFDA	Breast	Incidence	7.5
40	Feng Y (2022)	CN	cohort	Serum sample	Female	Occupational	PFOA, PFNA, PFDA, PFOS	Breast	Incidence	7
41	Li H (2022)	SW	cohort	Drinking water	Male, Female	Environmental	PFAS	Breast, Cervix, Ovarian, Uterus	Incidence	7.5
42	Cathey AL (2023)	USA	case-control	Serum sample	Female	Environmental	PFOA, PFOS, PFNA,	Breast, Ovarian, Uterus	Incidence	9
43	Law HD (2023)	AU	cohort		Male, Female	Environmental	PFAS	Breast, Ovarian, Uterus	Incidence	6.5
44	Chang VC (2023)	USA	case-control	Serum sample	Female	Environmental	PFOS, PFOA	Breast	Incidence	8
45	Winquist A (2023)	USA	cohort	Serum sample	Female	Environmental	PFNA, PFOA, PFOS	Breast	Incidence	9

*BMI: body mass index, PFAS: per- and poly-fluoroalkyl substances, PFOA: perfluorooctanoic acid, PFNA: perfluorononanoic acid, PFDA: perfluorodecanoic acid, PFOS: perfluorooctanesulfonic acid; Adjusted list other than gender and age, calendar period for each reference if available. Ref. 22: race. Ref. 25: BMI, pregnancy, cotinine, breast-feeding, menopausal status. Ref. 27: smoking, alcohol consumption, education. Ref. 28: diagnosis year, smoking status, insurance provider. Ref. 30: BMI before pregnancy, gravidity, OC use, menarche age, smoking during pregnancy, alcohol intake, maternal education and physical activity. Ref. 31: BMI, cotinine levels, parity, and breastfeeding. Ref. 33: Race/ethnicity, region of residence, date of blood draw, date of blood draw2, season of blood draw, total smoking pack-years, BMI, family history of breast cancer, age at first full-term pregnancy, menopausal status at blood draw, and pork consumption. Ref. 34: Total serum lipids, BMI , smoking status, physical activity, education level, personal history of benign breast disease, family history of breast cancer, parity*age at first full-term pregnancy, age at menarche, age at menopause, use of oral contraceptives, current use of menopausal hormone therapy, score of adherence to the Western diet and to the Mediterranean diet, age at blood draw, BMI at blood draw, menopausal status at blood draw and year of blood draw. Ref. 35: Pregnant history, oral contraception use, abortion, BMI, menopause, and education level. Ref. 36: Residential area, BMI, menopausal status, age at menopause, age at first childbirth, family history of breast cancer, smoking status, physical activity, age at menarche, number of births, breastfeeding duration, alcohol intake, isoflavone intake, and education level, fish and shellfish intake, vegetable intake. Ref. 37: Education, race/ethnicity, PIR, BMI, serum cotinine. Ref. 38: Region of residence, employment status, and monthly income. Ref. 39: BMI, smoking history, age at menarche, age of menopause, parity, breastfeeding duration, use of estrogen or estrogen replacement therapy, family history of breast cancer, education, monthly household income per capita, red meat consumption, pickled, fried, smoked, barbecued food consumption. Ref. 40: BMI, smoking, drinking, marital status, education level, occupation type, batch to enter the cohort, parity, menopausal status, history of mastitis, use of hormone replacement therapy, and family history of cancer. Ref. 42: Natural log-transformed cotinine, poverty-income ratio, race, education, body mass index, and an indicator variable for the NHANES cycle to capture changing exposure and outcome trends over time. Ref. 44: Study center, race/ethnicity, education, age at menarche, age at first live birth and number of live births, age at menopause, duration of MHT use, first-degree family history of female breast cancer, personal history of benign breast disease, MI, smoking status, vigorous physical activity. Ref. 45: Race, education, smoking status, and alcohol consumption.*

Table 2. Meta-analysis of results on the level of PFAS exposure.

Characteristic	PFAS type	Dose category	RR (95% CI)	p trend
Breast	PFOA	Low (9 studies)	0.89 (0.66-1.19)	0.78
		Medium (9 studies)	1.01 (0.81-1.27)	
		High (9 studies)	0.93 (0.69-1.25)	
	PFOS	Low (6 studies)	0.87 (0.60-1.26)	0.81
		Medium (6 studies)	0.97 (0.68-1.39)	
		High (6 studies)	0.81 (0.52-1.25)	
	PFDA	Low (3 studies)	0.69 (0.28-1.69)	0.75
		Medium (3 studies)	1.09 (0.43-2.76)	
		High (3 studies)	1.09 (0.20-5.91)	
	PFNA	Low (5 studies)	0.80 (0.55-1.17)	0.85
		Medium (5 studies)	0.65 (0.35-1.22)	
		High (5 studies)	0.74 (0.41-1.34)	
Female genital	PFAS + PFOA	Low (2 studies)	0.95 (0.85,1.06)	0.20
		High (2 studies)	1.13 (0.89,1.42)	

** The p-value of the test for linear trend.*
PFAS: per- and polyfluoroalkyl substances, PFOA: perfluorooctanoic acid, PFNA: perfluorononanoic acid, PFDA: perfluorodecanoic acid, PFOS: perfluorooctanesulfonic acid.

for each exposure category and performed a meta-regression of the linear trend using weights 1, 2, and 3 for the respective exposure categories. Lastly, we assessed publication bias by creating a funnel plot and applying a regression asymmetry test [21]. Finally, a sensitivity analysis (e.g., removing one study at a time) was performed to identify potential outliers and influential studies. All statistical analyses were completed using the STATA version 17 (Stata, College Station, TX, USA).

3. Results

Figure 1 shows the flow diagram for literature search and study selection. We included 24 independent studies [22-45].

