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PFAS and cancer, a scoping review of the epidemiologic evidence

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Abstract

Background: The number of studies addressing per- and polyfluoroalkyl substances (PFAS) and cancer is increasing. Many communities have had water contaminated by PFAS, and cancer is one of the important community concerns related to PFAS exposure.

Objectives: We critically reviewed the evidence relating to PFAS and cancer from an epidemiologic standpoint to highlight directions for future research that would be the most likely to meaningfully increase knowledge.

Methods: We conducted a search in PubMed for studies of cancer and PFAS (through 9/20/2020). We identified epidemiologic studies that provided a quantitative estimate for some measure of the association between PFAS and cancer. Here, we review that literature, including several aspects of epidemiologic study design that impact the usefulness of study results.

Results: We identified 16 cohort (or case-cohort) studies, 10 case-control studies (4 nested within cohorts and 6 non-nested), 1 cross sectional study and 1 ecologic study. The cancer sites with the most evidence of an association with PFAS are testicular and kidney cancer. There are also some suggestions in a few studies of an association with prostate cancer, but the data are inconsistent.

Discussion: Each study's design has strengths and limitations. Weaknesses in study design and methods can, in some cases, lead to questionable associations, but in other cases can make it more difficult to detect true associations, if they are present. Overall, the evidence for an association between cancer and PFAS remains sparse. A variety of studies with different strengths and weaknesses can be helpful to clarify associations between PFAS and cancer. Long term follow-up of large-sized cohorts with large exposure contrasts are most likely to be informative.

Keywords

PFAS; PFOA; PFOS; cancer; review

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1. Introduction

There is growing concern regarding the health effects of per- and polyfluoroalkyl substances (PFAS), as an ever-increasing number of sites of local contamination are being discovered in many countries [e.g., the United States (https://www.atsdr.cdc.gov/pfas/atsdr_sites_involvement.html, https://www.ewg.org/interactive-maps/2019_pfas_contamination/); Sweden (Andersson et al., 2019); Italy (Girardi and Merler, 2019; Ingelido et al., 2018 and 2020); Germany (Skutlarek et al., 2006; Hölzer at al., 2008); China (Li et al., 2019)]. Since the phasing out of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) by major producers and users, serum concentrations of PFOA and PFOS in the general population have decreased in the United States (decrease of 50% for PFOA and 75% for PFOS during 2003–2014 in the general U.S. adult population (Jain, 2018; Kato et al., 2011)) and in Europe (EFSA CONTAM Panel et al, 2020, Appendix B; Land et al., 2018). However, serum concentrations of other types of PFAS (such perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), and perfluoroundecanoic acid (PFUnDA)) have increased or remained stable in various parts of Europe (EFSA et al, 2020, Appendix B) and serum concentrations of PFOA and PFOS have increased in some areas of China (Land et al., 2018, Bao et al., 2017). During 2003–2014, >98% of adult U.S. residents had detectable serum levels of PFOA, PFOS, PFHxS, and PFNA (Jain, 2018); and several types of PFAS were detected in most adults studied in several areas in Europe during 2007–2016 (EFSA CONTAM Panel et al, 2018 and 2020). The primary sources of human PFAS exposure are thought to include drinking water, indoor dust and air, and food (including contamination from food packing) (Sunderland et al., 2019). During 2013–2015 in the United States, PFAS concentrations above the minimum reporting levels were found in 194 of 4864 tested public water supplies. An estimated 6 million people served by 66 public water systems were exposed via their drinking water to levels of PFOA and PFOS above currently EPA-recommended levels of 70 ng/L (for PFOA and PFOS individually or combined) (Hu et al., 2016). Various types of PFAS have also been found in drinking water samples collected during 2013–2015 in several European locations [e.g., among samples from the Netherlands, France and Spain (PFOS detected in 5–38% of samples and PFOA detected in 21–35% (Zafeiraki et al., 2015; Schwanz et al, 2016)] and Brazil [e.g., detection of PFOS in 100% of samples and of PFOA in 33% of samples (Schwanz et al., 2016)]; and in drinking water samples collected during 2017 in 79 cities in China (all samples had detectable levels of at least one type of PFAS) (Li et al, 2019).

Cancer is one of the health effects of interest in relation to PFAS exposures. Part of the reason for concern about PFAS and cancer is that, in rats, administration of PFOA has been associated with development of testicular Leydig cell adenomas, pancreatic acinar cell adenomas, and hepatocellular adenomas or carcinomas, and with promotion of hepatocellular carcinoma development after treatment with N-nitrosodiethylamine (IARC, 2017); and PFOS administration has been associated with development of hepatocellular adenomas and thyroid follicular cell adenomas (Lau et al., 2007; Chang et al., 2014). Studies in rainbow trout found evidence that PFOA promoted development of liver tumors after initiation by aflatoxin B or N-methyl-N’-nitro-N-nitrsoguanidine (IARC, 2017). A recent study by the National Toxicology Program (NTP), that included rats with both prenatal and

postnatal exposure to PFOA, found PFOA exposure to be associated with development of benign and malignant liver and pancreatic tumors in male rats and with increased pancreatic tumors in female rats, with no clear difference between rats with both prenatal and postnatal exposure and those exposed only postnatally. That report concluded that there was clear evidence of carcinogenicity in male rats and some evidence of carcinogenicity in female rats (NTP, 2020). However, in some instances the mechanism by which PFOA is thought to cause tumors in rats (PPARα activation) does not appear as relevant in humans (ATSDR, 2018, p. 446 (Cancer Mechanisms)). In addition, the testicular tumors observed in rats were Leydig tumors, which are very rare in humans (Kennedy, et al., 2004).

In light of the uncertain relevance of studies of PFAS and cancer in rodents to human cancers, epidemiologic studies of PFAS and cancer can provide valuable additional information. There have been a relatively large number of studies of human cancer and PFAS. Our purpose here is to review that evidence critically from an epidemiologic standpoint, to identify the types of study designs that have been used, along with their strengths and weaknesses, and to try to highlight directions for future research that would be the most likely to meaningfully increase knowledge. We used the approach of a scoping review for this assessment (Tricco et al., 2018) because we sought to summarize the information available from studies with a wide variety of study designs for a variety of types of PFAS and cancer types. Several previous reviews focused on PFAS and cancer have been published (e.g., IARC, 2017; ATSDR, 2018; EFSA CONTAM Panel et al., 2018; Chang et al., 2014; Arrieta-Cortes, 2017), and some have commented on study design issues. However, we sought to provide an up-to-date review with a more in-depth consideration of features of study design.

2. Methods

We sought to identify and summarize the available studies in a structured way. First, we examined several recent reviews of PFAS and cancer, including those by the International Agency for Research on Cancer (IARC, 2017), the Agency for Toxic Substances and Disease Registry (ATSDR, 2018), the European Food Safety Authority (EFSA) (EFSA CONTAM Panel et al., 2018), as well as a review by Sunderland et al., 2019. We updated the results of all of these reviews via a PubMed search using keywords for various types of PFAS (or terms for PFAS as a group), and various cancer-related terms. An initial search was conducted in February, 2020 and a final search to identify any additional studies was conducted on September 20, 2020 (including all studies that had been entered into PubMed through the time of the search, with no earlier time limit). The full text of the final search terms is included in the supplemental material. We reviewed the titles of all articles identified by the search and reviewed abstracts and full manuscripts when necessary to identify studies meeting our inclusion criteria. We included all primary epidemiologic studies that reported a quantitative estimate of association between at least one type of PFAS and at least one type of cancer. We excluded reviews, studies that were not epidemiologic studies (e.g., studies about mechanisms of action, in vitro studies, animal studies), and human studies that lacked a quantitative estimate for some measure of the association between PFAS and cancer.

For the included studies, information was abstracted using a tabular format, using only published information. We abstracted information about important study design features, types of PFAS studied, type of exposure assessment, PFAS serum concentrations in the cohort or study population (referring to referenced studies or other available studies when necessary), cancer types considered, study population characteristics and size, methods for control for confounding, and the main study findings. In summarizing study findings, we noted the type of measure of association reported and summarized any notable effect estimates and their associated confidence intervals, including whether or not there was evidence of a dose-response relationship. Because many studies had a very large number of effect estimates (e.g., for various cancer types, various types of PFAS, different exposure measures) it was not possible to record all effect estimates. In addition, the types of measures of association varied between studies, precluding specification of a single threshold for estimates to report. Therefore, we sought to include estimates that were notably elevated or protective, whether they were statistically significant or not. We then reviewed the evidence from the identified studies, in groups by overall study design, with consideration of study design features to summarize the strength of the evidence regarding the links between PFAS and cancer and to identify study design features that would be most likely to yield informative results in future studies.

3. Results

Eighteen published studies meeting our inclusion criteria were identified from the review articles. The final PubMed search yielded a total of 378 published articles, of which 27 met the inclusion criteria. After combining the studies identified in these ways, 28 studies were included in the review (17 identified from both from the previous reviews and the PubMed search, 1 identified only through the previous reviews, and 10 identified only through the PubMed search) (see Supplemental Figure). Details of the study designs and findings of the individual studies are presented in Table 1.

3.1 Cohort or case-cohort studies

There have been 16 cohort or case-cohort studies, primarily focused on PFOA or PFOS (Table 1); 11 of which considered 3 U.S. (or primarily U.S.) occupational cohorts with high exposures (PFOA: median serum concentrations in various groups of exposed workers 113–5200 ng/ml, maximum concentration reported 92,030 ng/ml; PFOS: geometric mean concentrations for workers at plant using PFOS 941 ng/ml, maximum concentration reported 10,600 ng/ml) [Alexander et al., 2003; Olsen et al., 2004; Alexander and Olsen, 2007; Grice, et al., 2007; Leonard et al., 2008; Steenland and Woskie, 2012; Consonni et al., 2013 (primarily U.S. cohort); Steenland et al., 2015; Gilliland and Mandel, 1993; Lundin et al., 2009; Raleigh et al., 2014], and 1 of which was for an occupational cohort in Italy with high exposures (geometric mean serum concentrations: PFOA 4,048 ng/ml, PFOS 148.8 ng/ml; maximum concentrations reported: PFOA 91,900 ng/ml, PFOS 3,386 ng/ml) (Girardi and Merler, 2019) (Table 1). No published occupational studies have focused on other types of PFAS. Most of the occupational studies included exposure estimates based on either job title or estimated/modeled serum levels.

The occupational studies, whether focused on PFOS (3M plant in Alabama) or PFOA (Dupont plant in West Virginia, 3M plant in Minnesota, and plant in Veneto, Italy), do not show a consistent pattern of elevation of the incidence of cancer at any specific site. However, there are instances of an association between increased exposure, based on work histories and various types of retrospective exposure assessment methods (see Table 1 for details), and prostate cancer (in 3 cohorts, two with PFOA exposure and one with PFOS exposure), kidney cancer (in one cohort with PFOA exposure), liver cancer (in one cohort with PFOA exposure), colorectal cancer (in one cohort with PFOS exposure), bladder cancer (in 1 cohort with PFOS exposure and 1 cohort with PFOA exposure), and hematopoetic and lymphatic malignancies (in 2 cohorts with PFOA exposure).

Four studies were general-population cohort or case-cohort studies, of which one considered PFOA only, one considered PFOA and PFOS, and two others considered PFOA, PFOS, and other PFAS. The general-population study focused on PFOA had high exposure contrasts (measured serum PFOA concentrations in 2005–2006 in community cohort: median 24.2 ng/ml, range 0.25–4,752 ng/ml, also see Winquist et al., 2013) due to water contamination (Barry et al., 2013). The second study was of a general population-based cohort exposed to background levels of PFOA and PFOS, with gender-specific median serum concentrations of 5.4–6.9 ng/ml (5th-95th percentile ranges 2.2–14.0) and 29.3–35.1 ng/ml (5th-95th percentile ranges 14.0–62.4) for PFOA and PFOS respectively (Eriksen et al, 2009). The third study was of a general population-based cohort of women exposed to background levels of PFOA (mean serum concentration 5.2 ng/ml), PFOS (mean serum concentration 30.6 ng/ml) and other types of PFAS (Bonefeld-Jorgensen et al., 2014). The fourth study was of 2003–2006 U.S. National Health and Nutrition Examination Survey (NHANES) participants aged ≥60 years, with general U.S. population-level PFAS exposures (Fry and Power, 2017) (Table 1).

