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Use of fertility medications and cancer risk: A review and update

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Structured Abstract

Purpose of Review—There is increasing use of fertility medications for ovulation induction and ovarian stimulation for *in vitro* fertilization in the treatment of female infertility. In this review, recent literature regarding the association between fertility medication and cancer risk is reviewed.

Recent Findings—Several important publications have recently addressed the relationship between use of fertility medications and cancer risk. There are methodological limitations to many of these studies, including unique challenges in studying rare cancers that often develop several years after the time of fertility medication exposure. While infertility *per se* is a risk factor for some female cancers, including breast, endometrial, and ovarian cancer, most studies do not show a significant risk of these cancers with the use of fertility medications. Some studies, however, have shown a possible increased relative risk of borderline ovarian cancer, although the increased absolute risk is small without a clear causal relationship.

Summary—The collective data regarding the risk of developing cancer from use of fertility medications are reassuring, although several methodological issues in these studies limit definitive conclusions.

Keywords

cancer risk; fertility medications; IVF; ovarian stimulation

Introduction

With approximately 9% of the population experiencing infertility, an increasing number of couples are seeking fertility treatment. Use of *in vitro* fertilization (IVF) has steadily risen, contributing to 1.5% of live births in the United States, and adding to those pregnancies resulting from ovulation induction and superovulation [1]. Consequently, concerns exist regarding long-term risks of fertility medications causing cancer, since despite their multiple modes of action, all can induce multiple ovulation and alter steroidogenesis [2]. Moreover, some cancers, including female reproductive and breast cancers, are hormone-dependent, offering a physiological mechanism behind an association between fertility medication use

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Conflicts of interest

The authors have no conflict of interest to report.

and cancer risk [3]. Nevertheless, although some epidemiologic studies have also suggested such a link, most others offer conflicting results often difficult to interpret.

Studying cancer risk in infertile couples poses several challenges. Several conditions, including anovulation, endometriosis and nulliparity accompany infertility and themselves increase the risk of cancer. Additionally, most of these cancers are rare and tend to occur several years after the time of fertility treatment, making proof of causal relationship difficult. Most studies are case-control and cohort studies due to rare disease outcomes, but introduce selection and recall biases, respectively [4]. In particular older studies are limited by short-term follow-up, confounding factors, improper controls and multiple causes and treatments of infertility.

Although limitations exist, recent studies have improved knowledge through better study design, including using long-term follow-up, identifying type of infertility and method of treatment, selecting appropriate controls and assessing specific individuals at high risk for disease. In this review, literature on fertility medication use and cancer risk is discussed with an emphasis on recent publications.

Ovarian Cancer

Ovarian cancer is a rare but often fatal disease, accounting for 3% of all annual cancer diagnoses in women. This complex, multifactorial disease is often diagnosed at a late stage, since effective screening techniques for early disease detection do not yet exist. Risk factors for invasive ovarian cancer include nulliparity, infertility, late-onset menopause, family history and genetic susceptibility; while factors protective against disease are multiparity, breastfeeding and oral contraceptive use [5] [6]. Each of these factors must be considered when examining the mechanistic relationship between ovarian cancer and use of fertility medications.

Uninterrupted ovulation causing repeated ovarian epithelial surface damage underlies the 'incessant ovulation theory' [7] [2], based upon the theory that factors decreasing lifetime ovulation rates, such as multiparity, concomitantly reduce ovarian cancer risk. Conversely, use of fertility medications could increase ovarian cancer risk by promoting polyfollicular ovulation [7]. This theory has been questioned by recent data that serous ovarian tumors can originate from the fallopian tube rather than the ovary itself [8]. An alternate mechanism underlying the relationship between fertility treatment and ovarian cancer is the 'elevated gonadotropin level' theory, which postulates that elevated gonadotropin levels resulting from fertility medications stimulate the ovarian epithelium and induce malignant changes [9].