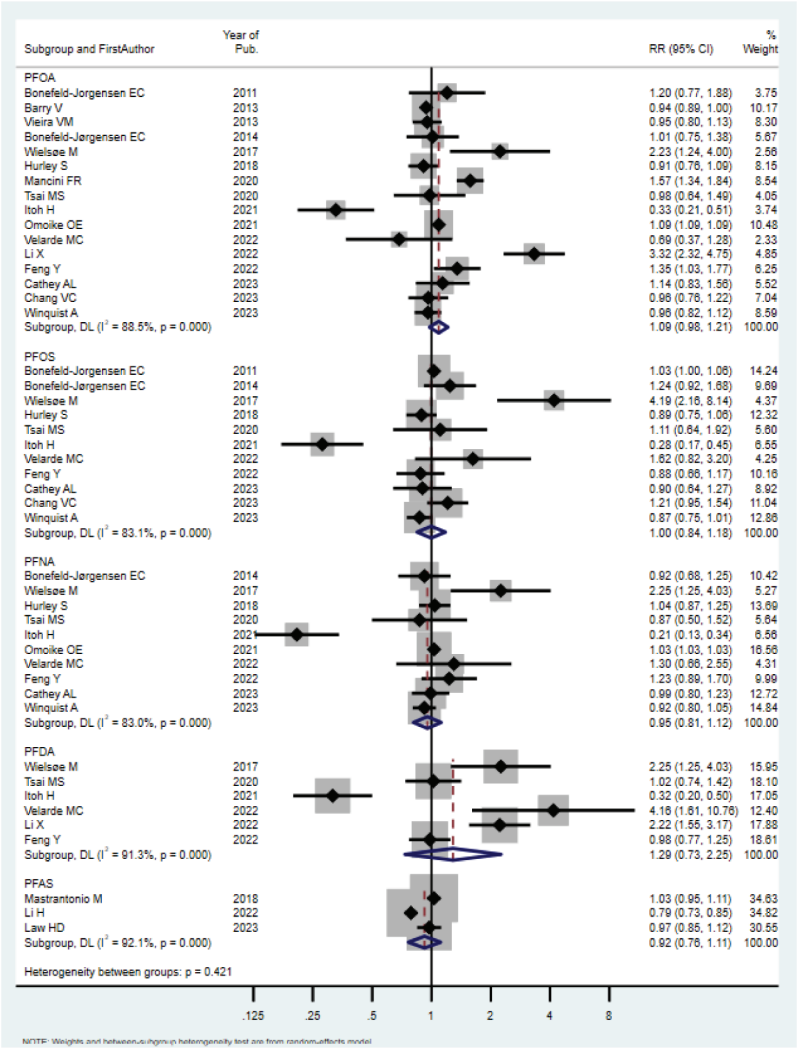
The review comprised 10 cohort studies [22- 24, 26, 27, 29, 40, 41, 43, 45], 13 case-control studies [25, 28, 30, 31, 33-39, 42, 44], and one ecological study [32]. All studies had individual-level assessments of PFAS exposure except for three studies in which the assessment was not mentioned [32, 41, 43]. Details on these studies are provided in Table 1.

The studies reported 52 risk estimates for breast cancer and 27 for female genital cancer. When looking at the subgroup analysis for each PFAS type considering cancer incidence (46 risk estimates) or mortality (6 risk estimates), the summary RR of breast cancer incidence for PFOA exposure was 1.09 (95% CI = 0.98-1.21; I^2=88.5%, p-het=0.000; n=16). The subgroup analysis for PFOS for breast cancer incidence reveals the summary RR to be 1.00 (95% CI = 0.84-1.18; I^2 = 83.1%, p-het= 0.000; n=11) (Figure 2 and Supplementary Table 3).

The summary RR of different female genital cancer types included: 1) RR of cervical cancer was 0.94 (95% CI = 0.79-1.12; I^2 = 0.0%; p-het=0.858, n= 3); 2) RR of ovarian cancer was 1.07 (95% CI = 1.04-1.09; I^2 = 99.3%; p-het = 0.000, n=12); and 3) RR of uterus cancer was 0.93 (95% CI = 0.84-1.04; I^2 = 100.0%; p-het = 0.000, n=12) (Figure 3, Supplementary Table 4).

The results of stratified meta-analyses are reported in Supplementary Tables 3 and 4. No differences by type of PFAS were detected for breast cancer overall or by different outcomes. The stratification by quality score, year of publication, and

A Incidence



B Mortality

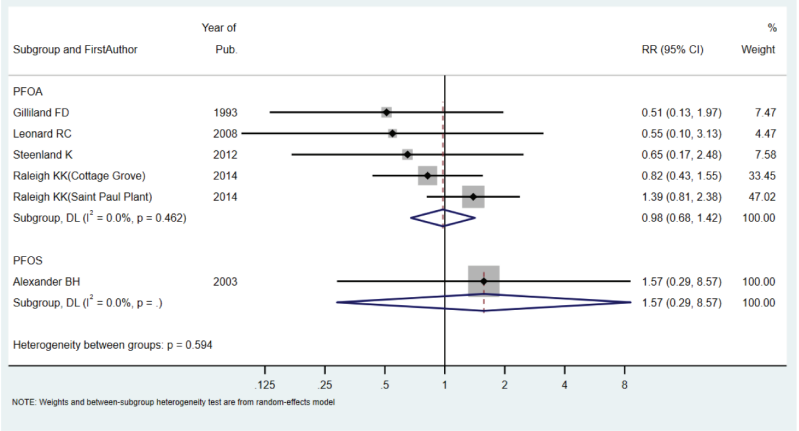


Figure 2: Forest plot (random-effects model) of results on the association between PFAS exposure and breast cancer by outcome a) incidence, b) mortality.

