Oncologic Safety of Assisted Reproductive Technologies: Implications for Breast, Ovarian, and Endometrial Cancer

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Abstract

Introduction

The use of assisted reproductive technologies (ART), including in vitro fertilization and ovulation induction, has increased substantially over the past several decades in parallel with rising infertility rates and delayed childbearing. Given the supraphysiologic hormonal exposures associated with many ART protocols, concerns have been raised regarding potential long-term risks of hormone-sensitive malignancies, particularly breast, ovarian, and endometrial cancers.

Purpose

This narrative review aims to synthesize current epidemiologic and mechanistic evidence on the relationship between ART and the risk of breast, ovarian, and endometrial cancer, to contextualize findings within baseline infertility-related risk factors, and to identify key methodological challenges and knowledge gaps relevant to clinical counseling and future research.

Materials and methods

A narrative review of prospective cohort studies, population-based registries, systematic reviews, and meta-analyses was conducted, focusing on long-term cancer outcomes following ART exposure. Evidence was interpreted in light of underlying infertility diagnoses, reproductive history, specific fertility drugs and protocols, duration of follow-up, and guidance from professional societies such as the American Society for Reproductive Medicine.

Results

Across contemporary studies, ART exposure is not associated with a clinically meaningful increase in breast or endometrial cancer risk after adjustment for confounding factors. Breast cancer risk does not appear to vary by fertility drug type, number of cycles, or protocol intensity, including among BRCA mutation carriers, although data in high-risk subgroups remain limited. For ovarian cancer, a modestly increased risk—particularly for borderline ovarian tumors—has been observed, largely

confined to women with preexisting risk factors such as endometriosis, nulliparity, or prolonged infertility. Evidence suggests that infertility itself, rather than ART exposure, accounts for much of the observed excess risk. Significant methodological challenges, including confounding by indication, exposure misclassification, and insufficient long-term follow-up, limit definitive causal inference.

Keywords:

Assisted reproductive technologies; in vitro fertilization; breast cancer; ovarian cancer; endometrial cancer; infertility; fertility drugs; long-term cancer risk; hormone-sensitive malignancies**1.**

Introduction

Infertility affects approximately 17.5% of the population of reproductive age worldwide, with prevalence continuing to rise, particularly in regions with high and middle sociodemographic index (SDI) (1,2). The increase has been attributed to multiple factors, including delayed childbearing driven by educational, career, and socioeconomic priorities; a growing burden of metabolic and endocrine disorders; male-factor comorbidities; and increased exposure to environmental and occupational toxins. The burden of infertility is highest among women aged 35-39 years, reflecting the age-related decline in ovarian reserve and oocyte quality (3,4). In response, assisted reproductive technologies (ART) have become widely adopted as standard clinical interventions for achieving conception. Globally, more that 3.5 million ART cycles are performed annually, resulting in over 780,000 infants born per year (5,6). Over the past two decades, the use of ART, particularly protocols involving ovarian stimulation and in vitro fertilization, has increased steadily, prompting growing interest in the potential long-term health consequences of repeated and supraphysiologic hormonal exposure (1,7). This concern is particularly relevant in the context of hormone-sensitive female cancers, including breast, ovarian, and endometrial malignancies, whose development is strongly influenced by both endogenous and exogenous hormonal factors, such as cumulative exposure to estrogen and progesterone across the reproductive lifespan (8–10).

Although these hormonal exposures are generally short-term, concerns have been raised regarding the potential cumulative effects of repeated cycles and high peak estrogen levels on estrogen-responsive tissues. The purpose of this review is to summarize current knowledge on the relationship between ART and hormone-sensitive female cancers, highlight methodological challenges in the literature, and identify key gaps for future research and clinical counseling.