Invasive Ovarian Cancer

Although studies examining the relationship between fertility medication use and ovarian cancer risk show mixed results, most studies do not demonstrate a significant increase in risk [10] [11] [12] [13] [14] [15] [16] [17]. In the 1990s, two studies found an association between fertility medication use and ovarian cancer [18] [19] but were limited by specific disease characteristics, such as low prevalence and late onset (i.e., 7th decade of life), study design (i.e., inappropriate use of fertile controls, limited length of follow-up, lack of control

for parity and other diseases) and lack of stratification by type and duration of fertility medication use.

Most recent studies and systematic reviews show no overall association between fertility medication use and invasive ovarian cancer when using a subfertile control group or the general population [10] [11] [12] [13] [14] [15] [16] [17], although some studies finding such an association used the general population rather than a subfertile group as controls. Asante *et.al.* and Briton *et.al.* did not find an association between ovarian cancer and fertility treatment when using a subfertile control group [11] [20], even when women had undergone 4 cycles of IVF [20]. A meta-analysis of 9 cohort studies including 109,969 patients compared the ovarian cancer risk in women receiving fertility treatment with that in an infertile reference group and the general population. The ovarian cancer risk in women receiving fertility treatment was increased compared to the general population (relative risk [RR]: 1.50, 95% CI 1.17 – 1.92) [17], but similar to that of the infertile reference group (RR: 1.26, 95% CI 0.62 – 2.55). That subfertile women have an inherently increased risk for ovarian cancer compared to that of the general population likely explains why a cohort study of parous women found fertility treatment as a significant risk factor for ovarian cancer over a 25-year follow-up (hazard ratio [HR]: 3.9, 95% CI 1.2–12.6), based on only 3 women with invasive ovarian cancer following IVF [21].

A number of more recent studies have attempted to separately stratify for type of fertility treatment, use of IVF and administration of gonadotropins and/or clomiphene citrate. Those specifically studying women undergoing IVF have generally not found an increased risk in ovarian cancer [15] [12] [10]. One cohort study of 53,859 IVF patients found no association between invasive ovarian cancer and IVF compared to that in the population (standardized incidence ratio [SIR]: 0.96–1.18, NS). Paradoxically, IVF patients had a decreased risk of all cancers (SIR: 0.78, 95% CI 0.73–0.83), although a study limitation was a short average follow-up time of only 5 years [12]. Another population-based cohort study of parous women in Norway found no significant association between IVF and ovarian cancer risk (HR: 1.56, 95% CI 0.94–2.60). An increased risk of ovarian cancer occurred in IVF patients who had only had one child but no longer existed after adjusting for multiple comparisons [13]. Despite these reassuring findings, two cohort studies show that women failing to conceive after clomiphene citrate therapy have an increased risk for ovarian cancer [15] [14], warranting further investigation of this subgroup of women.

Two recent studies have assessed risk of ovarian cancer in BRCA mutation carriers undergoing fertility treatment, since this high-risk group may also be more likely to undergo fertility treatment for fertility preservation or diminished ovarian reserve [22]. Both studies are small in size but reassuring [23] [24]. One cohort study of 1,073 BRCA mutation carriers, of which 164 (15%) patients received fertility treatment, showed no associated between fertility treatment and ovarian cancer, regardless of type of fertility treatment [24]. Another matched case-control study of 941 pairs of BRCA mutation carriers with and without a cancer diagnosis found no significant relationship between fertility medication use and subsequent risk of ovarian cancer [23].

Borderline Ovarian Cancer

Borderline ovarian tumors (i.e., tumors of low malignant potential) are non-invasive, indolent tumors that differ from invasive ovarian cancer in having an excellent prognosis with a five-year survival rate of 95% and occurring more commonly in reproductive-aged women. These tumors also are rare, with an incidence of 1.8 – 4.8 per 100,000 women years, making the absolute versus relative risk of this disease an important consideration [25].