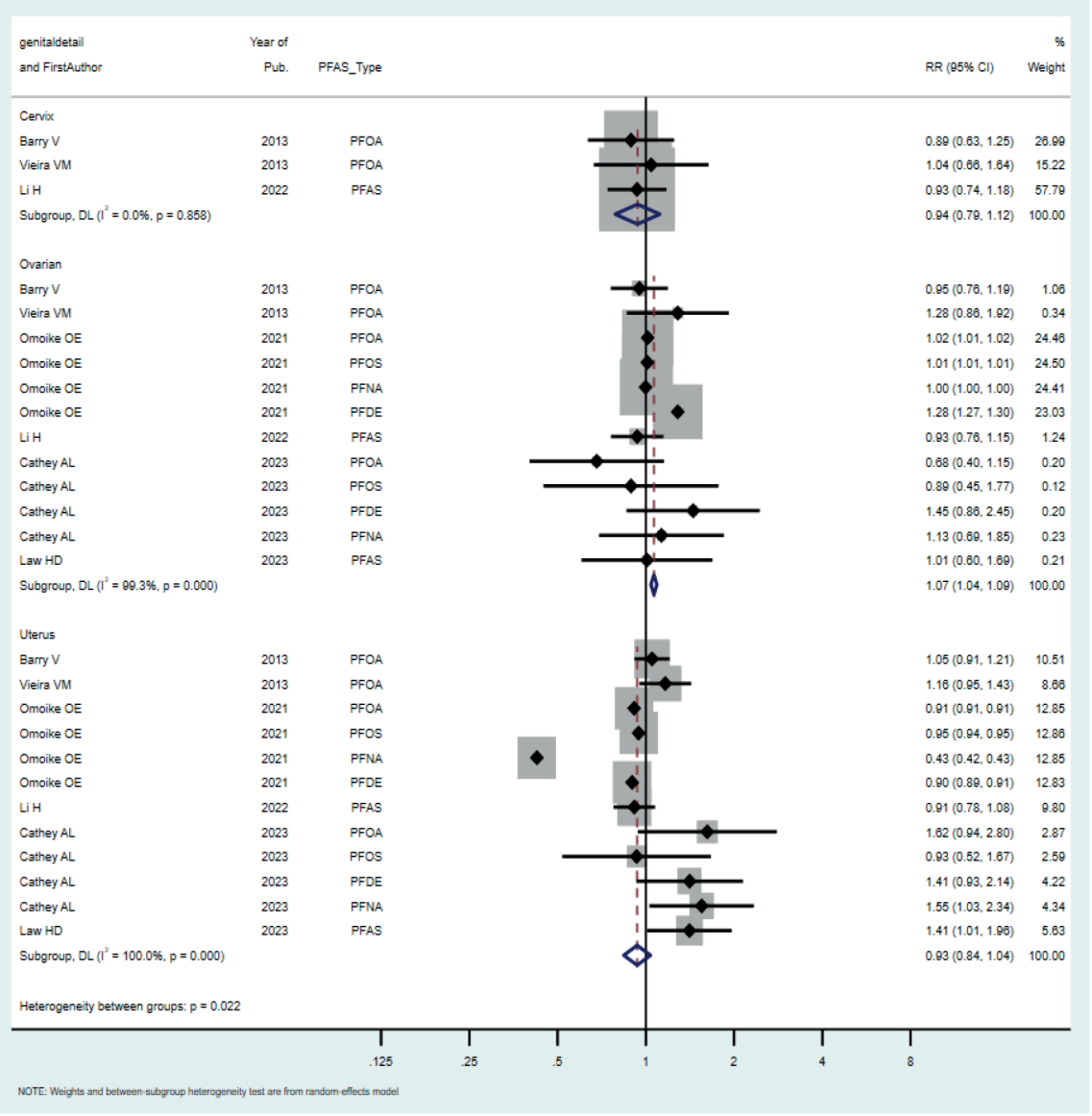


Figure 3: Forest plot (random-effects model) of results on the association between PFAS exposure and female genital cancers (cervix, ovarian, uterus) incidence.

exposure source did not show any differences in breast cancer overall or in terms of incidence and mortality. However, when considering both outcomes together, stratification by geographical region (p=0.01) and study design (p=0.03) did reveal differences with a focus on studies among European countries RR=1.36(95%CI=1.09, 1.71)and case-control design. RR=1.05 (95%CI=1.01-1.09). These results were consistent when we only looked at the incidence. Regarding mortality, all the studies were from North America and used a cohort study design (Supplementary Table 3). When we focused solely on PFOA exposure for stratification analysis, the results aligned with the overall exposure findings (Supplementary Table 3).

For ovarian cancer, stratification by geographical region, study design, outcome, quality score, year of publication, and exposure type did not reveal

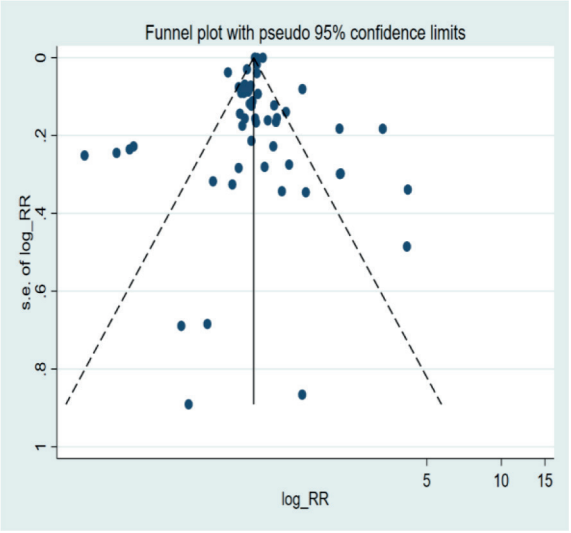


Figure 4: Funnel plot of results on the association between PFAS exposure and breast cancer. P = 0.30.

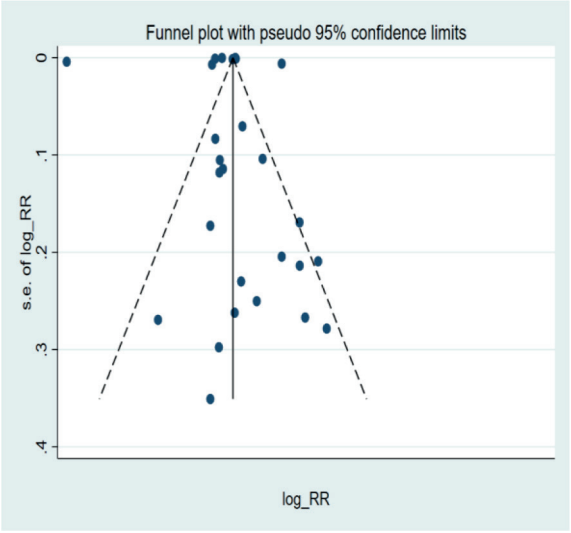


Figure 5: Funnel plot of results on the association between PFAS exposure and female genital cancers (cervix, ovarian, uterus). P = 0.55.

heterogeneity. However, the association between the North American region, case-control studies, and incidence outcomes was more effective. The results by kind of PFAS demonstrate heterogeneity (p<0.001), with emphasis on PFOS [RR=1.01 (95% CI =1.01, 1.02)], and PFDA [RR=1.28 (95% CI =1.27,1.30)]. For uterus cancer, stratification by study design, quality score, and type of PFAS did not reveal heterogeneity. However, stratification by geographical region (p=0.05) and year of publication (p=0.02) did.

Thirteen studies reported results on the levels (low, medium, and high) of different PFAS exposures. These results are summarized in Supplementary Tables 5 and 6. The meta-analysis of these results didn't reveal a trend in breast cancer or female genital cancer risk (Table 2). No publication bias was found for breast cancer (p=0.30) or female genital cancers (p=0.55). The funnel plots are shown in Figures 4 and 5.

In leave-one-out sensitivity analyses, pooled effect estimates for breast cancer incidence ranged from 1.02 to 1.07 (Supplementary Figure 1a), 0.76 to 1.04 for breast cancer mortality (Supplementary Figure 1b), and 0.99 to 1.3 for female genital cancer incidence (Supplementary Figure 1c), indicating that no single study substantially influenced the pooled estimate.

4. Discussion

In our systematic review and meta-analysis, we identified an association between ovarian cancer and overall PFAS exposure, as well as specific subtypes of PFOS and PFDA. However, we did not find a similar association for the cervix and uterus cancer. Additionally, we presented evidence suggesting a possible link between overall PFAS exposure, especially PFOA, and the incidence of breast cancer. Compared to others, this association was observed in specific subgroup analyses, such as studies conducted in European countries or those employing case-control study designs.