2. Assisted Reproductive Technologies: Clinical and Hormonal Context

ART encompass a heterogeneous group of clinical interventions designed to facilitate conception in individuals experiencing infertility. The most commonly utilized ART modality is in vitro fertilization (IVF), which entails the highest intensity and duration of hormonal exposure among all ART. The process typically begins with 10–14 days of controlled ovarian stimulation using exogenous gonadotropins, such as FSH or hMG, often preceded by GnRH agonist or antagonist suppression to prevent premature ovulation. This regimen elevates estradiol and progesterone levels to as much as 10-fold above physiological concentrations. Ovulation is then induced with an hCG or GnRH agonist trigger, followed by luteal phase support with progestogens or hCG. Additional hormonal supplementation is frequently employed in programmed embryo transfer cycles, further contributing to transient but marked elevations in ovarian steroid exposure (11–13). Other fertility treatments, such as ovulation induction and controlled ovarian stimulation without IVF, differ from full IVF cycles in both intensity and duration of hormonal exposure. These protocols typically involve lower doses of exogenous gonadotropins or selective agents such as clomiphene citrate or letrozole, administered over a shorter period, and generally result in smaller increases in estradiol and progesterone compared with IVF. By inducing the development of one or a few follicles rather than multiple oocytes, these approaches produce lower cumulative hormonal exposure, a factor that is central to assessing potential long-term health outcomes, including risks for hormonally mediated malignancies (14,15).

Importantly, ART protocols have advanced substantially over the past several decades, complicating comparisons across studies and time periods. Earlier treatment regimens often involved uniformly higher gonadotropin doses and a greater number of stimulation cycles, whereas contemporary protocols increasingly emphasize individualized dosing, milder stimulation strategies, and limitations on the number of cycles performed (16,17). Advances in embryo culture, cryopreservation, and single-embryo transfer have further reduced the need for repeated high-intensity stimulation in some patients (18). When evaluating epidemiologic data on ART-related cancer risk, it is important to consider temporal changes in clinical practice, as both the intensity and timing of hormonal exposure can differ substantially between earlier treatment protocols and those used in contemporary cohorts.

3. Biological Mechanisms Linking Assisted Reproductive Technologies to Carcinogenesis

The potential association between ART and cancer risk is biologically plausible given the central role of hormonal signaling in the pathogenesis of hormone-sensitive malignancies. Estrogen and progesterone regulate cellular proliferation, differentiation, and survival across multiple reproductive tissues, and prolonged or intense activation of these pathways may contribute to carcinogenesis (19,20). Both hormones impact immune surveillance, potentially suppressing anti-tumor immunity and facilitating malignant transformation (21,22). Additionally, estrogen receptor–mediated signaling promotes cell proliferation and increases susceptibility to replication-associated DNA damage, while estrogen metabolism generates reactive oxygen species capable of inducing oxidative stress and DNA adduct formation (23,24).

ART introduces additional mechanistic considerations through transient but marked alterations in hormonal exposure. Controlled ovarian stimulation, particularly in IVF protocols, results in supraphysiologic estradiol concentrations, often several-fold higher than physiologic norms (11–13). Progesterone and gonadotropins used to stimulate follicular development may further influence local tissue environments indirectly by modulating steroidogenesis, growth factor signaling, and hormone-responsive pathways implicated in carcinogenesis (20,25). Repeated ART cycles can lead to recurrent peaks of estradiol and progesterone over short time intervals, raising questions about cumulative effects and potential dose–response relationships (26). Importantly, ART-related hormonal exposure is typically episodic rather than chronic, suggesting that any associated oncologic risk may be more consistent with promotion of preexisting occult lesions rather than initiating de novo malignant transformation (27). Interactions between ART-induced hormonal surges and underlying tissue susceptibility, genetic predisposition, or subclinical disease may therefore be critical determinants of individual cancer risk.

4. Baseline Reproductive and Infertility-Related Determinants of Cancer Risk in ART Populations

Cancer risk among individuals undergoing ART must be interpreted within the broader context of baseline reproductive and infertility-related characteristics that are highly prevalent in this population and are themselves strongly linked to malignancy risk (28,29). Breast, ovarian, and endometrial cancers are hormonally influenced diseases whose incidence is shaped by cumulative exposure to estrogen and progesterone, ovulatory patterns, and reproductive timing (9,10,20,25).