Unlike invasive ovarian cancer, studies have found a more consistent association between borderline ovarian cancer and use of fertility medication. Early studies, including a cohort study demonstrated a significant association between borderline ovarian tumors and women receiving fertility treatment versus those not receiving treatment (SIR: 3.3, 95% CI 1.1–7.8), based on 5 cases of borderline ovarian cancer [18]. Larger recent studies using infertile controls have found similar results [26] [10]. A Dutch cohort study of 19,861 women undergoing IVF versus 6,604 subfertile women with an average follow-up of 14.7 years found an increased risk of borderline ovarian tumors in the former women, adjusting for age, parity and fertility diagnosis (SIR: 1.79, 95% CI 1.16–2.56) [10]. Another cohort study found a similarly increased rate of borderline ovarian cancer in women who received IVF, controlling for confounders (HR: 2.66, CI 1.2–5.04). Unlike its invasive counterpart, borderline ovarian cancer has not been associated with parity, endometriosis or prior surgery [26].

Conversely, not all evidence demonstrates an association between fertility treatment and borderline ovarian tumors [27] [11] [28]. A recent case-cohort study of 96,545 Dutch subfertile women, including 142 cases of borderline ovarian tumors, found no association between all subtypes of ovarian borderline cancer and fertility medication use (RR: 1.00, 95% CI 0.67–1.51), which was consistent across fertility treatment cycles and follow-up duration [27]. An increased association between serous borderline ovarian tumors and progesterone use currently lacks biologic explanation.

Although a large systemic review shows heterogeneity of data [16], a possible link between borderline ovarian tumors and fertility medications cannot be ignored. Despite possible surveillance bias, most borderline ovarian tumors have been diagnosed up to 7 to 9 years after fertility treatment [26], raising concern about such an association, although the absolute increased disease risk is extremely small, given the low incidence of disease.

Other Gynecologic Cancers

Endometrial Cancer

Endometrial cancer is the most common cancer of the female reproductive track and the fourth most common cancer diagnosed in women. Risk factors for endometrial cancer include polycystic ovarian syndrome (PCOS), anovulatory infertility, obesity, age, family history, and tamoxifen use [29]. Type I endometrial cancer is hormone-dependent, with unopposed estrogen increasing risk and progesterone having a protective effect. Several recent studies have examined the relationship between endometrial cancer and use of fertility medications, but are limited by small sample size, short follow-up and several confounding factors, such as ovulatory dysfunction and PCOS.

While some studies demonstrate an increased risk in endometrial cancer in women using specific fertility medications [21] [14], most studies have found no such association. A recent meta-analysis of 6 studies comprising 776,224 patients found no increased risk of endometrial cancer between treatment versus non-treatment infertility populations (OR: 0.78, 95% CI 0.39–1.57) [30]. These results agree with other recent cohort studies showing no significant increased risk of endometrial cancer in patients undergoing fertility treatment [20] [13] [12].

A recent registry-based cohort study found an increased risk of endometrial cancer in women receiving clomiphene citrate (HR: 2.91, 95% CI 1.87–4.53) but not women undergoing IVF (HR: 1.62, 95% CI 0.70–3.85) compared with the general population. This study was limited by lack of control for confounding factors [14]. A retrospective cohort study of 12,193 women evaluated for infertility found no significant association between use of any fertility treatment and endometrial cancer risk [31]. These findings agree with a meta-analysis that found an increased risk in endometrial cancer in women undergoing IVF, but only when compared to the general population, not the group of subfertile women [17]. These studies again emphasize the importance of using infertile women as controls to better adjust for pre-existing endometrial cancer risk factors that may exist in infertile women.

Cervical Cancer

Several studies assessing the risk of cervical cancer following fertility medication use have consistently shown no increased risk of cervical cancer compared to both the general population and infertile patients as controls [17] [14] [13] [21]. A subset of studies have found a decreased incidence of cervical cancer in IVF patients [20] [32], although the mechanism behind this phenomenon is unclear but perhaps related to better access to care with more frequent cervical cytology screening in women undergoing fertility treatment.

Breast Cancer

Breast cancer is the most common malignancy in women worldwide, affecting one in eight women. Factors that increase the risk for breast cancer include exogenous sex steroid exposure and increased endogenous sex steroid actions through early menarche and late menopause in combination with nulliparity [3]. Fertility treatments can temporarily induce supra-physiological circulating sex steroid levels and therefore could theoretically increase breast cancer risk. Studies to date, however, have not shown a consistent relationship between breast cancer risk and fertility treatment, often suffering from the same shortcomings of other cancer-related studies, particularly short-term follow-up and other confounding variables.