Based on previous epidemiological and experimental research, it has been consistently demonstrated that exposure to different types of PFAS through environmental or occupational sources can impact health and the activities of various organs in the human body [46]. Mechanisms such as oxidative stress and epigenetics contribute to the development of renal disorders [47, 48]. Moreover, these mechanisms can interfere with lipid metabolism, causing non-alcoholic fatty liver disease and ultimately leading to the subsequent development of cancer [49, 50]. Furthermore, the impact of PFAS on the human body remains an ongoing topic of discussion, especially concerning its adverse effects

on the endocrine and immune systems. Different endocrine glands and hormones may be targeted in this process, resulting in reproductive repercussions for both males and females [51].

Consequently, glands such as the thyroid, ovary, and testicular, as well as organs like the breast, are influenced by hormones and can potentially lead to the development of diseases and cancers. This is because the PFASs interact with nuclear receptors, specifically estrogen receptors (ERs) and androgen receptors (ARs), according to the in vivo and in vitro studies [52, 53, 54]. Moreover, additional studies have indicated that PFASs, as a group of endocrine-disrupting chemicals (EDCs), may increase estrogen levels or mimic its effects, potentially contributing to the development of conditions such as breast and ovarian cancer [39]. Future research could focus on different types of breast cancer (luminal A, luminal B, HER2-positive, and triple-negative) to deepen our understanding of this relationship [63].

Several studies have indicated that the activity of PFAS on endocrine organs can be influenced by the length of the chain [55]. Long-chain PFASs such as PFOA, PFOS, PFNA, and PFDA are considered more significant. However, it is worth noting that certain short-chain PFASs, like PFHxS, can have a more negative effect [55]. Aside from chain length, the potential impact of PFAS also depends on various exposure factors, including concentration, functional group type, half-life, duration, route of exposure, and more. Additionally, factors such as age, sex, ethnicity, health status, and genetic predisposition play a role in determining the effects of PFAS exposure [56, 57]. Our study found PFOA, PFOS, and PFDA to be the most effective PFAS types. However, we should recognize that more studies focus on these subsites than others, which should be considered in future studies. Furthermore, PFAS exposure reduces mammary differentiation, induces malignant transformation of normal breast epithelial cells, and increases mammary fibroadenomas in vitro [64]. Finally, maternal PFAS exposure causes adverse birth outcomes [65], which is shown by some evidence that in-utero exposure to PFASs has been linked to breast cancer risk [66].

A recent case-control study (n=102 cases) reported a sizable, statistically significant association between in-utero exposure to EtFOSSA (a precursor to PFOS) and the risk of breast cancer in the presence of high maternal perinatal total cholesterol [67]. This result is consistent with the hypothesis that breast cancer originates in utero. Larger population-based studies are urgently needed to confirm or refute these preliminary findings.

As mentioned above, several factors related to agents and individuals can affect results. However, there are also confounding risk factors associated with outcomes. Regarding breast cancer, major risk factors include age at menarche, age at the first pregnancy, age at menopause, hormone use, alcohol consumption, obesity, and nulliparity [58]. Concerning female genital cancers, particularly the cervix, ovary, and uterus, we can mention human papillomavirus (HPV), low socioeconomic status, smoking, genetics, family history, hormone replacement therapy, nulliparity, and dietary fat [59, 60]. Of 24 studies, around 17 included in our analysis used adjusted models considering important confounders. Most of the adjusted reporters were related to the case-control studies that showed a stronger association than cohort studies.

The regional stratification analysis showed significant heterogeneity, with European and American countries differing notably from other locations, particularly concerning Asian countries, in terms of breast cancer. It is possible to interpret this phenomenon as being attributable to the elevated quantity and prolonged duration of occupational and environmental sources of pollution within these regions. Although agencies such as the Environmental Protection Agency (EPA) and the European Chemicals Agency (ECHA) have started preparing action plans to control PFAS pollution, it will take time to see beneficial results [61, 62].

To the best of our knowledge, this systematic review and meta-analysis represents the first comprehensive examination of the potential link between environmental and occupational exposure to PFAS and breast and female genital cancers. However, it is essential to acknowledge that our review has certain limitations. One major constraint is the limited number of available studies, particularly those investigating the effects of exposure to specific PFAS compounds other than PFOA. Additionally, there is a scarcity of studies reporting results from

regions outside of North America and Europe, such as East Asia and sub-Saharan Africa, especially related to female genital cancers. It is worth noting that only one study focused on male breast cancer; thus, conducting stratified analyses by gender was not efficient for breast cancer. Furthermore, the number of studies examining female genital cancers other than those affecting the ovary and uterus was also limited.

5. Conclusion

In summary, our research has suggested a link between general PFAS exposure, which is known as a possible EDC, and the development of ovarian and possibly breast cancer. Specifically, evidence appears to be stronger for PFOA, PFOS, and PFDA. In addition, our findings yielded no definitive results regarding the cervix and uterus.

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Data Availability Statement: The data supporting this study's findings are available from the corresponding author upon reasonable request.

Author Contributions: PB, TZ, and MSS conceived and designed the study; MSS, EK, and SZ selected the studies and extracted the data; MSS conducted the statistical analysis; MSS and EK drafted the manuscript; SZ, TZ, and PB provided substantial comments to the results and manuscript.

Conflicts of Interest: PB acted as an expert in litigation involving PFAS exposure, which is unrelated to the present work. Other authors declare no conflict of interest.

Declaration on the use of AI: None.

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Supplementary Materials:

Supplementary Table 1. Detailed search strategy used on the different databases.