The general population study with high exposure to PFOA resulting from drinking water contamination (Barry et al., 2013) found an excess of kidney and testicular cancer with increased estimated cumulative serum PFOA levels (although this excess was apparent only in the community population (87 cases), but not in the subset of workers (18 cases)). The general population study in Denmark by Eriksen et al (2009) found no marked excesses of four types of cancer with increasing baseline serum PFAS concentrations, but found a slight but not strictly monotonic positive trend of increased prostate cancer incidence with higher baseline PFOS serum concentrations and a slight, but not monotonic, trend of increased pancreatic cancer incidence with higher baseline PFOA serum concentrations. The third general population study, focused on breast cancer and found a weak positive association with baseline serum PFOSA concentrations without a monotonic trend (Bonefeld-Jorgensen et al., 2014). The fourth general population study was of U.S. NHANES participants aged ≥60 years, and found no evidence of an association between four types of PFAS and all-cancer mortality (Fry and Power, 2017).

3.2 Case-control studies

There have been ten case-control studies, four of which were nested within cohorts and 6 of which were not. Six, including 3 nested case-control studies (Hurley et al., 2018; Mancini et

al., 2020; Cohn et al., 2020) and 3 non-nested studies (Bonefeld-Jorgensen et al., 2011; Wielsoe et al., 2017; Tsai et al., 2020), focused on breast cancer; one non-nested study focused on prostate cancer (Hardell et al., 2014); one nested case-control study focused on kidney cancer (Shearer et al., 2020); one non-nested study focused on multiple cancer sites (Vieira et al., 2013); and one non-nested study on cancer without specification of the site (Vassiliadou et al., 2010) (Table 1). Most have looked at PFOA and PFOS (n=2) or PFOA and PFOS in combination with a variety of other PFAS (n=7), and one was limited to PFOA (Viera et al., 2013). Six (Hurley et al., 2018; Vassiliadou et al., 2010; Bonefelt-Jorgensen et al., 2011; Wielsoe et al.,2017; Hardell et al., 2014; Tsai et al., 2020) analyzed serum levels of PFAS at the time of, or after, diagnosis. One study used modeled serum PFOA (Vieira et al., 2013) prior to diagnosis. The three other studies used serum collected at baseline, before diagnosis (Mancini et al., 2020; Cohn et al., 2020; Shearer et al., 2020). All considered low background general-population levels of PFAS, with the exception of the study by Vieria et al. (2013), which was conducted in a high exposure area near the Dupont plant in West Virginia (median PFOA serum concentrations 28.2 ng/ml, range 0.2–22,412 ng/ml in study area) (Table 1). Case numbers ranged widely (apart from Vieira, et al., 2013, case numbers ranged from 31 to 902; in Vieira, et al., 2013 total number of cases ranged from 61 for liver and testicular cancer in the Ohio-only analysis to 4,926 for lung cancer in the analysis for Ohio and West Virginia).

Overall, for the breast cancer studies, investigators generally found little or no association between disease and serum PFAS levels (estimated or measured). Two breast cancer case-control studies, in the same Inuit population in Greenland, with either 31 or 77 cases, found positive associations between a variety of types of PFAS and breast cancer (Bonefeld-Jorgensen et al., 2011; Wielsoe et al., 2017). One study found evidence of associations between breast cancer and PFOS, PFHxS and perfluoroundecanoic acid (PFUnDA) only among women aged ≤50 years, and specifically those with estrogen receptor-positive tumors (Tsai et al., 2020), and a second study found an association between breast cancer and PFOS only for estrogen- and progesterone-receptor positive tumors (Mancini et al, 2020). Five other studies with data on breast cancer (including the Hurley et al., 2018; Cohn et al., 2020, and Vieira et al., 2013 case-control studies; as well as the Barry et al., 2013 cohort study; and the Bonefeld-Jorgensen et al., 2014 case-cohort study) found no marked associations (indeed in the Barry et al. 2013 study with a large number of cases, there was a borderline negative association with PFOA, although the RR (0.94 per log unit exposure) was not markedly lowered). In addition to the breast cancer studies described above, there are some sub-analyses looking at gene-exposure interactions in the breast cancer case-control studies in Denmark and Greenland (Wielsoe et al., 2018; Ghisari et al., 2014; Ghisari et al., 2017), without any consistent findings.

The case-control study of prostate cancer found no association with PFOA or PFOS for all cases considered but did find associations with PFOA, PFOS, PFHxS, PFNA, perfluorodecanoic acid (PFDA), and perfluoroundecanoic acid (PFUnDA) for cases with first-degree relatives with prostate cancer (Hardell et al., 2014). The case-control study of kidney cancer (renal cell carcinoma) found positive exposure-response associations with kidney cancer for several PFAS including PFOA, PFOS, and PFHxS. However, only the association with PFOA remained apparent after adjustment for all three chemicals (Shearer

et al., 2020). The association with PFOA remained in analyses restricted to individuals without evidence of diminished kidney function and in cases diagnosed ≥8 years after phlebotomy. Serum PFAS concentration contrasts in that study were relatively small, as they reflected general population levels (the lowest PFOA concentration quartile was <4 ng/ml, while the uppermost was >7.3–27.2 ng/ml). The only case-control study with high exposure contrasts was the one conducted by Vieira et al. (2013) in the mid-Ohio valley (see data above on exposure contrasts in this population), which found excesses of kidney and testicular cancer and non-Hodgkin lymphoma associated with higher estimated PFOA exposure.

3.3 Cross-sectional study

There is one cross-sectional study of prevalent colorectal cancer in a high exposure setting [median (range) of serum concentrations: PFOA 27.9 (<0.5–22,412) ng/ml; PFOS 20.2 (<0.5–759.2) ng/ml], with serum levels measured after cancer diagnosis at the same time as retrospective outcome ascertainment (Innes et al., 2014). This study provides little additional information due to its cross-sectional design and accompanying potential for reverse-causation.

3.4 Ecologic study

There has been one ecologic study of PFAS exposure and cancer (Mastrantonio et al., 2018) in a geographic area with PFAS contamination. The specific type of PFAS exposure in that study is not specified. That study found higher rates of kidney and breast cancer deaths among women in contaminated areas than in uncontaminated areas. Among men the association between kidney cancer death and living in a contaminated area was weaker than the association observed among women. In addition, there were higher rates of testicular cancer and leukemia deaths among men in PFAS-contaminated areas than in uncontaminated areas.

4. Discussion

Several study design issues can affect the studies of PFAS and cancer and are important to consider when interpreting the findings of these studies. We discuss these issues prior to giving our overall summary of the evidence.

4.1. Study-design and methods considerations for cohort studies

One advantage of the high-exposure cohorts is that most were able to rank subjects into broad categories of high and low exposure that are likely to have been consistent over time (e.g., the occupational cohorts and the cohort in the mid-Ohio valley). In general, low exposure contrasts can make it difficult, if not impossible, to observe measurable disease contrasts in relation to exposure level (assuming PFAS has a causal effect on disease). However, cohorts with high exposures can be limited in the number of cancers that are observed. All of the occupational cohort studies had a relatively small number of cases (the highest number of deaths for specific reported cancer types in occupational mortality studies was 84 for lung cancer in Steenland and Woskie, 2012 and the highest number of cases of a specific reported cancer type in occupational incidence studies was 188 for prostate cancer

in Raleigh et al., 2014). There is one large high-exposure community-based cohort with incidence data (Barry et al., 2013; highest number of cases for a specific cancer type was 559 for breast cancer), although cancer incidence data may be available from other highly exposed community cohorts in the future. For rare cancers, such as testicular cancer, liver cancer, and pancreatic cancer, which have been implicated in rodent studies, data are sparse in all of the cohort studies. Small numbers of cases can lead to chance associations, but they also can lead to low power for detection of true associations (and thus p-values that are not < 0.05). On the other hand, low-exposure cohorts are more applicable to the exposures of most of the population, and if large enough, may also provide important evidence (e.g., Eriksen et al. 2009) if it can be demonstrated that there are important effects at low exposures.

Cohort studies are often considered one of the strongest observational epidemiologic study designs in situations in which randomized trials are not possible. However, it should be noted that cohort studies can have inherent limitations. Ideally, observation of a cohort would start at the time of first exposure but many cohorts are ‘left truncated’, beginning at a specific point of time in a population with prior exposure (e.g., Barry et al. 2013; Raleigh, et al., 2014, in which cancer incidence data were not available until 40 years after the first exposures). People exposed earlier in the target population may have died before the start time and would not be observed, and those most susceptible to the effects of exposure on disease may have already developed disease (if susceptibility to effects of exposure on disease varies in the population) which can lead to a downward bias in measures of association (Applebaum et al., 2011; Hernan et al., 2008). On the other hand, bias due to left truncation would not be expected if susceptibility to the effects of exposure on disease does not vary and exposure is not related to survival (Applebaum et al., 2011; Barry, et al., 2015). In addition, in the presence of varying susceptibility to the effects of exposure on disease, average hazard ratios (calculated across the whole follow up period) can decrease with increasing follow-up time (Hernan 2010). Whether these factors might have impacted the studies of PFAS and cancer is uncertain.

Cohort studies can also suffer from some types of selection bias. Loss to follow up, which could be different in different groups, can be one source of selection bias (examples of studies with loss to follow up include Alexander and Olsen, 2007 and Grice et al., 2007, in which survey response was lowest among those with highest exposures; and Steenland et al., 2015, in which interview data were more likely to be obtained for workers who had not died than for workers who had died) . A different kind of selection bias in occupational studies can occur with the “healthy worker effect”, when workers are compared to a general population referent, making associations with disease that might be present among workers harder to detect. Although often thought to be most prominent for cardiovascular disease, there is evidence that the healthy worker effect also can affect cancer (Kirkeleit et al. 2013). The presence of an apparent “healthy worker effect” was noted in several of the PFAS occupational cohorts when results of internal comparisons, or comparisons with other groups of workers, revealed positive associations not observed in comparisons with general population rates (e.g., Leonard et al., 2008). On the other hand, workers may benefit from increased screening for cancer, which could lead to increased incidence (e.g., for prostate cancer), but less mortality. Selection bias can also occur in retrospective cohort studies in which subjects volunteer for study participation (e.g., Barry, et al., 2013; Alexander and

Olsen, 2007; Grice et al., 2007) if the probability of a person participating in the study depends on both past exposure and past disease. However, this might be less of a concern for any one outcome in studies that consider a variety of outcomes (e.g., Barry, et al., 2013 and Grice et al., 2007).

Methods of case ascertainment can also impact the informativeness of cohort studies. Studies that consider only mortality outcomes are not informative about diseases that are typically not fatal, such as testicular cancer. However, other methods of case-ascertainment can also have limitations. Self-report can be inaccurate, with greater inaccuracies for some outcomes than others (e.g., inaccurate self-reporting of melanoma in Grice et al., 2007 and Barry et al., 2013). Matching with cancer registries can be limited if people in the cohort move out of the registry catchment area.

4.2 Study-design and methods considerations for case-control studies

Six of ten case-control studies measured PFAS serum levels after disease occurrence. This is a concern because PFAS serum levels at the time of diagnosis or later might not accurately reflect PFAS levels at a time that would be relevant to cancer causation, accounting for the time needed for cancer development and detection (latency). It is also a concern because it creates the potential that the disease or treatment might have altered PFAS metabolism or excretion (reverse causality) (Dhingra et al., 2017), which is an important limitation.

Another limitation of case-control studies can be selection of controls. If controls differ from cases in important ways such as location (as in Vassiliadou et al., 2010), the study might not support clear conclusions. If controls are selected from people with other diseases (e.g., Vieira et al., 2013 and some controls in Wilsoe et al., 2017), measures of association can be biased downward if the control conditions (that are used for selection of the comparison group) are associated with exposure. Issues related to improper control selection can be minimized if both cases and controls are selected from a previously defined cohort (nested case-control studies), ideally using density sampling (as in Mancini et al., 2020 and Shearer et al., 2020). Nested case-control studies that use density sampling can provide an estimate of the rate ratio in the overall cohort (Rothman and Greenland, 1988), and have similarities with case-cohort studies (Kim, 2015).