Many women pursuing ART are nulliparous or experience their first full-term pregnancy at advanced ages, both of which are established risk factors for breast and endometrial cancers and reflect prolonged exposure of relatively undifferentiated hormone-responsive tissues to cyclic ovarian stimulation (28,30). Underlying infertility diagnoses further complicate risk assessment; ovulatory dysfunction may be associated with altered progesterone exposure and unopposed estrogen effects on the endometrium, while endometriosis confers an increased risk of specific ovarian cancer subtypes and may influence systemic inflammatory and hormonal environments (30,31). These baseline factors can substantially modify cancer susceptibility independent of fertility treatment exposure and often co-occur with ART use, making it challenging to isolate treatment-related effects. Accordingly, observed associations between ART and cancer outcomes must be carefully contextualized within the reproductive histories and underlying conditions of treated individuals, rather than interpreted as reflecting a direct causal effect of assisted reproduction itself (26,28,32).

5. Epidemiologic Evidence on Breast Cancer Risk Following Assisted Reproductive Technologies

Recent prospective cohort studies and meta-analyses provide largely consistent and reassuring evidence regarding the oncologic safety of ART with respect to breast cancer. Across contemporary studies, including large population-based cohorts from Denmark and Israel, breast cancer incidence among women treated with ART appears comparable to that observed in women undergoing other forms of medically assisted reproduction and, in some analyses, to the general population. Reported risk estimates are typically close to unity, and no clear dose–response relationships have been identified with respect to the number of treatment cycles, stimulation intensity, or specific pharmacologic agents, supporting the absence of a clinically meaningful association (33,34). Importantly, several large cohort studies and pooled analyses have further differentiated breast cancer risk according to specific fertility drugs and stimulation protocols, consistently demonstrating that the use of clomiphene citrate, gonadotropins, or IVF regimens is not associated with an increased long-term risk when compared with infertile women not exposed to these agents or with population controls. Across these analyses, no significant variation in risk has been observed by drug class, cumulative number of cycles, or protocol intensity, reinforcing the overall consistency of findings (30,33,35).

These conclusions are supported by a recent clinical guideline issued by the American Society for Reproductive Medicine, which synthesizes evidence from systematic reviews and meta-analyses

and concludes that commonly used fertility treatments, including clomiphene citrate, gonadotropins, and IVF, do not confer an increased breast cancer risk compared with infertile women who do not undergo ART or with population controls (30). Although some studies have reported modest risk elevations among women initiating ART at advanced ages, particularly beyond 40 years, such associations are likely attributable to age-related baseline risk and the reproductive and hormonal characteristics underlying late-presenting infertility, rather than to treatment-related effects (30,36). Available data also do not suggest an increased breast cancer risk among women with BRCA mutations exposed to ART, although evidence in this subgroup remains limited and largely based on short- to intermediate-term follow-up. In this context, both the American Society for Reproductive Medicine and the Society of Gynecologic Oncology have noted that fertility medications do not appear to increase breast cancer risk in BRCA mutation carriers or breast cancer survivors, and that the use of estrogen-suppressive strategies, such as letrozole-based stimulation protocols, does not compromise oncologic outcomes during fertility preservation (33,37,38). Collectively, the current literature supports a cautious but reassuring interpretation of ART exposure in relation to long-term breast cancer risk. Ongoing surveillance is warranted, but the absolute risk increase, if any, is small and primarily limited to older women or those with specific risk factors (30,34,36).

6. Epidemiologic Evidence on Ovarian Cancer Risk Following Assisted Reproductive Technologies

Recent prospective cohort studies and meta-analyses have examined the relationship between ART and long-term ovarian cancer risk, with findings suggesting a modest elevation in risk when ART-treated women are compared with the general population (30,32,34,39). Reported relative risk estimates for invasive ovarian cancer typically range from 1.19 to 1.70, while higher associations have been observed for borderline ovarian tumors, ranging from 1.36 to 1.87. This excess risk is not uniform across all treated women and appears to be most pronounced among those with underlying infertility-related risk factors, particularly endometriosis and low parity. Across studies, the observed association is driven largely by borderline ovarian tumors rather than invasive epithelial ovarian cancers, underscoring the importance of distinguishing between these entities in both mechanistic and epidemiologic analyses (30,34). Borderline tumors are characterized by distinct biological behavior and etiologic pathways, which may confer heightened sensitivity to reproductive and hormonal influences, including those associated with infertility and ovarian stimulation (40).