Database	Search String
PubMed	((“PFOA”[Text Word] OR “Perfluorooctanoic Acid”[Text Word] OR “PFOS”[Text Word] OR “Perfluorooctane Sulfonic Acid”[Text Word] OR “PFAS”[Text Word] OR “per and poly fluoroalkyl substances”[Text Word]) AND (“cancer”[Text Word] OR “malignant”[Text Word] OR “carcinoma” [Text Word] OR “neoplasm”[Text Word] OR “tumor”[Text Word] OR “myeloid”[Text Word] OR “lymphoma”[Text Word] OR “Hematologic”[Text Word])) AND (humans[Filter])
Scopus	(TITLE-ABS-KEY (“PFOA”) OR TITLE-ABS-KEY (“Perfluorooctanoic Acid”) OR TITLE-ABS-KEY (“pfosa”) OR TITLE-ABS-KEY (“Perfluorooctane Sulfonic Acid”) OR TITLE-ABS-KEY (“pufas”) OR TITLE-ABS-KEY (“per and poly fluoroacyl substances”)) AND (TITLE-ABS-KEY(“cancer”) OR TITLE-ABS-KEY(“malignant”) OR TITLE-ABS-KEY(“carcinoma”) OR TITLE-ABS-KEY(“neoplasm”) OR TITLE-ABS-KEY(“tumor”) OR TITLE-ABS-KEY(“myeloid”) OR TITLE-ABS-KEY(“lymphoma”) OR TITLE-ABS-KEY(“Hematologic”)) AND (LIMIT-TO (SRCTYPE, “j”)) AND (LIMIT-TO (DOCTYPE, “ar”)) AND (LIMIT-TO (LANGUAGE, “English”)) AND (LIMIT-TO (EXACTKEYWORD, “Human”) OR LIMIT-TO (EXACTKEYWORD, “Humans”) OR LIMIT-TO (EXACTKEYWORD, “Male”) OR LIMIT-TO (EXACTKEYWORD, “Female”)) AND (EXCLUDE (SUBJAREA, “ARTS”) OR EXCLUDE (SUBJAREA, “EART”) OR EXCLUDE (SUBJAREA, “SOCI”) OR EXCLUDE (SUBJAREA, “VETE”) OR EXCLUDE (SUBJAREA, “MATE”) OR EXCLUDE (SUBJAREA, “ENGI”) OR EXCLUDE (SUBJAREA, “COMP”) OR EXCLUDE (SUBJAREA, “CENG”) OR EXCLUDE (SUBJAREA, “MULT”) OR EXCLUDE (SUBJAREA, “BIOC”) OR EXCLUDE (SUBJAREA, “PHAR”) OR EXCLUDE (SUBJAREA, “NURS”) OR EXCLUDE (SUBJAREA, “AGRI”) OR EXCLUDE (SUBJAREA, “IMMU”) OR EXCLUDE (SUBJAREA, “CHEM”) OR EXCLUDE (SUBJAREA, “NEUR”) OR EXCLUDE (SUBJAREA, “PSYC”) OR EXCLUDE (SUBJAREA, “DENT”) OR EXCLUDE (SUBJAREA, “PHYS”))

Supplementary Table 2. NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE.

CASE CONTROL STUDIES (maximum score: 9)

Note: A study receives one star for each numbered item within the Selection and Exposure categories. For comparability, a maximum of two stars can be awarded.

Selection

1. **Is the case definition adequate?**
   a. yes, with independent validation **(1)**
   b. yes, e.g., record linkage **(1)** or based on self-reports **(0.5)**
   c. no description **(0)**
2. **Representativeness of the cases**
   a. consecutive or obviously representative series of cases **(1)**
   b. potential for selection biases or not stated **(0)**
3. **Selection of Controls**
   a. community controls **(1)**
   b. hospital controls **(0.5)**
   c. no description **(0)**
4. **Definition of Controls**
   a. no history of disease (endpoint) **(1)**
   b. no description of source **(0)**

Comparability

1. **Comparability of cases and controls based on the design or analysis**
   a. study controls for age, gender, province **(0)**
   b. study controls for age, gender, province +smoking **(1)**
   c. study controls for age, gender, province +smoking + other additional factors **(2)**

Exposure

1. **Ascertainment of exposure**
   a. secure records (e.g., surgical records) **(1)**
   b. structured interview where blind to case/control status **(1)**
   c. interview not blinded to case/control status **(0.5)**
   d. written self-report or medical record only **(0.5)**
   e. no description **(0)**
2. **Same method of ascertainment for cases and controls**
   a. yes **(1)**
   b. no **(0)**
3. **Non-response rate**
   a. one or both groups over 90% **(1)**
   b. one or both groups between 60- 90% **(0.5)**
   c. one or both groups under 60% **(0)**
   d. no statement **(0)**

(*Continued*)

COHORT STUDIES (maximum score: 10)

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1. **Representativeness of the exposed cohort**
   a. truly representative of the average _____ (describe) in the community **(2)**
   b. somewhat representative of the average _____ in the community **(1)**
   c. selected group of users, e.g., nurses and volunteers **(0.5)**
   d. no description of the derivation of the cohort **(0)**
2. **Selection of the non-exposed cohort**
   a. drawn from the same community as the exposed cohort **(1)**
   b. drawn from a different source **(0.5)**
   c. no description of the derivation of the non-exposed cohort **(0)**
3. **Ascertainment of exposure**
   a. secure records (e.g., surgical records) **(1)**
   b. structured interview **(1)**
   c. written self-report **(0.5)**
   d. no description **(0)**
4. **Demonstration that the outcome of interest was not present at the start of the study**
   a. yes **(1)**
   b. no **(0)**

Comparability

1. **Comparability of cohorts based on the design or analysis**
   a. study controls for age, gender, province **(0)**
   b. study controls for age, gender, province +smoking **(1)**
   c. study controls for age, gender, province +smoking + other additional factors **(2)**

Outcome

1. **Assessment of outcome**
   a. independent blind assessment **(1)**
   b. record linkage **(1)**
   c. self-report **(0.5)**
   d. no description **(0)**
2. **Was follow-up long enough for outcomes to occur**
   a. yes (select an adequate follow-up period for the outcome of interest) **(1) (average 15 years)**
   b. no **(0)**
3. **Adequacy of follow-up of cohorts**
   a. complete follow-up - all subjects accounted for over 90% **(1)**
   b. subjects lost to follow-up unlikely to introduce bias - small number lost - > ____ % (select an
   c. adequate %) follow up, or description provided of those lost) between 60-90% **(0.5)**
   d. follow-up rate < ____% (select an adequate %) and no description of those lost under 60% **(0)**
   e. no statement **(0)**

Supplementary Table 3. Results of the meta-analyses of breast cancer stratified by region, study design, quality score, outcome, gender, year of publication, exposure type, and PFAS type.