4.3 Study-design and methods considerations for other study designs

In cross sectional studies, exposure is typically assessed at the same time as the outcome leading to concerns about latency, and when exposure is based on serum measurements (as in Innes et al., 2014) there is a potential for reverse causation, as discussed above. It should be noted that cross sectional studies also have the limitation of examining prevalent disease (which can be influenced by both incidence and survival) rather than incident disease only. While ecologic studies (in which exposure, outcomes, and possibly potential confounders, are measured at the group level, e.g., Mastrantonio et al., 2018)) can be helpful for answering some questions, it should be noted that associations at the group level observed in ecologic studies do not necessarily reflect associations at the individual level (Webster, 2007).

4.4 General study design and methods considerations

As a general problem in epidemiology, the time windows when PFAS exposure might be most likely to lead to cancer, if it does, are unknown. Some investigators have hypothesized that windows of susceptibility could be as early as in-utero exposures (Cohn et al., 2020; NTP 2020), which can be far removed from the time of disease onset. Even if relevant exposures are closer in time to disease onset than in-utero exposures, the choice of exposure lags for examination can be important (e.g., Steenland et al., 2015 and Barry et al., 2013).

A second general problem is exposure assessment. Measured water levels may be helpful for ecologic studies, if there are large contrasts (e.g., Vieira et al., 2013; Mastrantonio et al., 2018; and in Sweden, see Li et al., 2018), but measured water levels might not accurately reflect individual-level exposures. Serum levels are valuable as individual biomarkers but have their own disadvantages (Weisskopf et al. 2017). If measured at one point in time (such as at baseline, e.g., Eriksen et al., 2009 and Shearer et al., 2020), they might not be good reflections of cumulative exposure and might miss changes in exposure levels over time. Historical reconstruction of past serum levels for longitudinal studies is ideal when feasible (e.g., Shin et al., 2011a, 2011b), but requires good data to estimate historical emissions, likely amounts in water systems over time, residential histories, and estimated water consumption over time. Often many of these data sources may not be available.

A third general problem in epidemiologic studies relates to the potential for confounding. Confounding by other chemical exposures, including exposures to other types of PFAS, can be a particular problem in studies of PFAS and cancer because exposures to multiple chemicals or multiple types of PFAS often occur together. Occupational cohorts can have exposure to several other chemicals in addition to PFAS exposure. This issue can be illustrated by the association between PFOA exposure and mesothelioma that was observed by Steenland and Woskie (2012). That association was felt to be most likely due to asbestos exposure being associated with PFOA exposure, leading to confounding by asbestos in the observed association between mesothelioma and PFOA. Another example is co-exposure to PFOA and tetrafluoroethylene (TFE) in the study by Consonni et al. (2013), in which the two exposures could not be separated. Co-occurring exposure to TFE could also be a potential issue for the other studies of workers at the Parkersburg, West Virginia plant. In many contexts, there can be relatively strong correlations between exposures to various PFAS (e.g., Hurley et al., 2018), which can lead to difficulties separating the effects of specific chemical constituents.

4.5. Summary of evidence

While there are no associations between PFAS and cancer that have been both marked and consistent across studies, there is some evidence for an association of PFOA with testicular cancer. Two studies of this association (one cohort (Barry et al., 2013) and one case-control (Vieira et al., 2013)) coincided in finding a strong positive exposure-response for this cancer, which was also found to be associated with PFOA exposure in rodent studies. However, the Leydig cell testicular tumor found in rats is very rare in humans (Kennedy, et al., 2004). It should also be noted that there is some overlap of testicular cancer cases in these two studies (Barry et al. 2013, Vieira et al. 2013), which is a limitation. One ecologic study of PFAS

exposure and cancer also found higher rates of testicular cancer in PFAS-exposed areas (Mastrantonio et al., 2018). Testicular cancer is rare and not fatal, and these are the only studies which have reported on it with a substantial number of cases, limiting conclusions.

The evidence for kidney cancer, implicated by Barry et al. (2013), Vieira et al. (2013), and Steenland and Woskie (2012), also is suggestive. The recent large case-control study by Shearer et al. (2020) found a strong exposure-response trend with PFOA, but not other PFAS. Mastrantonio, et al. (2018) also found higher kidney cancer mortality rates in PFAS-exposed areas. Combined, these studies strengthen the case for a kidney cancer association with PFOA, although not with other PFAS. However, kidney cancer has not been found to be associated with PFOA exposure in the other high-PFOA-exposure occupational cohort of 3M workers (Raleigh et al., 2014), using either mortality or incidence data, nor were kidney tumors observed in the studies in rats (ATSDR, 2018).

There is little evidence for a relationship of PFOA with either liver or pancreatic cancer, tumors that have been associated with PFOA in rodent studies, with the exception of the liver cancer excess recently seen in Italian workers exposed to PFOA (Girardi and Merler, 2019). On the other hand, only a few studies have had enough power to have been able to study these rare cancers, and there is some debate about whether the liver and pancreatic tumor findings in rodents are relevant to humans due to a mechanism in rodents which is less present in humans. In our view there is also some, more limited, suggestive evidence for prostate cancer, but results are inconsistent. Overall, the evidence from epidemiologic studies of PFAS in relation to cancer is strongest for testicular and kidney cancer but remains limited.

In summary, epidemiologic studies of PFAS and cancers have been informative, but not entirely conclusive. Each study design has strengths and limitations which need to be carefully considered when interpreting study findings. Weaknesses in study design can, in some cases, lead to questionable associations, but in other cases study design weaknesses can make it more difficult to detect true associations if they are present. No study will be perfect, so a variety of studies, with different strengths and weaknesses, can be helpful to clarify associations between PFAS and cancer. Long term follow-up of large-sized cohorts with large exposure contrasts, and preferably data on cancer incidence, or case-control studies nested within them, may be most likely to detect a cancer effect if there is one. To date the only large, long-term cohort of an exposed community with data on incident disease is the PFOA-exposed cohort in the mid-Ohio valley (Barry et al., 2013, and Vieira et al., 2013), but similar studies could be possible in other locations. Two such large general population cohorts, with good exposure contrasts, have been formed in Ronneby, Sweden (primarily PFHxS and PFOS; see Li et al., 2018) and Veneto, Italy (PFOA; see Pitter et al., 2020). These cohorts are likely to contribute to knowledge of PFAS and cancer. Low-exposure cohorts, if large enough, may also provide important evidence applicable to the exposures of most of the population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Epidemiologic studies of PFAS and cancer

Study	Design	PFAS Studied*	Exposure Assessment	Measured or estimated PFAS serum concentrations†	Cancer types	Population	Size	Control for confounding	Main findings*	Notes on study design, methods and findings
Cohort Studies and Case-Cohort Studies (N=16)										
Occupational Cohorts										
Occupational Cohort, Decatur, Alabama, USA										
Alexander et al. 2003	Occupational cohort mortality study	Primarily PFOS	Job history, categorized as no exposure, low potential exposure and high potential exposure (based on knowledge of major job-specific serum levels), some analyses also included years in each category	From study of random sample of workers (Olsen et al., 2003) Geometric mean (GM) and range of serum concentrations: Chemical plant workers (n=126, "low exposure" and "high exposure")-PFOS 941 (91–10,600) ng/ml; PFOA 899 (21–6,160) ng/ml; Film plant workers (n=60, "no exposure")-PFOS 136 (15–946) ng/ml; PFOA 49 (6–298) ng/ml	Reported on several cancer categories including all malignant neoplasms; all digestive organs and peritoneum; esophagus; large intestine; biliary passages and liver; all respiratory system; bronchus, trachea and lung; breast; urinary organs; bladder and other urinary; malignant melanoma; and lymphatic and hematopoietic	Workers with at least 1 year of cumulative employment during 1961–1997 at a manufacturing site producing PFOS	2083 cohort members, followed through 1998, 145 deaths, including 39 cancer deaths (highest number of deaths for a specific reported cancer type was 15 for cancers of the bronchus, trachea and lung)	Calculated standardized mortality ratios (SMRs) for comparison with state or regional mortality rates standardized by age, gender, and calendar period	Risk of bladder cancer among plant workers (3 deaths) compared with Alabama population: SMR and 95% confidence interval (CI) 4.81 (0.99–14.06), all bladder cancer deaths among high-exposed workers	-No quantitative exposure assessment -Dose-response analysis not possible because all bladder cancer deaths were in highest exposure group.
Olsen et al. 2004	Retrospective occupational cohort study of episodes of care of workers	Primarily PFOS	Job history, categorized as working at exposed (chemical) plant or working at non-exposed (film) plant; some analyses were restricted to long-term workers	From study of random sample of workers (Olsen et al., 2003) Geometric mean (GM) and range of serum concentrations: Chemical plant workers (n=126, "low exposure" and "high exposure")-	Reported on several cancer categories including colon, liver, rectum, lower respiratory tract, malignant melanoma, bladder, prostate and thyroid; also reported on	Workers as of 1/1/1993 with at least 1 year of employment at a manufacturing site producing PFOS (same site as Alexander et al. 2003)	652 employees at a plant that produced PFOS and 659 employees at a non-exposed plant (film plant), followed during 1993–1998 (highest number of	Compared each group of workers with other 3M workers using indirect standardization by age in 3 categories (<40, 40–49 and ≥50 years) and sex	Comparison used the ratio of two indirect standardized ratios (referred to as "risk ratio episodes of care (RREpC))". Comparable episodes of care were observed for most diseases between PFOS-exposed and non-exposed workers,	-Full time employees who retired were eligible for care after retirement and were included in the study. -No dose-response analysis.

Study	Design	PFAS Studied*	Exposure Assessment	Measured or estimated PFAS serum concentrations†	Cancer types	Population	Size	Control for confounding	Main findings*	Notes on study design, methods and findings
				PFOS 941 (91–10,600) ng/ml; PFOA 899 (21–6,160) ng/ml; Film plant workers (n=60, “no exposure”)- PFOS 136 (15–946) ng/ml; PFOA 49 (6–298) ng/ml	some benign neoplasms		episodes of care for a specific cancer type in PFOS plant workers was 5 (for melanoma and prostate cancer)		notable associations for malignancies [RREpC (95% CI)] included: colon cancer (n=4 among exposed workers) 5.4 (0.5->100), prostate cancer (n=5 among exposed workers) 7.7 (0.9->100) and melanoma (n=5 among exposed workers) 12 (1.0->100).	
Alexander and Olsen, 2007	Retrospective occupational cohort study via survey of occupational cohort (medical records confirmation sought for self-reported cancers) and death certificate matching.	Primarily PFOS	Job history, categorized as no exposure, low potential exposure and high potential exposure (based on knowledge of major job-specific serum levels), some analyses also included a cumulative exposure measure that considered weighted years in each category	From study of random sample of workers (Olsen et al., 2003) Geometric mean (GM) and range of serum concentrations: Chemical plant workers (n=126, “low exposure” and “high exposure”)- PFOS 941 (91–10,600) ng/ml; PFOA 899 (21–6,160) ng/ml; Film plant workers (n=60, “no exposure”)- PFOS 136 (15–946) ng/ml; PFOA 49 (6–298) ng/ml	Bladder cancer only	Workers with at least 1 year of cumulative employment at a manufacturing site producing PFOS (same site as Alexander et al. 2003)	1588 in analysis (included 188 who had died and 1400 who had not died and responded to the survey), follow up through 2002 (total of 11 bladder cancer cases)	Calculated standardized incidence ratios (SIR) with the U.S. population (SEER data) as the reference population, standardized by age, gender and calendar period. Rate ratios (RRs) for internal comparisons were adjusted for age and gender	Bladder cancer incidence compared with SEER reference population [SIR (95% CIs)]: group with ever high exposure (6 cases) 1.74 (0.64–3.79); group with ever low exposure (7 cases) 2.26 (0.91–4.67) In internal comparison, bladder cancer incidence RRs (95% CIs) from lowest to highest exposure groups (total of 11 cases in all groups): 1.0, 0.83 (0.15–4.65), 1.92 (0.30–12.06), 1.52 (0.21–10.99)	-Data limited to self-reported cancers that were not disconfirmed on validation and cancers identified on death certificates, numbers low -Exposure classification was limited -Response rate to survey among surviving cohort members was 74% overall and 67% in the most highly exposed group. - Although work histories started in 1961, the follow-up period for the incidence analysis started in 1970 because SEER reference data were only