Meta-analyses and umbrella reviews further support a nuanced interpretation of ovarian cancer risk following ART, demonstrating statistically significant but modest increases in the incidence of ovarian cancer and borderline tumors associated with in vitro fertilization, clomiphene citrate, and, in some analyses, human menopausal gonadotropin exposure. These associations are most consistently observed among nulliparous women and those with underlying infertility, particularly endometriosis, and are less evident in women treated for male factor or unexplained infertility. Although some studies suggest higher relative risks with increased numbers of treatment cycles or greater cumulative drug exposure, these findings have not been uniform, and across the literature no consistent dose–response relationship has been demonstrated with respect to the number of ART cycles or specific stimulation regimens (32,34,41–43). Importantly, comparisons between ART-treated women and infertile women not exposed to ART frequently show attenuation of risk estimates, supporting the conclusion that infertility itself, rather than fertility treatment exposure, accounts for much of the observed excess risk (28,30).

Population-based data from Great Britain and Norway further illustrate this pattern, showing that increased ovarian cancer and borderline tumor risk following ART is largely confined to women with endometriosis or persistent nulliparity and is not observed among women treated for male factor infertility (30,34,42). In nulliparous women exposed to clomiphene citrate or ART, higher relative risks have been reported, with hazard ratios reaching up to 2.5 for ovarian cancer, highlighting the importance of parity as a key effect modifier (42). Current evidence does not demonstrate an increased ovarian cancer risk among BRCA mutation carriers exposed to ART, although available data are limited and largely restricted to short-term follow-up, leaving long-term safety in this subgroup incompletely characterized (30,33).

Consistent with these findings, clinical guidance from the American Society for Reproductive Medicine emphasizes that any increased ovarian cancer risk associated with ART is confined to women with preexisting risk factors such as endometriosis, low parity, or prolonged infertility and is not observed in the broader infertile population (30,34). From a clinical and public health perspective, these data support a cautious and contextualized interpretation in which ART is not considered an independent major risk factor for ovarian cancer. While ongoing surveillance remains appropriate given the long latency of ovarian malignancies, the absolute risk increase associated with ART is small, and heightened vigilance is most relevant for clearly defined high-risk subgroups rather than for ART-treated women as a whole (30,34,39,41).

7. Epidemiologic Evidence on Endometrial Cancer Risk Following Assisted Reproductive Technologies

Evidence from recent prospective cohort studies and meta-analyses indicates that ART, including in vitro fertilization, are not associated with a clinically meaningful increase in long-term endometrial cancer risk (32,34,43–45). Large population-based cohorts with extended follow-up, including studies spanning more than two decades, have consistently shown that endometrial cancer incidence among women exposed to ART is comparable to that observed in both the general population and in subfertile women who did not undergo fertility treatment (44). Importantly, these analyses have not demonstrated increasing risk with longer duration of follow-up, greater cumulative exposure, or a higher number of ART cycles, providing reassurance regarding potential long-term effects (32,43,45).

Meta-analytic evidence further supports these findings, with pooled risk estimates for endometrial cancer consistently close to unity among women exposed to fertility treatments compared with unexposed controls. While endometrial carcinogenesis is strongly influenced by hormonal factors, particularly prolonged unopposed estrogen exposure, current data suggest that fertility drugs and ART protocols do not independently contribute to this risk once key confounders are accounted for (30). Infertility itself is a recognized risk factor for endometrial cancer, often reflecting underlying conditions such as chronic anovulation, polycystic ovary syndrome (PCOS), obesity, and metabolic dysfunction, all of which are associated with altered estrogen–progesterone balance (30,34,44).