Most recent studies have not shown an association between breast cancer and fertility medication use when comparing women undergoing fertility treatment to both a general population and infertile controls [33] [12] [34] [35] [36]. Although two recent studies found an association of fertility treatment with breast cancer, the increased risk was modest [37] [38]. A recent cohort study of 19,158 IVF patients and 5,950 nonIVF-related patients receiving fertility treatment compared breast cancer risk to the general population with a median follow-up of 21.1 years. No increased risk of breast cancer occurred in IVF patients

compared to either the general population (SIR: 1.01, 95% CI 0.93–1.09) or nonIVF-related patients receiving fertility treatment (HR: 1.01, 95% CI 0.86–1.19) [33]. These data agree with a recent meta-analysis of 8 cohort studies that comprised 1,554,332 women and 14,961 breast cancer cases and demonstrated no increased risk of breast cancer in IVF patients versus the general (RR: 0.91, 95% CI 0.74–1.11) or infertile female population (RR: 1.02, 95% CI 0.88–1.18) [37]. Apart from IVF, a cohort study of 12,193 infertile women followed for 30 years found no increased risk of breast cancer after clomiphene citrate (HR: 1.05, 95% CI 0.9–1.22) or gonadotropin (HR: 1.14, 95% CI 0.89–1.44) exposure compared to infertile controls [34].

Nevertheless, some types of women may be at increased risk for breast cancer following fertility treatment, specifically those individuals who initiate such treatment at a young age [36] [39] [40] or undergo a high cumulative number of clomiphene citrate cycles [34] [40].

Other Malignancies

Thyroid Cancer

Thyroid disorders including cancer are more common in women than men, with a peak incidence during the reproductive years [41]. Furthermore, the presence of estrogen receptors in thyroid cancers [42] implicates sex steroid action with thyroid cancer. With the rising incidence of thyroid cancer in the United States, perhaps from improved surveillance and diagnostic testing [43], several studies have investigated the relationship between fertility medication use and thyroid cancer. Most studies have found no such association [44] [45].

In a retrospective cohort of 8,422 women evaluated for infertility, neither clomiphene citrate (RR: 1.42, 95% CI 0.5–3.7) nor gonadotropin (RR: 1.1; 95% CI 0.2–4.9) use demonstrated an increased risk of thyroid cancer (18 cases) (RR: 1.42; 95% CI 0.5–3.7) [46]. It is possible that clomiphene citrate use may have had a stronger effect on thyroid cancer risk among women who remain nulliparous (RR: 4.23; 95% CI 1.0–17.1), although 6 of 18 thyroid cancer cases in this study were missing parity data. Another recent retrospective cohort study [47] showed a non-significant increase in thyroid cancer risk with the use of clomiphene citrate (HR: 1.57; 95% CI 0.89–2.75), based upon 55 cases of thyroid cancer in a cohort of 9,892 women. Thyroid cancer risk was greatest among those women (HR: 1.96; 95% CI 0.92–4.17) who received >2,250 mg of clomiphene citrate, although gonadotropin administration was unrelated to increased risk of any of the assessed cancers (HR: 1.16; 95% CI 0.52–2.58).

A Danish cohort of 54,362 women with infertility, however, did show a significant association between fertility medication use and thyroid cancer [48], in which clomiphene citrate use increased the risk of thyroid cancer, based upon 29 cases (RR: 2.29; 95% CI 1.08–4.82). This increased risk was primarily associated with clomiphene citrate use in parous women. An increased risk of thyroid cancer was not found after gonadotrophin use (RR: 1.43; 95% CI 0.54–3.83), but was observed following progesterone use (RR: 10.14; 95% CI 1.93–53.34), although based upon only two patients.