Study	Design	PFAS Studied*	Exposure Assessment	Measured or estimated PFAS serum concentrations†	Cancer types	Population	Size	Control for confounding	Main findings*	Notes on study design, methods and findings
										available for 1970–1999. -Internal comparisons were limited by the small number of cases. -Some suggestion of dose-response pattern but not monotonic.
Grice et al. 2007	Retrospective follow-up study via survey of occupational cohort (medical records confirmation sought for self-reported cancers).	Primarily PFOS	Job history, categorized as no exposure, low potential exposure and high potential exposure (based on knowledge of major job-specific serum levels), some analyses also included a cumulative exposure measure that considered weighted years in each category	From study of random sample of workers (Olsen et al., 2003) Geometric mean (GM) and range of serum concentrations: Chemical plant workers (n=126, “low exposure” and “high exposure”)-PFOS 941 (91–10,600) ng/ml; PFOA 899 (21–6,160) ng/ml; Film plant workers (n=60, “no exposure”)-PFOS 136 (15–946) ng/ml; PFOA 49 (6–298) ng/ml	Reported on several cancer types including breast, colon, liver, melanoma, prostate and thyroid	Workers with at least 1 year of cumulative employment at a manufacturing site producing PFOS (same site as Alexander et al. 2003)	1400 survey respondents out of 1895 surviving current and former employees, plus death certificate information for 188 decedents, follow up through 2002 (highest number of cases for an analyzed cancer type was 54 for prostate cancer)	Calculated odds ratios for each exposure group relative to the never exposed group adjusted for age and gender	Only the 3 types of cancer with a substantial number of cases were analyzed. -For PFOS exposure, classified as ever low or high, low or high ≥1 year, or high >1 year, respectively; ORs (95% CIs) compared with never exposed group: colon cancer (total of 44 cases of which 22 were self-reported) 1.21 (0.51–2.87), 1.37 (0.57–3.30), 1.69 (0.68–4.17); prostate cancer (total of 54 cases of which 29 were self-reported) 1.34 (0.62–2.91), 1.36 (0.61–3.02), 1.08 (0.44–2.69)	-Analysis used self-reported cancers and cancers recorded on death certificates (except for melanoma for which only validated cases were used), numbers low -Exposure classification was limited -Response rate to survey among surviving cohort members was 74% overall and 67% in the most highly exposed group. -Some suggestion of dose-response pattern for colon cancer and prostate cancer (not monotonic for prostate cancer).
Occupational cohort, Parkersburg, West Virginia, USA										

Study	Design	PFAS Studied*	Exposure Assessment	Measured or estimated PFAS serum concentrations†	Cancer types	Population	Size	Control for confounding	Main findings*	Notes on study design, methods and findings
Leonard et al, 2008	Occupational cohort mortality study	PFOA	Workers at an exposed plant were compared to the general population and to a regional worker population	Sample of 1025 volunteers among active employees in 2004 (Sakr et al., 2007) - Serum PFOA concentrations: range 5–9,550 ng/ml; median 494 among current PFOA workers, and 114–195 among other categories of workers	Reported on 29 cancer categories	Workers with any history of working during 1948–2002 at a plant that used PFOA	6,027 workers, mortality follow up through 2002; 806 deaths including 234 cancer deaths (highest number of deaths for a specific cancer type was 66 for lung cancer)	SMRs calculated relative to 3 reference populations (U.S. population, West Virginia population and DuPont regional worker population) standardized by sex, 5-year age category and 5-year time period	In analyses of SMRs relative to regional worker population [SMR (95% CI)]: kidney cancer mortality (12 deaths) 1.8 (0.9,3.2); laryngeal cancer mortality (3 deaths) 1.9 (0.4–5.7); thyroid and other endocrine cancer mortality (3 deaths) 6.3 (1.3–18.4); bone cancer mortality (2 deaths) 6.5 (0.8–23.4)	-No analysis by exposure level, small numbers of cancers -Analyses of SMRs in comparison with the U.S. or West Virginia populations were likely affected by healthy worker bias, analyses in comparison with the regional worker population reduced that bias.
Steenland and Woskie, 2012	Occupational cohort mortality study	PFOA	Workers at an exposed plant were compared to the general population and to a regional worker population; also estimated cumulative serum concentration (ppm-years) using work histories and a job-exposure matrix based on models using historical measured serum concentrations to estimate annual serum concentrations by job category/ group	Estimated average annual serum PFOA concentration: mean 350 ng/ml, median 230 ng/ml	Reported on several cancer categories including all cancers, liver, pancreas, lung, breast, prostate, testis, kidney, bladder, mesothelioma, non-Hodgkin's lymphoma and leukemia	Workers with any history of working during 1948–2002 at a plant that used PFOA and who had exposure estimates and dates of birth (subset of population in Leonard et al. 2008)	5,791 workers, mortality follow- up through 2008; 1084 deaths, including 304 cancer deaths (highest number of deaths for a specific cancer type was 84 for lung cancer)	SMRs calculated using NIOSH Life Table Analysis System, details of standardization variables and categories not specified	In analyses relative to a regional worker population [SMRs (95% CIs) for quartiles 1–4 of estimated cumulative exposure]: -Mesothelioma death (6 deaths) 0, 0, 1.73 (0.04–9.65), 6.27 (2.04–14.63), trend p-value 0.02 with no lag; and 0, 0, 3.08 (0.37–11.12), 4.66 (1.27–11.93), trend p-value=0.15 with 10-year lag -Kidney cancer death (12 deaths) 1.07 (0.02–3.62), 1.37 (0.28–3.99), 0 (0.00–1.42), 2.66 (1.15,5.24), trend p-value 0.02 with no lag; and 1.05 (0.13–3.79), 0.87 (0.11–3.15), 0.44 (0.01–2.44), and 2.82 (1.13–5.81),	-Cumulative serum levels estimated based on occupation and a large number of measured levels (Woskie et al. 2012) -Association between estimated PFOA exposure and mesothelioma was likely due to confounding by other occupational exposures, such as asbestos exposure. -Evidence of dose-response relationship for mesothelioma and kidney cancer, although not monotonic for kidney cancer

Study	Design	PFAS Studied*	Exposure Assessment	Measured or estimated PFAS serum concentrations†	Cancer types	Population	Size	Control for confounding	Main findings*	Notes on study design, methods and findings
									trend p-value=0.02, with 10-year lag	
Consonni et al. 2013	Occupational cohort mortality study	PFOA	Compared plant workers to general population, also estimated time-varying cumulative exposure (in arbitrary relative unit-years based on occupational histories and a job-exposure matrix)	PFOA serum concentrations or estimates were not provided (the main focus of the study was tetrafluoro-ethylene exposure)	Reported on 22 cancer categories	Workers in 6 plants (the largest of which was the Dupont plant in West Virginia, United States.; other plants were in New Jersey, United States; Germany; Italy; the Netherlands; and the United Kingdom)	4,773 male tetrafluoro-ethylene (TFE) workers exposed to TFE through 2002 were included in the analysis for PFOA; mortality follow up through 2001–2008 (varying by work site) (highest number of deaths for a specific cancer type across all exposure groups in the PFOA analysis was 59 for lung cancer)	Calculated SMRs relative to national reference rates for males only, standardized by 5-year age categories and 5-year calendar periods	SMRs (95% CIs) for low, medium and high PFOA exposure groups (excluding never exposed group) (from web table 3): liver cancer mortality (7 deaths among exposed) 0.70 (0.02–3.87), 1.25 (0.15–4.52), 2.14 (0.58–5.49), trend p-value 0.24; kidney cancer mortality (10 deaths among exposed) 1.57 (0.32–4.59), 1.50 (0.31–4.39), 2.00 (0.54–5.12), trend p-value 0.28; pancreatic cancer mortality (10 deaths among exposed) 0, 1.30 (0.35–3.33), 1.84 (0.67–4.00), trend p-value 0.34; leukemia mortality (11 deaths among exposed) 1.64 (0.45–4.20), 1.35 (0.28–3.94), 1.85 (0.50–4.74), trend p-value 0.58	-Focus was on TFE exposure estimated by job-exposure matrix, authors could not effectively separate PFOA exposure from TFE exposure for most cancers (PFOA was used to polymerize TFE). Stratification by levels of TFE and PFOA exposure simultaneously led to small counts and many strata with no cases (web table 4). SMRs could be calculated across PFOA exposure levels for kidney cancer among the group with medium TFE exposure [SMR (95% CI)]: low PFOA 3.20 (0.08–17.83); medium PFOA 2.15 (0.44–6.29), high PFOA 9.58 (1.16–34.56). Similar comparisons were not possible for other cancer types. -SMRs used

Study	Design	PFAS Studied*	Exposure Assessment	Measured or estimated PFAS serum concentrations†	Cancer types	Population	Size	Control for confounding	Main findings*	Notes on study design, methods and findings
										national reference rates -No clear trends across exposure groups but some suggestion of a trend for liver cancer and kidney cancer
Steenland et al. 2015	Occupational cohort incidence study (medical records confirmation sought for self-reported cancers)	PFOA	Modeled time-varying lifetime serum cumulative concentration (sum of estimated annual serum concentrations up to a given year), created by combining occupational estimates based on a work history and a job-exposure matrix (as in Steenland and Woskie, 2012) and residential exposure (from a multistage model estimating serum concentrations based on drinking water exposures).	Measured serum PFOA concentration in 2005–2006 (n=1881): mean 325 ng/ml, median 113 ng/ml	Reported on cancers with at least 20 cases, including bladder, colorectal, prostate and melanoma	Workers with any history of working during 1948–2002 at a plant that used PFOA and who had an interview or proxy interview and exposure estimates (subset of population in Leonard et al. 2008)	3,713 workers, incidence follow-up through final interview (during 2008–2011), 335 cancer cases with medical records validation (highest number of cases in the analysis for a specific cancer type for which results were reported was 129 for prostate cancer)	Cox regression models with age as time scale, controlled for gender, race (Caucasian/ non-Caucasian), education (4 categories), body mass index (4 categories) and time-varying smoking (current, former, never) and alcohol consumption (current, former, never)	Results reported only for sites with more than 20 cases (bladder, colorectal, prostate, melanoma)-rate ratios (RRs) and 95% CIs for quartiles 2–5 of estimated cumulative serum concentration relative to quartile 1: -Prostate cancer (129 cases) 1.92 (0.56–6.58), 1.89 (0.57–6.34), 2.15 (0.64–7.26), trend p-value=0.10 with 10-year lag -Bladder cancer (29 cases) 0.55 (0.12–2.61), 0.47 (0.10–2.21), 0.31 (0.06–1.54), trend p-value=0.03 with 10-year lag	-Serum levels estimated based on occupation and a large number of measured levels (Woskie et al. 2012) as well as estimated residential exposures (Shin, et al, 2011b) -Interviews available for 79% of workers who had not died and 48% of workers who had died -No clear trends across exposure levels for prostate cancer, decreasing trend in RRs across exposure levels for bladder cancer -Negative trend for bladder cancer contrasts with bladder cancer findings from earlier studies on same cohort [SMR=1.30 (0.52–2.69) for

Study	Design	PFAS Studied*	Exposure Assessment	Measured or estimated PFAS serum concentrations†	Cancer types	Population	Size	Control for confounding	Main findings*	Notes on study design, methods and findings
										bladder cancer mortality in Leonard, et. al, 2008; SMRs >1 for quartiles 1 and 2 relative to regional worker cohort in Steenland and Woskie, 2012]
Occupational cohort, Cottage Grove, MN, USA										
Gilliland and Mandel, 1993	Occupational cohort mortality study	Primarily PFOA	Job history, categorized as exposed (at least 1 month in chemical division) or unexposed; some analyses used months worked in chemical division	No measurements or estimates of PFOA serum concentrations are provided. Information available from a separate study of 122 plant workers voluntarily tested who did not take cholesterol-reducing medication (Olsen and Zobel, 2007) (n=122)- serum concentrations [median (range)]: PFOA-950 (10–92,030) ng/ml; PFOS 450 (30–4790) ng/ml	Reported on several cancer categories including all cancer, gastrointestinal, respiratory, breast, genital, and lymphopoietic among women; and all cancer, all gastrointestinal, colon, pancreas, all respiratory, lung, prostate, testis, bladder, and lymphopoietic among men	Workers employed for at least 6 months during 1947–1983 at a plant producing PFOA	3,573 workers, mortality follow-up through 1989, 398 deaths including 120 total cancer deaths (highest number of deaths for a specific cancer type analyzed was 29 for male lung cancer)	Calculated “stratified SMRs” relative to U.S. population and Minnesota population for sexes separately, standardized by 5-year age category, and calendar period; calculated RRs for internal comparisons using proportional hazard models with time from first employment as the time scale, controlling for age and year at first employment and duration of employment, stratified by gender	-SMRs relative to Minnesota population for men employed in the chemical division [SMR (95% CI)]: prostate cancer mortality (4 deaths among exposed) 2.03 (0.55–4.59); pancreatic cancer (4 deaths among exposed) 1.96 (0.53–5.01); testicular cancer (1 death among exposed) 2.28 (0.03–12.66) -Internal comparison using proportional hazards models [RR (95% CI)]: prostate cancer mortality (6 deaths): RR per 1-year increase in time in chemical division 1.13 (1.01–1.27), p=0.03	-Workers categorized as exposed or non-exposed based on job histories (exposed if 1 or more months in chemical division), also did analyses by number of months in chemical division -SMRs were calculated using a U.S. referent population for females and a Minnesota reference population for males -No clear dose-response relationships although SMRs relative to the MN population were higher for men employed in chemical division than for all male employees for prostate,