Some studies have examined whether specific fertility drugs modify endometrial cancer risk. Clomiphene citrate has been associated with slightly increased risk, particularly among nulliparous women or those exposed to high cumulative doses (>2000 mg) or multiple treatment cycles, though these findings are difficult to disentangle from underlying ovulatory dysfunction, obesity, or PCOS (15,30,42,46). A Cochrane review reported a risk ratio of 1.87 for endometrial cancer among subfertile women treated with clomiphene citrate; however, the review emphasized that confounding by baseline infertility characteristics likely contributed to the observed association. Data on gonadotropins are more limited and inconsistent, with potential risk elevation similarly confounded by patient characteristics (47). Overall, most contemporary studies, including meta-analyses and large cohort investigations, do not demonstrate a statistically significant increase in endometrial cancer risk attributable to ART or IVF itself once relevant confounders are considered (30).

Consistent with these observations, clinical guidance from the American Society for Reproductive Medicine emphasizes that any observed increases in endometrial cancer risk are

primarily attributable to patient-related characteristics rather than ART exposure. Subgroup analyses indicate that risk is concentrated among women with ovulatory disorders, obesity, or endometriosis, while women treated for male factor or unexplained infertility do not appear to experience excess endometrial cancer risk following ART. These data collectively support a cautious but reassuring interpretation of endometrial cancer risk in ART-treated populations, with ongoing surveillance recommended for women with additional baseline risk factors (30,32,43,44,47).

6. Methodological Challenges and Key Knowledge Gaps in Evaluating Cancer Risk After Assisted Reproduction

Interpretation of the epidemiologic literature assessing breast, ovarian, and endometrial cancer risk following ART is complicated by several recurring methodological challenges. Foremost among these is confounding by underlying infertility and patient characteristics. Women undergoing ART differ systematically from the general population with respect to established cancer risk factors, including nulliparity, delayed childbearing, chronic anovulation, endometriosis, and metabolic disorders. Many studies lack sufficient granularity to fully adjust for these factors, making it difficult to disentangle the independent effects of fertility treatment from the baseline risk associated with infertility itself. This limitation is particularly relevant for ovarian and endometrial cancers, where infertility-related diagnoses play a central etiologic role (15,30,45).

The selection of appropriate comparison groups further influences risk estimates. Studies that compare ART-treated women with the general population may overestimate cancer risk due to fundamental differences in reproductive history and hormonal exposure. Analyses using infertile women not exposed to ART as controls provide a more valid assessment of treatment-related effects, yet such designs remain underutilized (30,34,45). In addition, exposure misclassification is common, particularly in retrospective studies that rely on patient recall or incomplete medical records to ascertain drug type, cumulative dose, or number of treatment cycles. These limitations reduce the reliability of dose–response analyses and may obscure modest associations (30).

Short duration of follow-up represents another critical challenge. Many cohorts have not yet accrued sufficient follow-up into the postmenopausal years, when hormone-sensitive cancers are most likely to manifest. This is particularly important given that breast cancer incidence rises sharply after age 50, ovarian cancer peaks in the 60s–70s, and endometrial cancer risk increases predominantly after menopause. Consequently, a substantial proportion of ART-exposed women have not yet reached the age ranges in which these malignancies are most common, limiting the ability

to evaluate true long-term or lifetime risk. Even in large registry-based studies, the absolute number of cancer cases is often small, leading to wide confidence intervals and limited statistical power to detect small but potentially meaningful risk increases (7,30,44,45,47). This issue is compounded by clinical heterogeneity across study populations and treatment eras, as ART protocols have evolved substantially over time with respect to medication type, dosing, and cycle intensity (30,32).