Characteristic	RA, No.	RR (95% CI)	p- het.	RA, No.	RR (95% CI)	p-het.	RA, No.	RR (95% CI)	p-het.
		Overall			**Incidence**			**Mortality**	
Overall	52	1.01 (0.98-1.04)		46	1.01 (0.98-1.04)		6	1.00 (0.70-1.43)	
				Region					
North America	23	1.01 (0.97-1.04)	0.01	17	1.01 (0.97-1.04)	0.02	6	1.00 (0.69-1.43)	-
Europe	10	1.36 (1.09, 1.71)		10	1.36 (1.09-1.70)		0	-	
Other regions	19	0.93 (0.71,1.23)		19	0.93 (0.71-1.23)		0	-	
				Study design					
Case-control	35	1.05 (1.01-1.09)	0.03	35	1.05 (1.02- 1.09)	0.04	0	-	-
Cohort	16	0.94 (0.87-1.05)		10	0.94 (0.87-1.02)		6	1.00 (0.69-1.43)	
Ecological	1	1.03 (0.95-1.11)		1	1.03 (0.95-1.11)		0	-	
				Quality score					
Low (< 8)	33	1.01 (0.98-1.05)	0.95	30	1.01 (0.98-1.05)	0.93	3	0.79 (0.32-1.96)	0.65
High (>= 8)	19	1.01 (0.93-1.09)		16	1.01 (0.93-1.09)		3	1.00 (0.62-1.63)	
				Years of publication					
<2019	21	1.05 (0.98-1.13)	0.25	15	1.05 (0.97-1.14)	0.29	6	1.00 (0.69-1.43)	-
>=2019	31	1.00 (0.96-1.04)		31	1.00 (0.97-1.04)		0	-	
				Gender					
Men	1	0.53 (0.19-1.47)	0.13	1	0.53 (0.19-1.47)	0.12	0	-	0.31
Women	43	1.02 (0.99-1.05)		42	1.02 (0.98- 1.05)		1	0.51 (0.13-1.97)	
Both	10	0.94 (0.85-1.03)		5	0.93 (0.84-1.03)		5	0.93 (0.84-1.03)	
				Exposure					
Occupational	10	1.07 (0.93-1.23)	0.4	4	1.09 (0.89-1.32)	0.43	6	1.00 (0.69-1.43)	-
Environmental	44	1.01 (0.98-1.03)		44	1.01 (0.98-1.03)		0	-	
				Type of PFAS					
PFOA	21	1.08 (0.97-1.20)	0.56	16	1.09 (0.98-1.21)	0.42	5	0.98 (0.68- 1.42)	0.59
PFOS	12	1.00 (0.85-1.18)		11	1.00 (0.84-1.18)		1	1.57 (0.29-8.57)	
PFNA	10	0.95 (0.81-1.12)		10	0.95 (0.81-1.12)		0	-	
PFDA	6	1.29 (0.73-2.25)		6	1.29 (0.73-2.25)		0	-	
PFAS	3	0.92 (0.76-1.11)		3	0.92 (0.76-1.11)		0	-	
				PFOA					
				Region					
North America	13	0.99 (0.91-1.08)	0.15	8	0.99 (0.91-1.08)	0.15	5	0.98 (0.68-1.42)	-
Europe	3	1.45 (1.00-2.10)		3	1.45 (1.00-2.10)		0	-	
Other regions	5	1.01 (0.48-2.11)		5	1.01 (0.48-2.11)		0	-	
				Study design					
Case-control	13	1.10 (0.93-1.30)	0.35	13	1.10 (0.93-1.30)	0.48	0	-	-
Cohort	8	1.00 (0.88-1.13)		3	1.02 (0.87-1.18)		5	0.98 (0.68-1.42)	

(*Continued*)

Characteristic	RA, No.	RR (95% CI)	p- het.	RA, No.	RR (95% CI)	p-het.	RA, No.	RR (95% CI)	p-het.
Quality score									
Low (< 8)	11	1.09 (0.85-1.41)	0.76	9	1.13 (0.87-1.46)	0.65	2	0.61 (0.21-1.76)	0.40
High (>= 8)	10	1.05 (0.91-1.21)		7	1.05 (0.90-1.23)		3	1.00 (0.62-1.63)	
Years of publication									
<2019	11	0.98 (0.89-1.08)	0.27	6	0.99 (0.88-1.11)	0.33	5	0.98 (0.68-1.42)	-
>=2019	10	1.11 (0.91-1.35)		10	1.11 (0.91-1.35)		0	-	
Gender									
Men	0	-	0.05	0	-	0.04	0	-	0.32
Women	15	1.11 (0.95-1.29)		14	1.12 (0.96-1.31)		1	0.51 (0.13-1.97)	
Both	6	0.94 (0.89-1.00)		2	0.94 (0.89-0.99)		4	1.03 (0.70-1.51)	
Exposure									
Occupational	6	1.16 (0.89-1.51)	0.57	1	1.35 (1.03-1.77)	0.13	5	0.98 (0.68-1.42)	-
Environmental	15	1.07 (0.96-1.20)		15	1.07 (0.96-1.20)		0	-	

PFAS: per- and polyfluoroalkyl substances, PFOA: perfluorooctanoic acid, PFNA: perfluorononanoic acid, PFDA: perfluorodecanoic acid, PFOS: perfluorooctanesulfonic acid.

Supplementary Table 4. Results of the Female genital cancer (ovarian, uterus) meta-analyses stratified by region, study design, quality score, outcome, gender, year of publication, and PFAS type.

Characteristic	N risk estimates	RR (95% CI)	p heterogeneity
	Ovarian		
Region			
North America	10	1.07(1.04-1.09)	0.44
Europe	1	0.93(0.76-1.15)	
Other regions	1	1.01(0.60-1.69)	
Study design			
Case-control	9	1.07(1.04-1.09)	0.11
Cohort	3	0.95(0.82-1.09)	
Quality score			
Low quality (<8)	7	1.07(1.04-1.09)	0.40
High quality (>= 8)	5	0.98(0.81-1.19)	
Years of publication			
<2019	2	1.05(0.80-1.39)	0.93
>=2019	10	1.07(1.04-1.09)	
Outcome			
Incidence	12	1.07(1.04-1.09)	-
Mortality	0	-	
Type of PFAS			
PFOA	4	1.00(0.90-1.11)	<0.0001
PFOS	2	1.01(1.01-1.01)	
PFNA	2	0.99(0.99-1.00)	
PFDA	2	1.28(1.27-1.30)	
PFAS	2	0.94(0.78-1.14)	
	Uterus		
Characteristic	**N risk estimates**	**RR (95% CI)**	**p heterogeneity**
Region			
North America	10	0.91(0.81-1.02)	0.05
Europe	1	0.91(0.78-1.07)	
Other regions	1	1.41(1.01-1.96)	
Study design			
Case-control	9	0.89(0.79-1.01)	0.14
Cohort	3	1.05(0.88-1.27)	
Quality score			
Low quality (< 8)	7	0.85(0.76-0.96)	0.003
High quality (>= 8)	5	1.23(0.99-1.52)	
Years of publication			
<2019	2	1.08(0.97-1.22)	0.02
>=2019	10	0.90(0.80-1.01)	

(*Continued*)

Characteristic	N risk estimates	RR (95% CI)	p heterogeneity
Outcome			
Incidence	12	0.93(0.84-1.04)	-
Mortality	0	-	
Type of PFAS			
PFOA	4	1.05(0.89-1.24)	0.63
PFOS	2	0.94(0.94-0.95)	
PFNA	2	0.80(0.22-2.83)	
PFDA	2	1.07(0.69-1.65)	
PFAS	2	1.11(0.72-1.69)	

RR: relative risk, N: number.

Supplementary Table 5. The list of individual studies that included in the analysis of breast cancer by level of PFAS exposure.