Study	Design	PFAS Studied*	Exposure Assessment	Measured or estimated PFAS serum concentrations†	Cancer types	Population	Size	Control for confounding	Main findings*	Notes on study design, methods and findings
										pancreatic and testicular cancer mortality.
Lundin et al. 2009	Occupational cohort mortality study	Primarily PFOA	Job history, categorized as definite exposure, probable exposure and no exposure and by time in definite exposure job (≥6 months vs. <6 months); also estimated cumulative exposure based on duration of employment and a job exposure matrix with relative exposure weights	See above from Olsen and Zobel, 2007. In addition, Lundin, et al provide median serum concentrations for job categories based on serum PFOA concentrations measured on 131 employees in 2000: Definite exposure jobs-median 2600–5200 ng/ml, probable exposure jobs-median 300–1500 ng/ml	Reported on several cancer categories including all cancers; biliary passages and liver; pancreas; trachea, bronchus and lung; prostate; and bladder and other urinary organs	Workers employed for at least 365 days during 1947–1997 at a plant producing PFOA (overlaps with population in Gilliland and Mandel, 1993)	3,993 workers, mortality follow-up through 2002, 807 deaths including 246 cancer deaths (highest number of deaths for a specific cancer type reported was 75 for cancer of the trachea, bronchus and lung)	Calculated SMRs relative to Minnesota population, standardized by age, sex and calendar period; Calculated hazard ratios (HRs) for internal comparisons using Cox regression models with time from entry into the cohort as the time scale, controlling for sex and year of birth (also considered wage type and smoking)	-SMR (95% CI) relative to Minnesota population for prostate cancer: 2.1 (0.4–6.1) in ever definite exposure group (3 deaths), 0.9 (0.4–1.8) in the ever probable/ never definite exposure group (9 cases) and 0.4 (0.1–0.9) in the never exposed group (4 cases) -Internal comparisons for prostate cancer (16 cases) [HR (95% CI)]: moderate/ high vs. low exposure by job classification 3.2 (1.0–10.3); group with highest vs. lowest cumulative exposure 3.7 (1.3–10.4)	-Small number of specific cancers (e.g., 3 liver, 13 pancreas), few sites reported -Some SMRs calculated relative to Minnesota population -Internal analyses (for liver, pancreas and prostate cancers) used exposure categorized by job classification and cumulative exposure estimated based on job histories and exposure weights for specific job categories -Some evidence for dose-response relationship for prostate cancer by job classification category [HR and 95% CI relative to low exposure jobs: 3.0 (0.9–9.7) for moderate exposure jobs (10 deaths) and 6.6 (1.1–37.7) for high exposure jobs (2 deaths)]

Study	Design	PFAS Studied*	Exposure Assessment	Measured or estimated PFAS serum concentrations†	Cancer types	Population	Size	Control for confounding	Main findings*	Notes on study design, methods and findings
Raleigh et al. 2014	Occupational cohort mortality and incidence study	Primarily PFOA	Compared exposed and unexposed plants and estimated time-weighted average inhalation exposure using job history and a task-based job exposure matrix (incorporated industrial hygiene monitoring data, information from workers and hygiene professionals, and annual production levels)	Provided results for 148 participants in a biomonitoring program in 2000: serum PFOA concentration-overall GM=815 ng/ml; among those who worked only in PFOA-related areas (n=50) GM=2,538 ng/ml; among those with some work on PFOA areas (n=38) GM=979 ng/ml; among those who never worked in PFOA areas (n=60) GM=282 ng/ml	Reported on several cancer categories including all cancers, liver, pancreas, prostate, kidney, breast, and bladder	Workers employed for at least 365 days during 1947–2002 at a plant producing PFOA (overlaps with populations in Gilliland and Mandel, 1993 and Lundin et al. 2009) plus workers employed for at least 365 days before 1999 at a plant not producing PFOA	9,027 workers (4,668 at exposed plant and 4,359 at unexposed plant); mortality follow up through 2008, cancer incidence for 1988-"end of follow up" (end date not specified); 1,145 deaths at exposed plant and 1,824 at unexposed plant (at exposed plant- highest number of deaths for a specific reported cancer type was 24 for prostate cancer, highest number of incident cases for a specific cancer type was 188 for prostate cancer)	Calculated SMRs relative to the Minnesota population, standardized by age, sex and calendar period, for comparisons with workers at unexposed plant, used Cox regression models with age as the time scale, controlling for year of birth and sex	-No markedly elevated SMRs for any cancer site relative to Minnesota population -In comparison with unexposed plant [HRs (95% CIs) relative to unexposed workers]: bladder cancer mortality (8 total deaths) 1st and 2nd exposure quartiles 1.03 (0.27–3.96), 3rd and 4th exposure quartiles 1.96 (0.63–6.15); bladder cancer incidence (40 total cases) 1st exposure quartile 0.81 (0.36–1.81), 2nd exposure quartile 0.78 (0.033–1.85), 3rd exposure quartile 1.5 (0.8–2.81), 4th exposure quartile 1.66 (0.86–3.18)	-Mortality analysis started in 1960 and incidence analysis started in 1988 (Exposures first occurred in 1947) -SMRs calculated relative to Minnesota population -Improved exposure assessment with estimation of past cumulative inhalation exposure -Some evidence of dose-response relationship for bladder cancer but not monotonic for bladder cancer incidence.
Occupational cohort, Vento Region, Italy										
Girardi and Merler 2019	Occupational cohort mortality study	Primarily PFOA	Compared plant workers to regional populations, categorized workers by probability of exposure (ever exposed plant workers, never	Serum concentrations available for 120 workers during 2000–2013 [GM (range)]: PFOA 4,048 (19–91,900) ng/ml; PFOS 148.8	Reported on several cancer categories including all malignant neoplasms, esophagus, stomach, colon, liver, lung, malignant	Male workers employed for at least 6 months at a PFOA production plant or an unexposed workplace during 1960–	462 male employees at exposed plant, 1383 at unexposed workplace; follow-up during 1970–2018; 107 deaths	Calculated SMRs relative to regional mortality rates, standardized by gender, 5-year age groups and 5-year calendar periods. For comparison	-Among workers at exposed plant, SMRs (95% CIs) relative to regional population: Liver cancer mortality (7 deaths) 2.32 (1.11–4.87), mortality due to malignant neoplasms of	-High exposure cohort, limited by small numbers of deaths, exposures to other PFAS but mostly PFOA. -Workers classified as

Study	Design	PFAS Studied*	Exposure Assessment	Measured or estimated PFAS serum concentrations†	Cancer types	Population	Size	Control for confounding	Main findings*	Notes on study design, methods and findings
			exposed plant workers and office workers), and estimated time-dependent cumulative serum concentrations (based on work history and historical measured serum concentrations)	(10–3,386) ng/ml	neoplasms of lymphatic and hematopoietic tissue, and non-Hodgkin lymphoma	2008, and with available information on date of birth, birthplace, residence and period of employment	among exposed plant workers, 218 deaths among unexposed workplace workers (highest number of deaths for a specific reported cancer type among exposed workers was 7 for both liver cancer and malignant neoplasms of lymphatic and hematopoietic tissue)	with a cohort of workers at another factory, calculated mortality risk ratios using Poisson regression controlling for age at risk (continuous) and 10-year calendar period	lymphatic and hematopoietic tissue (7 deaths) 2.26 (1.08–4.73) -RRs (95% CIs) in comparison with worker reference group: liver cancer mortality 6.69 (1.71–26.2), mortality due to malignant neoplasms of lymphatic and hematopoietic tissue 3.20 (1.09–8.94)	"ever at PFAS department, "Never at PFAS department (but not exclusively working in offices), and "Offices", also estimated cumulative exposure based on work histories and some measured serum levels. -SMRs calculated relative to regional general population -Evidence of dose- response trend with increasing estimated exposure for liver cancer and malignant neoplasms of lymphatic and hematopoietic tissue relative to both the regional population and the unexposed worker cohort
Community Cohorts										
Eriksen et al. 2009	Cohort incidence study (case-cohort study design)	PFOA and PFOS	Measured concentrations in stored serum collected at cohort recruitment	Serum concentrations [median (5^{th}-95^{th} percentiles)]: PFOA- among men 6.8 (3.1–14.0) ng/ml in cancer patients and 6.9 (3.2–13.3) ng/ml in	Cancers of the prostate, bladder, pancreas and liver	General population, large cohort enrolled during 1993–1997, aged 50–65 years, matched with Danish Cancer Registry and	Overall cohort of 57,053 people-analysis included incident cancer cases: 713 prostate, 332 bladder, 128 pancreas,	Calculated incidence rate ratios using Cox proportional hazards models stratified by sex with age as the time scale, controlling for cancer type -	PFOA: No marked associations for any cancer type, RRs (95% CIs) for quartiles 2,3 and 4 relative to quartile 1: prostate cancer (713 total cases) 1.09 (0.78–1.53), 0.94 (0.67–1.32), 1.18 (0.84–1.65);	-Serum collected at time of enrollment -Cohort was enrolled at ages 50–65 -Suggestion of dose-response trends for prostate and

Study	Design	PFAS Studied*	Exposure Assessment	Measured or estimated PFAS serum concentrations†	Cancer types	Population	Size	Control for confounding	Main findings*	Notes on study design, methods and findings
				subcohort comparison group; among women 6.0 (2.6–11.0) mg/ml in cancer patients and 5.4 (2.2–11.6) ng/ml in subcohort comparison group. PFOS- among men 35.1 (17.4–60.9) ng/ml in cancer patients and 35.0 (16.8–62.4) ng/ml in subcohort comparison group; among women 32.1 (14.0–58.1) ng/ml and 29.3 (14.2–55.6) ng/ml in subcohhort comparison group.		Danish Pathology Data Bank through 2006	and 67 liver; comparison sub-cohort of 772 selected from overall cohort	specific variables (prostate cancer: years of school attendance, body mass index, fat intake, and fruit and vegetable intake; bladder cancer: smoking status, intensity and duration, years of school attendance and occupation associated with bladder cancer; pancreatic cancer: smoking status, intensity and duration, fat intake, and fruit and vegetable intake; liver cancer: smoking status, years of school attendance, alcohol intake and occupation associated with liver cancer)	pancreatic cancer (128 total cases) 0.88 (0.49–1.57), 1.33 (0.74–2.38), 1.55 (0.85–2.80) PFOS: No marked associations for any cancer type, RRs (95% CIs for quartiles 2,3 and 4 relative to quartile 1: prostate cancer (713 cases) 1.35 (0.97–1.87), 1.31 (0.94–1.82), 1.38 (0.99–1.93)	pancreatic cancers but not monotonic.
Bonefeld-Jorgensen et al. 2014	Cohort incidence study (case-cohort study design)	PFHxS, PFNA, PFOA, PFOS, PFOSA, and sums of PFAS groups	Measured concentrations in stored serum collected at baseline	Mean serum concentrations among controls: PFHxS 1.2 ng/ml, PFNA 0.5 ng/ml, PFOA 5.2 ng/ml, PFOS 30.6 ng/ml, PFOSA 3.5 ng/ml	Breast cancer only	Nested in cohort of pregnant women formed in 1996–2002 in Denmark, matched with Danish National Patient Registry through 2010	Overall cohort of about 100,000 pregnancies, 250 cases of breast cancer, 233 controls selected from overall cohort, frequency matched on age and parity	Controls were frequency matched to cases on age and parity. Unconditional logistic regression models were used to calculate relative risks controlling for age, pre-pregnancy body	PFOA: No association between baseline serum PFOA and later development breast cancer PFOS: No association between baseline serum PFOS and later development of breast cancer. Other PFAS: RRs (95% CIs for associations with	-Serum collected at baseline in 1996–2002, during first and second trimester of pregnancy -No clear dose-response relationships.