Colorectal Cancer

In a large cohort study [46], clomiphene citrate use did not significantly increase the risk of colon cancer (RR: 0.83; 95% CI 0.4–1.9). Furthermore in retrospective cohort study [47] of 9,892 women followed for a median of 30 years to detect 91 colorectal cancers, clomiphene citrate use was unrelated to colorectal cancer risk (HR: 0.82; 95% CI, 0.52–1.30). Another recent cohort study from the Netherlands [49] evaluated the risk of colorectal cancer in 19,158 women undergoing ovarian stimulation for IVF compared to both women receiving other fertility treatments or the general population. A total of 109 colorectal cancers were observed after a median follow-up of 21 years. The IVF group did not have an increased colon cancer risk compared to the general population (SIR: 1.00; 95% CI, 0.80–1.23) but did have an increased such risk compared to women receiving other fertility treatments (HR: 1.80; 95% CI, 1.10–2.94).

Melanoma

Given several studies examining occurrence of malignant melanoma following use of fertility treatments, most have not shown an increased risk of this disease [46] [50]. One retrospective cohort study from Australia [51] found that women giving birth following IVF had an increased rate of invasive melanoma versus women who failed to conceive after IVF, based on 139 invasive melanoma cases (HR: 3.61; 95% CI 1.79–7.26). There was, however, no increased risk in women receiving nonIVF-related fertility treatment (HR: 1.39; 95% CI 0.88–2.20). In another study, fertility treatment was not associated with malignant melanoma, except for an increased risk following use of gonadotrophins or gonadotropin-releasing hormone in parous women [52]. Finally, use of clomiphene citrate has been associated with increased risk of melanoma in some [53] [47] but not all [46] [52] studies.

Conclusion

Data on the association between fertility treatments and cancer risk are limited, being mostly derived from observational cohort or case-control studies. Many such studies have methodological problems including small sample size, heterogeneous populations and treatments, multiple co-variables and short-term follow-up. Additionally, infertility *per se* is a risk factor for certain cancers including those of the breast, ovary and uterus. Recent studies have attempted to address these limitations by investigating more homogeneous populations, employing longer follow-up intervals, assessing cancer risk in low- versus high-risk individuals and using infertile women as appropriate controls. Overall most studies show that fertility treatments do not increase the risks of invasive ovarian cancer, malignant melanoma or cancers of the endometrium, cervix, breast, thyroid or colon. There is, however, limited evidence that use of fertility treatments may modestly increase the risk of borderline ovarian cancer, although this risk is small in absolute terms and such an ovarian cancer with low-malignant potential, if found, has a favorable prognosis.

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References

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

1. Sunderam S, Kissin DM, Crawford SB, et al. Assisted reproductive technology surveillance--United States, 2011. *MMWR Surveill Summ.* 2014; 63:1–28.
2. Casagrande JT, Louie EW, Pike MC, et al. "Incessant ovulation" and ovarian cancer. *Lancet.* 1979; 2:170–173. [PubMed: 89281]
3. Collaborative Group on Hormonal Factors in Breast C. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. *Lancet Oncol.* 2012; 13:1141–1151. [PubMed: 23084519]
4. Practice Committee of the American Society for Reproductive Medicine. Electronic address Aao, Practice Committee of the American Society for Reproductive M. Fertility drugs and cancer: a guideline. *Fertil Steril.* 2016; 106:1617–1626. [PubMed: 27573989]
5. Titus-Ernstoff L, Perez K, Cramer DW, et al. Menstrual and reproductive factors in relation to ovarian cancer risk. *Br J Cancer.* 2001; 84:714–721. [PubMed: 11237375]
6. Beral V, Doll R, et al. Collaborative Group on Epidemiological Studies of Ovarian C. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. *Lancet.* 2008; 371:303–314. [PubMed: 18294997]
7. Tung KH, Wilkens LR, Wu AH, et al. Effect of anovulation factors on pre- and postmenopausal ovarian cancer risk: revisiting the incessant ovulation hypothesis. *Am J Epidemiol.* 2005; 161:321–329. [PubMed: 15692075]
8. Kurman RJ, Shih Ie M. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. *Am J Surg Pathol.* 2010; 34:433–443. [PubMed: 20154587]
9. Mandai M, Konishi I, Kuroda H, Fujii S. LH/hCG action and development of ovarian cancer--a short review on biological and clinical/epidemiological aspects. *Mol Cell Endocrinol.* 2007; 269:61–64. [PubMed: 17353087]
10. van Leeuwen FE, Klip H, Mooij TM, et al. Risk of borderline and invasive ovarian tumours after ovarian stimulation for in vitro fertilization in a large Dutch cohort. *Hum Reprod.* 2011; 26:3456–3465. [PubMed: 22031719]
11. Asante A, Leonard PH, Weaver AL, et al. Fertility drug use and the risk of ovarian tumors in infertile women: a case-control study. *Fertil Steril.* 2013; 99:2031–2036. [PubMed: 23552324]
- 12*. Luke B, Brown MB, Spector LG, et al. Cancer in women after assisted reproductive technology. *Fertil Steril.* 2015; 104:1218–1226. Large contemporary longitudinal cohort study suggests that the short-term risk of cancer is not increased among women of reproductive age who have had ART treatment. [PubMed: 26271227]
- 13*. Reigstad MM, Larsen IK, Myklebust TA, et al. Cancer risk among parous women following assisted reproductive technology. *Hum Reprod.* 2015; 30:1952–1963. Population-based cohort consisting of all women registered in the Medical Birth Registry of Norway. It showed an increase in overall cancer risk, as well as a 50% increase in risk of CNS cancer for women giving birth after ART, however the results were not significant after correcting for multiple analyses. [PubMed: 26113657]
14. Reigstad MM, Storeng R, Myklebust TA, et al. Cancer Risk in Women Treated with Fertility Drugs According to Parity status - A Registry-based Cohort Study. *Cancer Epidemiol Biomarkers Prev.* 2017