PFAS type	First Author, year	Exposure level	Dose detail	RR (95% CI)
PFNA	#Bonefeld-Jørgensen EC (2014)	Low	0.32-0.42	1.1(0.6,2.02)
		Medium	0.42-0.50	0.75(0.41,1.4)
		High	0.50-0.64	1.08(0.58,1.99)
		Very high	>0.64	0.8(0.43,1.47)
	*Wielsøe M (2017)	Low	2nd Tertile	2.43(1.07,5.51)
		High	3rd Tertile	2.07(0.9,4.76)
	*Hurley S (2018)	Medium	N/A	1.043(0.808,1.345)
		High	N/A	1.037(0.798,1.348)
	Itoh H (2021)	Low	2.01–2.79 (2.32)	0.38(0.18,0.82)
		Medium	2.80–3.79 (3.22)	0.15(0.06,0.35)
		High	3.81–22.37 (4.56)	0.12(0.05,0.32)
	Velarde MC (2022)	Low	1.29–1.79	1.28(0.4,4.11)
		Medium	1.79–4.48	1.33(0.42,4.3)
		High	2.31–7.91	1.29(0.4,4.1)
	Feng Y (2022)	Low	0.55, 0.79	1.08(0.68,1.7)
		Medium	0.80, 1.06	1.3(0.84,2.02)
		High	≥1.07	1.38(0.89,2.13)
	Winquist A (2023)	Low	0.450-<0.630	0.66(0.46,0.94)
		Medium	0.630-<1.000	0.57(0.39,0.82)
		High	>=1.000	0.81(0.55,1.19)
PFOS	#Bonefeld-Jørgensen EC (2014)	Low	20.42-25.31	1.51(0.81,2.71)
		Medium	25.31-30.20	1.51(0.82,2.84)
		High	30.20-39.07	1.13(0.59,2.04)
		Very high	>39.07	0.9(0.47,1.7)
	*Wielsøe M (2017)	Low	2nd Tertile	3.13(1.2,8.15)
		High	3rd Tertile	5.5(2.19,13.84)
	*Hurley S (2018)	Medium	N/A	0.88(0.69,1.12)
		High	N/A	0.89(0.69,1.16)
	Itoh H (2021)	Low	10.29–14.27 (12.2)	0.38(0.18,0.82)
		Medium	14.27–19.24 (16.27)	0.31(0.14,0.69)
		High	19.28–377.33 (24.67)	0.15(0.06,0.39)
	Velarde MC (2022)	Low	2.20–3.02	1.36(0.42,4.52)
		Medium	3.05–3.82	1.25(0.38,4.17)
		High	3.90–23.03	2.38(0.81,7.31)
	Feng Y (2022)	Low	6.39, 10.35	0.75(0.47,1.19)
		Medium	10.36, 15.66	1.05(0.66,1.67)
		High	≥15.67	0.87(0.54,1.39)

(*Continued*)

PFAS type	First Author, year	Exposure level	Dose detail	RR (95% CI)
	Chang VC (2023)	Low	N/A	1.21(0.84,1.74)
		Medium	N/A	1.3(0.96,1.99)
		High	N/A	1.1(0.77,1.79)
	Winquist A (2023)	Low	13.000-<18.000	0.66(0.45,0.97)
		Medium	18.000-<25.000	0.84(0.57,1.23)
		High	>=25.000	0.7(0.48,1.01)
PFDA	*Wielsøe M (2017)	Low	2nd Tertile	2.14(0.94,4.91)
		High	3rd Tertile	2.36(1.04,5.36)
	Itoh H (2021)	Low	0.56–0.77 (0.65)	0.31(0.15,0.64)
		Medium	0.78–1.07 (0.90)	0.46(0.21,0.99)
		High	1.07–3.84 (1.26)	0.18(0.07,0.47)
	Velarde MC (2022)	Low	0.56–0.74	1.62(0.33,9.17)
		Medium	0.74–0.99	4.09(1.03,21)
		High	1.00–6.57	9.26(2.54,45.1)
	Feng Y (2022)	Low	0.35, 0.54	0.94(0.61,1.45)
		Medium	0.55, 0.80	1.18(0.76,1.82)
		High	≥0.81	1.02(0.65,1.6)
PFOA	*Steenland K (2012)	Low	<1,520 ppm-years	1.49(0.18,5.39)
		High	≥1,520 ppm-years	0.87(0.02,4.83)
	#Raleigh KK (2014)	Low	N/A	0.8(0.26,1.86)
		Medium	N/A	0.88(0.18,2.56)
		High	N/A	0.73(0.09,2.62)
		Very high	N/A	1.02(0.03,5.69)
	#Bonefeld-Jørgensen EC (2014)	Low	3.69-4.59	0.97(0.53,1.75)
		Medium	4.59-5.42	1.02(0.56,1.89)
		High	5.42-6.53	1.14(0.62,2.12)
		Very high	>6.53	0.94(0.51,1.76)
	*Wielsøe M (2017)	Low	2nd Tertile	1.86(0.8,4.31)
		High	3rd Tertile	2.64(1.17,5.97)
	*Hurley S (2018)	Medium	N/A	0.901(0.705,1.152)
		High	N/A	0.925(0.715,1.197)
	Mancini FR (2020)	Low	13.6-17.3 ng/mL	1.78(1.37,2.34)
		Medium	17.3-22.5 ng/mL	1.48(1.12,1.97)
		High	22.5-85.3 ng/mL	1.44(1.09,1.89)
	Itoh H (2021)	Low	4.00–5.57 (4.71)	0.37(0.19,0.73)
		Medium	5.57–7.62 (6.46)	0.39(0.18,0.84)
		High	7.64–62.98 (9.31)	0.2(0.08,0.51)
	Velarde MC (2022)	Low	1.50–1.77	0.64(0.21,1.9)
		Medium	1.77–2.30	1.05(0.38,2.93)
		High	2.31–8.46	0.44(0.14,1.36)

PFAS type	First Author, year	Exposure level	Dose detail	RR (95% CI)
	Feng Y (2022)	Low	0.84, 1.18	0.88(0.56,1.39)
		Medium	1.19, 1.79	1.28(0.8,2.04)
		High	≥1.80	1.69(1.05,2.7)
	Chang VC (2023)	Low	N/A	0.91(0.64,1.3)
		Medium	N/A	1(0.73,1.55)
		High	N/A	1.01(0.66,1.55)
	Winquist A (2023)	Low	3.850-<5.100	0.8(0.56,1.15)
		Medium	5.100-<6.300	0.75(0.52,1.09)
		High	>=6.300	0.82(0.57,1.17)
	#Vieira VM (2013)	Very high	600–4,679μg/L-year	1.4(0.9,2.3)
		High	198–599μg/L-years	0.7(0.5,1)
		Medium	89–197μg/L-years	1.1(0.8,1.5)
		Low	3.9–88μg/L-years	0.9(0.7,1.2)

PFAS: per- and polyfluoroalkyl substances, PFOA: perfluorooctanoic acid, PFNA: perfluorononanoic acid, PFDA: perfluorodecanoic acid, PFOS: perfluorooctanesulfonic acid.