Study	Design	PFAS Studied*	Exposure Assessment	Measured or estimated PFAS serum concentrations†	Cancer types	Population	Size	Control for confounding	Main findings*	Notes on study design, methods and findings
								mass index, gravidity, oral contraceptive use, age at menarche, smoking during pregnancy, alcohol intake, maternal education and physical activity	breast cancer for quintiles 2–5 relative to quintile 1: PFHxS 0.64 (0.34–1.18), 0.70 (0.38–1.29), 0.38 (0.20–0.70), 0.61 (0.33–1.12); PFOSA 1.38 (0.75–2.52), 0.91 (0.49–1.66), 1.11 (0.60–2.05), 1.89 (1.01–3.54)	
Barry et al. 2013	Cohort incidence study (primarily retrospective, medical records confirmation sought for self-reported cancers).	PFOA	Modeled time-varying lifetime serum cumulative concentration (sum of estimated annual serum concentrations up to a given year), created by combining occupational estimates based on a work history and a job-exposure matrix (as in Steenland and Woskie, 2012) and residential exposure (from a multistage model estimating serum concentrations based on drinking water exposures).	Measured PFOA serum concentrations [median (range)] in 2005–2006: community 24.2 (0.25–4,752) ng/ml), workers 112.7 (0.25–22,412) ng/ml; Estimated annual PFOA serum concentrations [median (range)] across all years: community 19.4 (2.8–9,217) ng/ml, workers 174.4 (5.2–3,683) ng/ml	Reported on 21 cancer types	People aged 20 years and older who lived, worked or attended school for at least 1 year in a community with high PFOA exposure (near a chemical plant), recruited from participants in a prior survey (from 2005–2006) that had included approximately 81% of current residents, followed retrospectively from the later of age 20 or 1952 until the last completed survey (2008–2011) Also included chemical plant workers who completed surveys or had a proxy survey (subset	32,254 people in analysis (28,541 community, 3,713 workers), 2507 cancer cases validated by medical records review, 21 cancer sites (highest number of validated cases in the analysis for a specific reported cancer type was 559 for breast cancer)	Calculated hazards ratios using proportional hazards models with age as the time scale, controlling for time-varying smoking, time-varying alcohol consumption, sex, education and 5-year birth period.	Hazard ratios and 95% CIs for quartiles 2–4 relative to quartile 1 (no lag): For combined community and worker cohorts: testicular cancer (17 cases) 1.04 (0.26–4.22), 1.91 (0.47–7.75), 3.17 (0.75–13.45), trend p-value=0.04; kidney cancer (105 cases) 1.23 (0.70–2.17), 1.48 (0.84–2.60), 1.58 (0.88–2.84), trend p-value=0.18; thyroid cancer (86 cases) 1.54 (0.77–3.12), 1.48 (0.74–2.93), 1.73 (0.85–3.54),trend p-value =0.25. For community cohort only: testicular cancer (15 cases) 0.80 (0.16–3.97), 3.07 (0.61–15.36), 5.80 (0.97–34.58), trend p-value=0.05; kidney cancer (87 cases) 1.34 (0.71–2.52), 1.95 (1.03–3.70), 2.04 (1.07–	-Community cohort included only people who were alive at time of 2005–2006 survey -Estimated annual individual cumulative serum concentration based on fate-transport model using plant emissions (Shin et al. 2011a, 2011b), correlation coefficient 0.67 with measured levels in 2005–2006 -Dose-response trend observed for testicular cancer and kidney cancer, possible trend for thyroid cancer but not monotonic.

Study	Design	PFAS Studied*	Exposure Assessment	Measured or estimated PFAS serum concentrations†	Cancer types	Population	Size	Control for confounding	Main findings*	Notes on study design, methods and findings
						of cohort in Leonard et al, 2008)			3.88), trend p-value=0.20; thyroid cancer (78 cases) 1.54 (0.73–3.26), 1.71 (0.81–3.59), 1.40 (0.66–2.97),trend p-value =0.46.	
Fry and Power 2017	Cohort mortality study- cancer mortality after the time of the NAHNES examination was determined through the NCHS 2011 Public-use Linked Mortality Files	PFHxS, PFNA, PFOA, PFOS	Measured concentrations in serum collected through the U.S. National Health and Nutrition Examination Survey (NHANES)	Median concentrations for PFOA and PFOS reported in the paper (Table 2) are not consistent with NHANES data from 2003–2006. Values for GM serum concentrations among NHANES participants aged ≥60 years from Kato et al., 2011: PFHxS 2003–2004 GM=2.04 ng/ml, 2005–2006 GM=1.88 ng/ml; PFNA 2003–2004 GM=0.85 ng/ml, 2005–2006 GM=1.24 ng/ml; PFOA 2003–2004 GM=3.65 ng/ml, 2005–2006 GM=4.65 ng/ml; PFOS 2003–2004 GM=23.2 ng/ml, 2005–2006 GM=23.4 ng/ml	All cancer mortality combined	Participants in the 2003–2006 U.S. NHANES cycles who were aged ≥60 years at the time of examination, followed for a median of 5.5 years	1043 NHANES participants in analysis (4.5% died with a cancer cause of death during follow-up)	Calculated hazard ratios using Cox proportional hazards models with unspecified time scale, controlling for age, gender, race/ethnicity, education and smoking (in sensitivity analyses, also considered control for body mass index, family poverty income ratio and alcohol use)	No evidence of an association between serum PFAS concentrations and all-cancer mortality, HR (95% CI) for one standard deviation increase: PFHxS 1.06 (0.73–1.54), PFNA 0.89 (0.72–1.09), PFOA 0.94 (0.80–1.11), PFOS 1.01 (0.86–1.19)	-Serum collected at baseline (at NHANES examination) -Included only NHANES participants aged ≥60 years
Case-control studies (N=10)										
Studies nested in Cohorts (N=4)										

Study	Design	PFAS Studied*	Exposure Assessment	Measured or estimated PFAS serum concentrations†	Cancer types	Population	Size	Control for confounding	Main findings*	Notes on study design, methods and findings
Study of California Teachers										
Hurley et al. 2018	Nested case control study (did not state that they used density sampling)	MeFOSAA, PFHxS, PFNA, PFOA, PFOS, PFUnDA	Measured concentrations in serum collected from cases after diagnosis and from controls at the time of study enrollment	Serum concentrations [median (range)]: MeFOSAA- Cases 0.15 (0.01–4.00) ng/ml, Controls 0.17 (0.01–8.37) ng/ml; PFHxS- Cases 1.52 (0.01–40.70) ng/ml, Controls 1.61 (0.01–21.80); PFNA- Cases 0.85 (0.02–7.31) ng/ml, Controls 0.85 (0.02–10.40) ng/ml; PFOA- Cases 2.35 (0.04–39.10) ng/ml, Controls 2.48 (0.10–20.20) ng/ml; PFOS- Cases 6.70 (0.05–39.40) ng/ml, Controls 6.95 (0.05–99.80) ng/ml; PFUnDA- Cases 0.12 (0.01–1.03) ng/ml, Controls 0.13 (0.01–1.31) ng/ml	Breast cancer only	California teachers cohort (initially enrolled during 1995–1996), participants who had provided a blood sample and completed a questionnaire for a separate breast cancer case-control study during 2011–2015, excluding those whose blood sample was drawn prior to October 2011 or in the last two months of the prior case-control study.	902 breast cancer cases (diagnosed during 2006–2014, identified through California Cancer Registry linkage); 858 controls from the overall cohort, frequency matched by age, race/ethnicity, and region of residence	Controls frequency matched to cases by age at baseline, race/ethnicity, and region of residence. Calculated odds ratios using unconditional logistic regression, controlling for age at baseline, race/ethnicity, region of residence, date of blood draw, date of blood draw squared, season of blood draw, total smoking pack years, body mass index, family history of breast cancer, age at first full-term pregnancy, menopausal status at blood draw and pork consumption.	No association with case status for PFOA, PFOS or other or any of the other examined types of PFAS	-Serum collected mean of 35 months (range 9 months-8.5 years) after diagnosis (during 2011–2015)
French E3N study										
Mancini et al. 2020	Nested case control study (with density sampling of controls)	PFOA, PFOS	Measured concentrations in stored serum collected from cases and controls at baseline	Serum concentrations [median (range)]: PFOA 6.64 (1.29–21.39) ng/ml, PFOS 17.51 (5.83–85.26) ng/ml	Breast cancer only	Nested within cohort of 98,995 women enrolled in 1990, 25,000 with blood samples collected	Random sample of 194 incident post-menopausal breast cancer cases (identified through self-report, national	Controls matched with cases by age, menopausal status at blood collection (all post-menopausal), body mass index (< 25 or	-In fully adjusted model, OR (95% CI, total n) for association with breast cancer for quartiles 2–4 respectively, compared with quartile 1: PFOA 1.69 (0.89–3.21,	-Serum collected at baseline before case diagnosis. -No clear evidence of dose-response relationship in overall analysis, some

Study	Design	PFAS Studied*	Exposure Assessment	Measured or estimated PFAS serum concentrations†	Cancer types	Population	Size	Control for confounding	Main findings*	Notes on study design, methods and findings
						during 1994–1999	health insurance files, or death certificates) diagnosed through 2013 with pre-diagnosis blood samples and dietary data; 194 controls sampled from those free of breast cancer at the time of diagnosis of corresponding case and with blood samples, matched by age, menopausal status and BMI at blood collection and year of blood collection (density sampling)	≥25 kg/m²), and year of blood collection. Calculated odds ratios using conditional logistic regression (conditioned on matching factors), adjusted for total serum lipids, body mass index (continuous), smoking status, physical activity, education level, history of benign breast disease, family history of breast cancer, parity, age at first full-term pregnancy, breastfeeding duration, age at menarche, age at menopause, current use of menopausal hormone therapy, use of oral contraceptives, adherence to healthy and Western and Mediterranean diet patterns	n=118), 0.88 (0.43–1.80, n=91), 0.92 (0.43–1.98, n=94), trend p-value 0.43; PFOS 1.94 (1.00–3.78, n=109, 2.03 (1.02–4.04, n=99), 1.72 (0.88–3.36, n=100), trend p-value 0.25. -For association between case status and PFOS exposure for estrogen receptor positive tumors (ORs and 95% CIs) for quartiles 2–4 respectively, compared with quartile 1: PFOA-no clear association; PFOS-1.85 (0.90–3.82), 2.22 (1.05–4.69), 2.33 (1.11–4.90), trend p-value 0.04) -For association with progesterone receptor positive tumors (ORs and 95% CIs) for quartiles 2–4 respectively, compared with quartile 1: PFOA-no clear association; PFOS-1.84 (0.82–4.14), 2.47 (1.07–5.65), 2.76 (1.21–6.30), trend p-value 0.02.	evidence of a dose-response relationship for PFOS for estrogen- and progesterone-receptor positive tumors.
Child and Health Development Pregnancy Cohort										
Cohn et al. 2020	Nested case-control study of maternal serum PFAS	EtFOSAA, PFHxS, PFOA, PFOS	Measured concentrations in stored serum collected from	Maternal serum concentrations [median (25^{th}-75^{th}	Breast cancer only	Nested within Child Health and Development	102 breast cancer cases (identified through self-	Controls matched with cases by birth year and	No associations between breast cancer and maternal serum	-Serum collected from mothers at baseline before