15. Trabert B, Lamb EJ, Scoccia B, et al. Ovulation-inducing drugs and ovarian cancer risk: results from an extended follow-up of a large United States infertility cohort. *Fertil Steril*. 2013; 100:1660–1666. [PubMed: 24011610]
- 16*. Rizzuto I, Behrens RF, Smith LA. Risk of ovarian cancer in women treated with ovarian stimulating drugs for infertility. *Cochrane Database Syst Rev*. 2013 CD008215. Cochrane review that included 11 case-control studies and 14 cohort studies, which included a total of 182,972 women. Found no evidence of an increase in the risk of invasive ovarian tumours with fertility drug treatment. Suggested possible increased risk of borderline ovarian tumours in subfertile women who had IVF treatment.
- 17*. Siristatidis C, Sergentanis TN, Kanavidis P, et al. Controlled ovarian hyperstimulation for IVF: impact on ovarian, endometrial and cervical cancer--a systematic review and meta-analysis. *Hum Reprod Update*. 2013; 19:105–123. Systematic review and meta-analysis, that included 9 cohort studies, and a total of 109,969 women exposed to IVF. Concluded that IVF treatment does not seem to be associated with elevated cervical, ovarian, or endometrial cancer risk when the confounding effect of infertility was neutralized in studies allowing such comparisons. [PubMed: 23255514]
18. Rossing MA, Daling JR, Weiss NS, et al. Ovarian tumors in a cohort of infertile women. *N Engl J Med*. 1994; 331:771–776. [PubMed: 8065405]
19. Whittemore AS, Harris R, Itnyre J. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group. *Am J Epidemiol*. 1992; 136:1184–1203. [PubMed: 1476141]
20. Brinton LA, Trabert B, Shalev V, et al. In vitro fertilization and risk of breast and gynecologic cancers: a retrospective cohort study within the Israeli Maccabi Healthcare Services. *Fertil Steril*. 2013; 99:1189–1196. [PubMed: 23375197]
- 21*. Kessous R, Davidson E, Meirovitz M, et al. The risk of female malignancies after fertility treatments: a cohort study with 25-year follow-up. *J Cancer Res Clin Oncol*. 2016; 142:287–293. Population-based cohort study that included 106,031 women that were followed for a median of 12 years showing that a history of IVF treatment remained independently associated with ovarian and uterine cancer after controlling for confounding variables such as maternal age and obesity. [PubMed: 26337160]
22. Wang ET, Pisarska MD, Bresee C, et al. BRCA1 germline mutations may be associated with reduced ovarian reserve. *Fertil Steril*. 2014; 102:1723–1728. [PubMed: 25256924]
23. Gronwald J, Glass K, Rosen B, et al. Treatment of infertility does not increase the risk of ovarian cancer among women with a BRCA1 or BRCA2 mutation. *Fertil Steril*. 2016; 105:781–785. [PubMed: 26698676]
- 24*. Perri T, Lifshitz D, Sadetzki S, et al. Fertility treatments and invasive epithelial ovarian cancer risk in Jewish Israeli BRCA1 or BRCA2 mutation carriers. *Fertil Steril*. 2015; 103:1305–1312. Historical cohort study for women carrying BRCA mutations, showing no increased risk for developing invasive epithelial ovarian cancer after fertility treatment. This study also suggested that treatments for infertile BRCA mutation carriers should not be contraindicated or viewed as risk modifiers for invasive epithelial ovarian cancer. [PubMed: 25792249]
25. Fischerova D, Zikan M, Dundr P, Cibula D. Diagnosis, treatment, and follow-up of borderline ovarian tumors. *Oncologist*. 2012; 17:1515–1533. [PubMed: 23024155]
- 26*. Stewart LM, Holman CD, Finn JC, et al. In vitro fertilization is associated with an increased risk of borderline ovarian tumours. *Gynecol Oncol*. 2013; 129:372–376. This was a whole-population cohort study of women aged 20–44 years seeking hospital infertility treatment or investigation in Western Australia in 1982–2002. It showed that women who underwent IVF treatment had 2.5 times the risk of borderline tumours compared with women having non-IVF infertility treatment. [PubMed: 23385152]
- 27*. Bjornholt SM, Kjaer SK, Nielsen TS, Jensen A. Risk for borderline ovarian tumours after exposure to fertility drugs: results of a population-based cohort study. *Hum Reprod*. 2015; 30:222–231. A retrospective case-cohort study was designed with data from a cohort of 96,545 Danish women with fertility problems referred to all Danish fertility clinics in the period 1963–2006, with a median length of follow up of 11.3 years. An increased risk for serous borderline