These methodological constraints contribute to several key knowledge gaps in the current literature. Long-term data extending into later life remain insufficient, and evidence differentiating cancer risk by specific fertility drugs, cumulative exposure, or stimulation protocols is limited (28,30,32,45). Uncertainty persists regarding risk in high-risk subgroups, including women with endometriosis, refractory infertility, or genetic susceptibility such as BRCA mutations (15,30,33,38). Furthermore, mechanistic understanding of observed associations, particularly for borderline ovarian tumors, remains incomplete (30,34). Collectively, these gaps underscore the need for large, prospective studies with extended follow-up, precise exposure assessment, appropriate infertile comparison groups, and robust adjustment for confounders, as emphasized by the American Society for Reproductive Medicine, to more definitively characterize the long-term oncologic safety of ART (30).

8. Ethical, Psychosocial, and Public Health Considerations

The use of ART raises important ethical considerations that extend beyond clinical efficacy and epidemiologic risk estimates. Central to ethical practice is the obligation to provide transparent, evidence-based counseling regarding the long-term risks of breast, ovarian, and endometrial cancer. While infertility itself is a recognized risk factor for hormone-sensitive malignancies, current evidence does not support a clinically meaningful increase in breast or endometrial cancer risk attributable to ART or commonly used fertility drugs. In contrast, a modestly increased risk of ovarian cancer, particularly borderline ovarian tumors, has been observed, especially in women with underlying risk factors such as endometriosis or low parity (30,32,34,43). Ethical counseling therefore requires not only disclosure of these differential risks but also discussion of the limitations, residual uncertainties, and evolving nature of the evidence. Professional societies, including the American Society for Reproductive Medicine, emphasize that such discussions should be an integral component of the informed consent process, supporting reproductive autonomy while avoiding overstatement of risk (30).

Psychosocial considerations are closely intertwined with these ethical obligations. Infertility is frequently associated with substantial emotional distress, anxiety, and depressive symptoms, which may be exacerbated by concerns about future cancer risk. Women with personal or family histories of hormone-sensitive malignancies, or those with known genetic predispositions, may experience heightened anxiety and decisional conflict when considering ART (48–50). Although large cohort studies and meta-analyses provide reassuring data for most cancer outcomes, persistent uncertainty, particularly regarding ovarian cancer, necessitates individualized, empathetic counseling. Addressing psychosocial well-being should include acknowledgment of patient fears, provision of clear and contextualized risk information, and access to supportive services throughout fertility treatment. The cumulative psychological burden of repeated ART cycles and increased medical surveillance also warrants consideration within patient-centered care models (30,48,51).

From a public health perspective, the expanding use of ART underscores the importance of ongoing population-level monitoring of long-term health outcomes. Even small absolute increases in cancer risk may have broader implications as the number of ART-exposed individuals grows. Surveillance systems must account for confounding by infertility, surveillance bias, and evolving treatment protocols to ensure accurate risk estimation (15,30,34). Equitable access to fertility care, informed counseling, and long-term follow-up remains a critical concern, as disparities in healthcare access may influence both exposure to ART and subsequent cancer detection (30). Collectively, these ethical, psychosocial, and public health considerations highlight the need for transparent communication, individualized risk assessment, and sustained surveillance to support informed decision-making and responsible integration of ART into clinical practice.

10. Conclusion

The cumulative evidence reviewed herein indicates that ART are not associated with a clinically meaningful increase in long-term breast or endometrial cancer risk and that observed associations with ovarian cancer are modest, heterogeneous, and largely driven by underlying infertility-related risk factors rather than ART exposure itself. Distinctions by cancer subtype, baseline reproductive characteristics, and infertility diagnoses are critical to accurate risk interpretation, particularly for ovarian and borderline ovarian tumors. Methodological limitations, including confounding by infertility, evolving treatment protocols, and limited long-term follow-up, continue to constrain definitive causal inference, underscoring the need for well-designed prospective studies extending into later life. From a clinical standpoint, current data support the overall oncologic

safety of ART for most women, while highlighting the importance of individualized counseling, especially for those with established risk modifiers such as endometriosis, nulliparity, or genetic susceptibility. As ART utilization continues to expand globally, transparent communication, ongoing surveillance, and integration of emerging evidence into clinical guidelines will remain essential to balancing reproductive goals with long-term health considerations.

Disclosure

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