Study	Design	PFAS Studied*	Exposure Assessment	Measured or estimated PFAS serum concentrations†	Cancer types	Population	Size	Control for confounding	Main findings*	Notes on study design, methods and findings
	levels and breast cancer in daughters (appears to have used density sampling)		mothers of cases and controls at baseline	percentiles)]: EtFOSAA- Cases 0.3 (0.1–0.6) ng/ml, Controls 0.3 (0.1–0.5) ng/ml; PFHxS- Cases 2.0 (1.0–3.6) ng/ml, Controls 2.3 (1.0–3.5) ng/ml; PFOA- Cases 0.4 (0.3–0.6) ng/ml, Controls 0.4 (0.2–0.6) ng/ml; PFOS- Cases 30.5 (14.1–55.8) ng/ml, Controls 32.1 (14.9–58.2) ng/ml		Studies pregnancy cohort in California with baseline maternal blood samples (collected during 1959–1967), total cohort size 20,754 pregnancies; 9,300 live-born female offspring	report, cancer registry matching and death certificates) diagnosed by age 52 in daughters; 310 controls (selected at random from daughters not known to have been diagnosed with breast cancer at the age of diagnosis of the case) matched by birth year and trimester of maternal blood draw	trimester of maternal blood draw. Calculated odds ratios using age-matched conditional logistic regression, stratified by total maternal cholesterol (in light of apparent interaction), and adjusted for maternal age, race, overweight in early pregnancy, parity, maternal history of breast cancer, maternal serum DDE and DDT concentrations, and whether the daughter was breastfed.	PFOA or PFHxS concentrations. PFOS and EtFOSAA were included in same model (because PFOS is a metabolite of EtFOSAA). The authors present results from a model with linear terms for $\log_2$ transformed EtFOSAA, PFOS and cholesterol concentrations and the EtFOSAA-cholesterol interaction. From this model, among daughters of mothers with total cholesterol at the median of its highest quartile, ORs (95% CIs) for an increment from the median of the first PFAS quartile to the median of the 4th PFAS quartile: maternal PFOS 0.3 (0.1–0.9), maternal EtFOSAA 3.6 (1.1–11.6)	case diagnosis in daughters. -Multiple comparisons examined, including interactions of PFASs with cholesterol -Stratification by cholesterol might be problematic because cholesterol might be affected by the exposure -Dose-response relationships cannot be assessed.
Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial										
Shearer et al. 2020	Nested case control study (with density sampling of controls)	EtFOSAA, MeFOSAA, PFDA, PFHxS, PFNA, PFOA, PFOS, PFUnDA	Measured concentrations in stored serum collected from cases and controls at baseline	Serum Concentration quartile end points among controls (Q1, Q2, Q3, Q4): EtFOSAA 0.7, 1.2, 2.4, 60.4 ng/ml; MeFOSAA 0.9, 1.4, 2.1, 8.2 ng/ml;	Kidney cancer [renal cell carcinoma (RCC)] only	Nested within cohort of participants in screening arm of PLCO trial (overall trial ~150,000 adults aged 55–74 years enrolled in 1993–2001)	324 RCC cases (identified through the overall study, methods of case identification not specified) with serum PFAS measure-	Controls matched with cases on age at enrollment, sex, race/ ethnicity, study center and study year of blood draw. Calculated odds ratios using	In conditional logistic regression models ORs (95% CIs) comparing quartiles 2–4 to quartile 1 in single-pollutant models: PFOA 1.47 (0.77–2.80), 1.24 (0.64–2.41), 2.63 (1.33–5.20), trend p-value 0.007;	-Serum collected at baseline before case diagnosis. -Evidence of dose-response relationship for PFOA, PFOS and PFHxS in single-PFAS models, some evidence for

Study	Design	PFAS Studied*	Exposure Assessment	Measured or estimated PFAS serum concentrations†	Cancer types	Population	Size	Control for confounding	Main findings*	Notes on study design, methods and findings
				PFDA quartile cut points not provided, maximum 2.1 ng/ml; PFHxS 2.2, 3.4, 5.5, 37.4 ng/ml; PFNA 0.5, 0.7, 1.0, 4.9 ng/ml; PFOA 4.0, 5.5, 7.3, 27.2 ng/ml; PFOS 26.3, 38.4, 49.9, 154.2; PFUnDA quartile cut points not provided, maximum 1.7 ng/ml			ments; 324 controls who were at risk for RCC at the time of diagnosis of the matched case, individually matched on age, sex, race/ethnicity, study center, and study year of blood draw	conditional logistic regression (conditioned on matched sets), controlling for eGFR, body mass index, smoking status, history of hypertension, prior freeze-thaw cycles and calendar year of blood draw.	PFOS 1.67 (0.84–3.30), 0.92 (0.45–1.88), 2.51 (1.28–4.92), trend p-value 0.009; PFHxS 1.41 (0.75–2.64), 1.14 (0.59–2.20), 2.07 (1.06–4.04), trend p-value 0.04. ORs (95% CIs) comparing PFOA quartiles 2–4 to quartile 1 in models controlling for PFOS and PFHxS: 1.41 (0.69–2.90), 1.12 (0.52–2.42), 2.19 (0.86–5.61), trend p-value 0.13	dose-response relationship (although not monotonic) for PFOA in models controlling for PFOS and PFHxS. -Association with PFOA remained in analyses restricted to individuals without evidence of diminished kidney function and in cases diagnosed ≥8 years after phlebotomy.
Non-nested studies (N=6)										
Study of cancer in Greece										
Vassiliadou et al. 2010	Case-control study	PFOA, PFOS	Measured concentrations in serum collected from cancer patients (presumably after diagnosis), and from other patients at the time of a clinic visit	Serum concentrations across males and females in 3 groups: PFOA medians 1.70–3.14 ng/ml, maximums 3.26–10.21 ng/ml; PFOS medians 7.03–13.69 ng/ml, maximums 16.63–40.36 ng/ml	Group of patients with cancers of various types (not specified)	Convenience sample, clinical care populations in Greece, all samples collected during 2009	40 hospitalized cancer patients from hospital in Athens; 86 and 56 healthy controls from two clinics (from Argolida and Athens respectively)	Compared PFAS serum concentrations between groups for men and women separately. No other control for confounding.	No differences between cancer patients and controls for either PFOA or PFOS serum concentrations	-Serum collected from patients presumably after diagnosis. -Patient groups were from different areas of Greece. -No specific types of cancers were studied.
Greenland Inuit Studies										
Bonefeld-Jorgensen et al. 2011	Case-control study	PFOA, PFOS, and sums of PFAS groups	Measured concentrations in serum collected from cases at the time	Serum concentrations [median (range)]: PFOA- Cases	Breast cancer only	General population Inuit, Greenland, enrolled	31 hospital-based breast cancer cases; 115 controls from two	Cases and controls frequency matched on age and district.	Breast cancer cases (n=31) had significantly higher levels of PFOA, PFOS, and sums of	-Serum collected at time of diagnosis, multiple

Study	Design	PFAS Studied*	Exposure Assessment	Measured or estimated PFAS serum concentrations†	Cancer types	Population	Size	Control for confounding	Main findings*	Notes on study design, methods and findings
			of diagnosis and from controls at the time of study enrollment	2.5 (0.2–7.2) ng/ml, Controls 1.6 (0.2–7.6) ng/ml; PFOS- Cases 45.6 (11.6–124) ng/ml, Controls 21.9 (1.5–172) ng/ml		during 2000–2003	previous cross-sectional studies, frequency matched to cases by age and district (only 98 cases and 31 control included in comparison of PFAS means, 69 controls and 7–15 cases included in fully adjusted logistic regression models for various PFAS measures)	Compared ln-transformed PFAS serum concentrations between cases and controls using ANCOVA analysis adjusted for age, body mass index, number of pregnancies and smoking. Calculated odds ratios using unconditional logistic regression, controlling for "identified confounders"-considered age, body mass index, number of full-term pregnancies, breastfeeding, menopausal status and serum cotinine but variables actually included in final models are not listed	perfluorosulfonated acids and perfluorinated carboxylated acids in their serum at time of diagnosis compared to controls (n=115) (presented only p-values for this comparison, no adjusted effect measure). Adjusted OR (95% CI), per unspecified increase in serum PFAS concentration in fully adjusted models: PFOA (69 controls and 7 cases) 1.20 (0.77–1.88); PFOS (69 controls and 9 cases) 1.03 (1.001–1.07); sum of PFOS, PFHxS and PFOSA 1.03 (1.00–1.05); sum of PFHpA, PFOA, PFNA, PFDA, PFUnDA and PFTrA 1.07 (0.96–1.18)	comparisons, small population -Adjusted logistic regression analysis excluded a large number of cases and controls (presumably because of missing data) -Matched cases and controls on district but did not control for district in analysis. -Only analyses of continuous variables presented, so difficult to assess dose-response pattern.
Wielsoe et al. 2017	Case-control study	PFDA, PFDoDA, PFHpA, PFHxS, PFNA, PFOA, PFOS, PFUnDA, and sums of PFAS groups	Measured concentrations in serum collected from cases at the time of diagnosis and from controls at the time of study enrollment	Serum concentrations [median (range)]: PFDA- Cases, 1.30 (0.20–11.10) Controls 1.01 (0.05–6.41); PFDoDA- Cases 0.40 (0.15–5.71), Controls 0.21 (0.15–6.49);	Breast cancer only	General population, Inuit, Greenland (population partially overlapping with Bonefeld-Jorgensen et al. 2011), enrolled during 2000–	77 hospital-based breast cancer cases; 81 controls with PFAS measurements from two previous cross-sectional studies (2000–2003) or hospital-based patients	Cases and controls were matched on age and geographic area, Compared ln-transformed PFAS serum concentrations between cases and controls using ANCOVA analysis adjusted for	Serum PFAS levels were significantly higher in breast cancer cases than controls in age-adjusted analysis for PFHxS, PFOS, the sum of perfluorinated sulfonic acids, and the sum of all PFAS types considered. ORs (95% CI) for 2nd	-Serum collected at time of diagnosis -Some controls were patients hospitalized for non-malignant conditions. -Matched cases and controls on geographic area but did not control for

Study	Design	PFAS Studied*	Exposure Assessment	Measured or estimated PFAS serum concentrations†	Cancer types	Population	Size	Control for confounding	Main findings*	Notes on study design, methods and findings
				PFHpA- Cases 0.11 (0.03–1.55), Controls 0.08 (0.03–0.59); PFHxS- Cases 2.52 (0.19–23.40), Controls 1.14 (0.16–13.90); PFNA- Cases 3.28 (0.30–38.60), Controls 1.83 (0.25–12.50); PFOA- Cases 2.08 (0.20–9.52) ng/ml, Controls 1.48 (0.20–6.29) ng/ml; PFOS- Cases 35.50 (4.23–187.0) ng/ml, Controls 18.2 (1.70–133.0) ng/ml; PFUnDA- Cases 2.23 (0.20–24.90), Controls 2.02 (0.03–20.0)		2003 and 2011–2014	with non-malignant conditions (2011–2014), frequency matched on age and geographic area (fewer in adjusted analyses)	age. Calculated odds ratios using unconditional logistic regression, controlling for "identified confounders"- considered age, body mass index, breastfeeding, parity and serum cotinine but variables actually included in final models are not listed	and 3rd tertiles relative to first tertile in adjusted analyses: PFDA 2.14 (0.94–4.91), 2.36 (1.04–5.36); PFHxS 1.13 (0.48–2.66),2.69 (1.23–5.88); PFOA 1.86 (0.80–4.31), 2.64 (1.17–5.97); PFOS 3.13 (1.20–8.15), 5.50 (2.19–13.84)	geographic area in analysis. -Some evidence of dose-response relationships.
West Virginia-Ohio Study										
Vieira et al. 2013	Case-control study (two studies)- compared incident cases of cancer in persons aged 15 years and older at 18 cancer sites with controls which consisted of all other cancers except kidney, pancreatic,	PFOA	For 13 counties in Ohio and West Virginia: Categorization by water district, comparing water districts with various levels of historic water contamination For 5 counties in Ohio only: did analyses by modeled time-varying annual or cumulative serum	Serum PFOA concentrations in cross sectional study of >69,000 residents in the area: median 28.2 ng/ml, range 0.2–22,412 ng/ml	Reported on 18 cancer types	13 high-exposure and low exposure counties in Ohio and West Virginia, near plant that used PFOA- one study in Ohio only and one in both Ohio and West Virginia; incident cancers during 1996–2005	Analysis included a total of 7,869 cancer cases (all types) in Ohio and 17,238 cancer cases (all types) from West Virginia, cancer-specific total number of cases ranged from 61 for liver and testicular cancer in the	Calculated odds ratios using logistic regression controlling for age, sex, diagnosis year, smoking status, and insurance provider in both analyses; also controlled for race (white/non-white) in Ohio-only analysis	Based on individually estimated annual serum levels in Ohio only, ORs (95% CIs, number of cases) for comparison with other cancer types for high and very high estimated PFOA exposure groups, respectively: kidney cancer 2.0 (1.3–3.2, n=22), 2.0 (1.0–3.9, n=9); testicular cancer 0.3 (0.0–2.7, n=1),	-Exposure estimated water district contamination for the combined Ohio and West Virginia analysis -Modeled annual and cumulative exposure assigned to individuals in Ohio, ten-year latency and residence assumed.