**Studies with only two categories (low and high, without any results for medium category excluded from analysis): Wielsøe M (2017), Hurley S (2018), Steenland K (2012).*

#If a study reported four categories, we used high and very high to calculate one category as the high group: Bonefeld-Jørgensen EC (2014), Vieira VM (2013), Raleigh KK (2014).

Supplementary Table 6. The list of individual studies that included in the analysis of female genital cancer by the level of PFAS exposure.

PFAS type	First Author, year	Cancer type	Exposure level	Dose detail	RR (95% CI)
PFOA	Vieira VM (2013)	Cervix	Low	N/A	0.87(0.48,1.57)
			High	N/A	1.33(0.66,2.70)
		Uterus	Low	N/A	1.04(0.81,1.34)
			High	N/A	1.41(1.00,2.00)
		Ovarian	Low	N/A	1.03(0.59,1.81)
			High	N/A	1.62(0.90,2.90)
PFAS	Li H (2022)	Cervix	Low	N/A	0.97(0.73,1.26)
			High	N/A	0.81(0.45,1.33)
		Uterus	Low	N/A	0.94(0.77,1.13)
			High	N/A	0.82(0.55,1.17)
		Ovarian	Low	N/A	0.87(0.68,1.11)
			High	N/A	1.12(0.72,1.65)

PFAS: per-poly-fluoroalkyl alkyl substances, PFOA: perfluorooctanoic acid.

Supplementary Table 7a. PRISMA Checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify the effect measure(s) (e.g., risk ratio, mean difference) used in synthesizing or presenting results for each outcome.	
Synthesis methods	13a	Describe the processes to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling missing summary statistics or data conversions.	

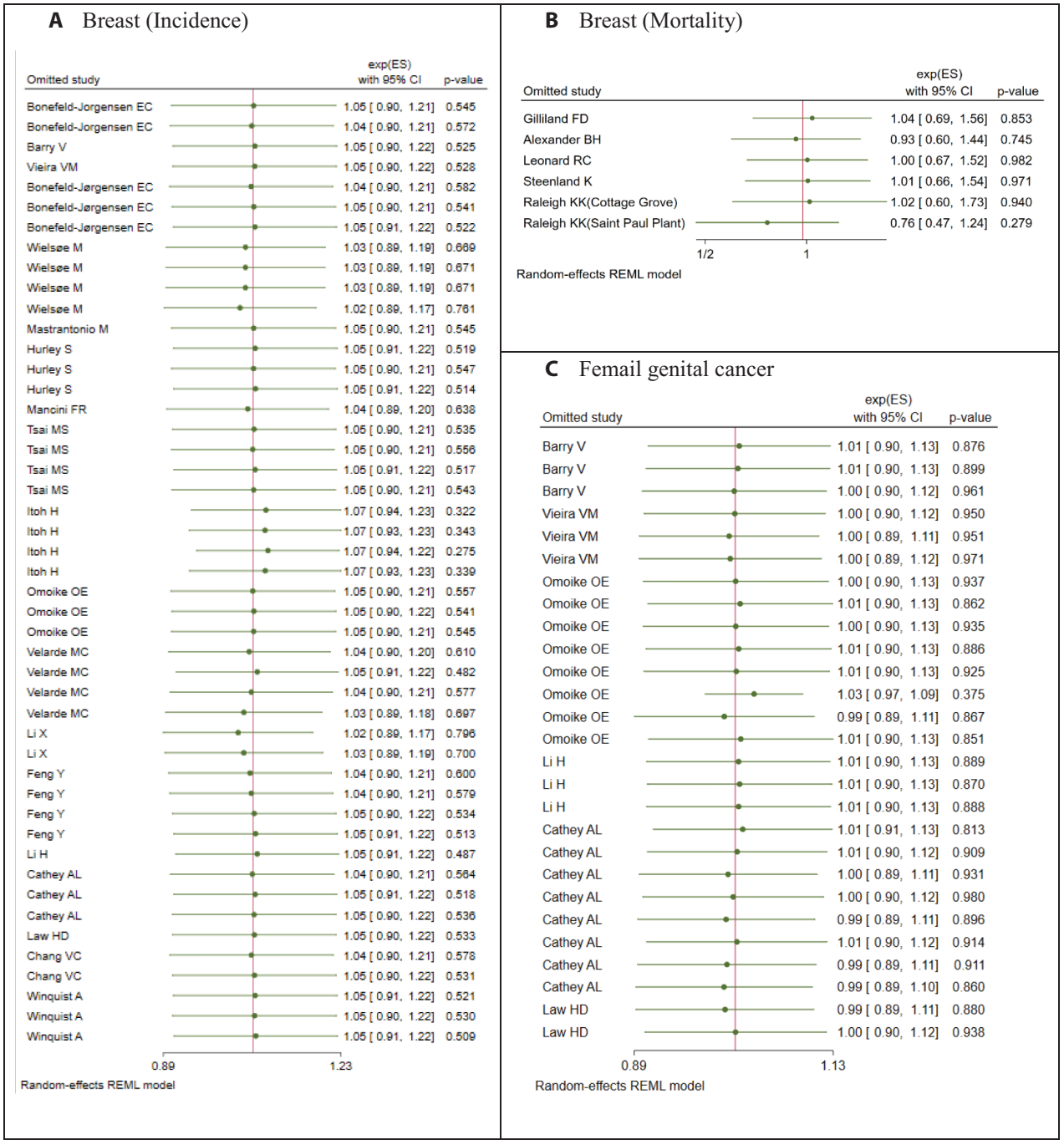
(*Continued*)

Section and Topic	Item #	Checklist item	Location where item is reported
	13c	Describe any methods used to tabulate or visually display the results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimates and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	

Section and Topic	Item #	Checklist item	Location where item is reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

Supplementary Table 7b. PRISMA Abstract Checklist.

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	
Synthesis of results	6	Specify the methods used to present and synthesise results.	
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	
Interpretation	10	Provide a general interpretation of the results and important implications.	
OTHER			
Funding	11	Specify the primary source of funding for the review.	
Registration	12	Provide the register name and registration number.	



Supplementary Figure 1: Leave-one-out meta-analysis for the association between Per- and poly-fluoroalkyl Substances (PFAS) exposure and risk of breast a) incidence, b) modtality, and c) female genital cancers incidence.