Study	Design	PFAS Studied*	Exposure Assessment	Measured or estimated PFAS serum concentrations†	Cancer types	Population	Size	Control for confounding	Main findings*	Notes on study design, methods and findings
	testicular, and liver.		concentration (sum of estimated annual serum concentrations up to a given year), created based on residence at diagnosis (assuming residence at that address for the prior 10 years) using environmental and pharmacokinetic models (Shin 2011 a and b)				Ohio-only analysis to 4926 for lung cancer in the analysis for Ohio and West Virginia		2.8 (0.8, 9.2, n=6); non-Hodgkin lymphoma 1.1 (0.7–1.19, n=17), 1.8 (1.0–3.4, n=11); ovarian cancer 1.4 (0.7–2.9), n=8), 2.1 (0.8–5.5, n=5); prostate cancer 0.8 (0.5–1.1, n=47), 1.5 (0.9–2.5, n=31); female breast cancer 0.7 (0.5, 1.0, n=45), 1.4 (0.9, 2.3, n=29). -For analysis of combined Ohio and West Virginia cases, OR (95% CI, n) for comparison with other cancer types for the highest exposure water district (Little Hocking): testicular cancer 5.1 (1.6–15.6, n=8); ovarian cancer 1.8 (0.7–4.4) n=5); kidney cancer 1.7 (0.9–3.3, n=10); non-Hodgkin lymphoma 1.6 (0.9–2.8, n=14); prostate cancer 1.4 (0.9–2.3, n=36)	-Some overlap of cases with Barry et al. (2013) community cohort. -Small numbers of cases for some cancers. No detailed residence data for West Virginia Cases. -Controls were cases of other cancers, which might not be representative of the source population. -No clear evidence of dose-response relationships
Swedish Study										
Hardell et al. 2014	Case-control study	PFDA, PFHxS, PFNA, PFOA, PFOS, PFUnDA	Measured concentrations in serum collected from cases after diagnosis and from controls at the time of	Serum concentrations [median (range)]: PFDA- Cases 0.30 (0.03–1.2) ng/ml, Controls 0.27 (0.02–1.0)	Prostate cancer only	General population, Sweden, enrolled during 2007–2011	201 hospital-based cases, 186 population controls selected from population registry (matched on	Controls matched with cases on age and geographic area (cases from hospital in Örebro county and controls from	PFOA and PFOS: No difference in PFOA or PFOS serum levels between cases and controls in overall analysis. In examination of interaction between	-Serum collected after diagnosis of cases (same year as diagnosis to 3 years after diagnosis) -Did not assess

Study	Design	PFAS Studied*	Exposure Assessment	Measured or estimated PFAS serum concentrations†	Cancer types	Population	Size	Control for confounding	Main findings*	Notes on study design, methods and findings
			study enrollment	ng/ml; PFHxS- Cases 0.91 (0.09–16) ng/ml, Controls 0.87 (0.15–3.0) ng/ml; PFNA- Cases 0.61 (0.05–4.6) ng/ml, Controls 0.57 (0.09–2.1) ng/ml; PFOA- Cases 2.0 (0.32–15) ng/ml, Controls 1.9 (0.35–8.4) ng/ml; PFOS- Cases 9.0 (1.4–69) ng/ml, Controls 8.3 (1.7–49) ng/ml; PFUnDA- Cases 0.26 (0.02–1.3) ng/ml, Controls 0.25 (0.02–1.5) ng/ml			age and county), fewer cases (105–118) and controls (87–93) in logistic regression analyses for the various types of PFAS	same county), calculated odds ratios using unconditional logistic regression controlling for age, body mass index, and year of sampling.	heredity and PFAS, OR (95% CI) for comparison with the group with no first degree relatives with prostate cancer and PFAS levels below the median: group with first degree relatives with prostate cancer and PFAS levels above the median- PFDA 2.6 (1.1–6.1), PFHxS 4.4 (1.7–12), PFNA 2.1 (0.9–4.8), PFOA 2.6 (1.2–6.0), PFOS 2.7 (1.04–6.8), and PFUnDA 2.6 (1.1–5.9); no associations for the group with no first degree relatives with prostate cancer and PFAS levels above the median, or the group with first degree relatives with prostate cancer and PFAS levels below the median.	dose-response relationship.
Taiwanese Study										
Tsai et al. 2020	Case-control study	PFDA, PFDoDA PFHxS, PFNA, PFOA, PFOS, PFTrDA, PFUnDA	Measured concentrations in serum collected from cases after diagnosis but before treatment, and from controls at the time of study enrollment	Across all participants, geometric mean serum concentrations: PFDA 0.77 ng/ml, PFDoDA 0.24 ng/ml, PFHxS 0.64 ng/ml, PFNA 0.99 ng/ml, PFOA 1.77	Breast cancer only	Patients at National Taiwan University Hospital and controls from hospital and community recruited through posters and flyers (cases and controls enrolled	120 case patients and 119 control participants – not matched	Calculated odds ratios using logistic regression controlling for pregnancy history, oral contraceptive use, abortion, body mass index, education level, menopause, and stratified	No associations with case status for any of the types of PFAS in overall analyses. Among cases (n=60) and controls (n=60) aged ≤50 years, adjusted ORs (95% CIs) per unit increase in natural log transformed PFAS concentration:	-Blood samples collected after diagnosis of breast cancer in cases but before start of treatment. -Dose-response pattern could not be assessed.

Study	Design	PFAS Studied*	Exposure Assessment	Measured or estimated PFAS serum concentrations†	Cancer types	Population	Size	Control for confounding	Main findings*	Notes on study design, methods and findings
				ng/ml, PFOS 4.77 ng/ml, PFTrDA 0.59 ng/ml PFUnDA 2.14 ng/ml		during 2014–2016)		by age category (≤50 years and > 50 years).	PFHxS 1.59 (0.99–2.57), PFOS 2.34 (1.02–5.38), PFUnDA 1.66 (0.85–3.24); In analyses stratified by tumor estrogen receptor status, positive associations for PFHxS, and PFOS only among estrogen receptor positive cases in patients aged ≤50 years; negative associations for PFDA and PFNA among estrogen receptor negative cases in patients aged ≤50 years.	
Cross-sectional study (N=1)										
Innes et al. 2014	Cross-sectional prevalence study	PFOA and PFOS	Measured concentrations in serum collected at the same time as ascertainment of a history of colorectal cancer	Serum concentrations [median (range)]: PFOA 27.9 (<0.5–22,412) ng/ml; PFOS 20.2 (<0.5–759.2) ng/ml	Colorectal cancer only	Highly exposed general population in mid-Ohio valley, aged ≥21 years who completed a survey during 2005–2006, had not received a diagnosis of cancer other than colon cancer, and had complete information on covariates of interest.	Total of 47,359 adults (208 with validated diagnosis of colorectal cancer; 47,151 cancer-free)	Calculated odds ratios using logistic regression controlling for age, sex, race/ethnicity, marital status, years of education, family income, employment status, regular exercise, vegetarian diet, smoking, current alcohol consumption, menopausal status, use of hormone replacement therapy, body mass index, reported physician diagnosis of	In models adjusted for age, inverse association between PFOS and PFOA serum levels and colorectal cancer case status-ORs (95% CIs) for 2nd-4th quartiles compared with 1st quartile: PFOA 0.50 (0.33–0.77), 0.53 (0.36–0.78), 0.64 (0.45–0.92), trend p-value <0.01; PFOS 0.39 (0.26–0.57), 0.33 (0.23–0.48), 0.27 (0.19–0.39), trend p-value <0.01; similar results in models adjusted for other variables	-Serum PFAS concentration measured after diagnosis -Use of prevalent cases -Control for factors that might be caused by PFAS or by colorectal cancer could be problematic.

Study	Design	PFAS Studied*	Exposure Assessment	Measured or estimated PFAS serum concentrations†	Cancer types	Population	Size	Control for confounding	Main findings*	Notes on study design, methods and findings
								other conditions (heart, kidney, liver thyroid immune or connective tissue disease; stroke; hypertension; dyslipidemia; diabetes; chronic obstructive pulmonary disease; or asthma), and current treatment for hypertension or hyperlipidemia. Some models also controlled for physician diagnosis of rheumatoid arthritis, osteoarthritis, or fibromyalgia; gastrointestinal symptoms; anemia; and serum concentrations of folate, cholesterol, c-reactive protein, uric acid, estradiol and other PFAS.		
Ecologic study (N=1)										
Mastrantonio et al. 2018	Ecologic mortality study	Not specified	Compared areas with known PFAS contamination in drinking water with areas without PFAS contamination	Not provided for the population in this study. A separate biomonitoring study (Ingelido et al., 2018) of 257 adults in	Reported on several cancer types including liver, kidney, bladder, pancreas, leukemia, non-Hodgkin's	Population in Vento Region of Italy, excluding three province chief towns, comparing mortality	Total number of deaths in contaminated areas was 41,841 (21,149 in men and	Calculated mortality rates standardized to the Italian population by age group, stratified by sex, and	Rate Ratios (95% CIs) comparing contaminated areas to uncontaminated areas: Among women: kidney cancer deaths 1.32 (1.06–1.65), 103	-Compared PFAS contaminated areas with uncontaminated areas, but did not do analyses by PFAS level

Study	Design	PFAS Studied*	Exposure Assessment	Measured or estimated PFAS serum concentrations†	Cancer types	Population	Size	Control for confounding	Main findings*	Notes on study design, methods and findings
			in drinking water	contaminated areas of the Vento Region of Italy showed median serum concentrations of 13.77 ng/ml for PFOA, 8.69 ng/ml for PFOS, and 2.98 ng/ml for PFHxS.	lymphoma, breast, prostate, testis, and ovary	during 1980–2013 (excluding 2004–2005) in municipalities with PFAS concentrations above specified levels during 2013–2015 and in municipalities not found to have ground water contamination in 2013–2014.	20,692 in women)	calculated rate ratios; compared deprivation index and smoking prevalence in contaminated areas and uncontaminated areas to assess potential for confounding by those factors.	deaths in contaminated areas; bladder cancer deaths 1.15 (0.86–1.55), 57 deaths in contaminated areas; breast cancer deaths 1.11 (1.02–1.20), 809 deaths in contaminated areas; leukemia deaths 1.12 (0.94–1.33), 166 deaths in contaminated areas; ovarian cancer deaths 1.08 (0.92–1.26), 201 deaths in contaminated areas. -Among men: testicular cancer deaths 1.86 (0.81–4.27), 8 deaths in contaminated areas; leukemia deaths 1.16 (0.99–1.35), 210 deaths in contaminated areas; bladder cancer deaths 1.12 (0.97–1.30), 225 deaths in contaminated areas; pancreatic cancer 1.11 (0.99–1.25), 361 deaths on contaminated areas; kidney cancer deaths 1.07 (0.90–1.28), 155 deaths in contaminated areas.	or specific PFAS type -No analysis of dose-response relationship

*EtFOSAA = N-ethyl-perfluorooctane sulfonamide acetic acid; MeFOSAA=2-(N-Methyl-perfluorooctane sulfonamido) acetic acid; PFDA = perfluorodecanoic acid; PFDoDA=perfluorododecanoic acid; PFOA = perfluorooctanoic acid; PFHpA=perfluoroheptanoic acid; PFHxS = perfluorohexane sulfonate; PFNA = perfluorononanoic acid; PFOS = perfluorooctane sulfonate; PFOSA= perfluorooctanesulfonamide; PFTrDA =perfluorotridecanoic acid; PFUnDA = perfluoroundecanoic acid

† Serum concentration information from the paper cited is presented if available. If information is not available from the paper, information from other references pertaining to the same cohort or study area is presented. If summary information about serum concentrations is available for the overall study population, that information is presented. Otherwise, if information is available only for sub-groups, information is presented by sub-group.