ovarian tumours was observed after the use of progesterone, but not with the use of fertility drugs. [PubMed: 25376453]

28. Mosgaard BJ, Lidegaard O, Kjaer SK, et al. Ovarian stimulation and borderline ovarian tumors: a case-control study. *Fertil Steril*. 1998; 70:1049–1055. [PubMed: 9848294]
29. Saso S, Chatterjee J, Georgiou E, et al. Endometrial cancer. *BMJ*. 2011; 343:d3954. [PubMed: 21734165]
- 30*. Saso S, Louis LS, Doctor F, et al. Does fertility treatment increase the risk of uterine cancer? A meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2015; 195:52–60. Meta-analysis that included included 6 studies in the final analysis, which comprised 776,224 patients in total. Of these, 103,758 had undergone fertility treatment and 672,466 had not. No significant difference was found in the incidence of uterine cancer in relation to fertility treatment. The degree of heterogeneity was high between these studies. [PubMed: 26476799]
31. Brinton LA, Westhoff CL, Scoccia B, et al. Fertility drugs and endometrial cancer risk: results from an extended follow-up of a large infertility cohort. *Hum Reprod*. 2013; 28:2813–2821. [PubMed: 23943795]
32. Yli-Kuha AN, Gissler M, Klemetti R, et al. Cancer morbidity in a cohort of 9175 Finnish women treated for infertility. *Hum Reprod*. 2012; 27:1149–1155. [PubMed: 22343550]
- 33*. van den Belt-Dusebout AW, Spaan M, Lambalk CB, et al. Ovarian Stimulation for In Vitro Fertilization and Long-term Risk of Breast Cancer. *JAMA*. 2016; 316:300–312. Historical cohort that included 19,158 women who underwent IVF treatment and 5,950 women who started other fertility treatments in all 12 IVF clinics in the Netherlands. IVF treatment was not associated with increased risk of breast cancer compared with non-IVF fertility treatment after a median follow up of 21 years. [PubMed: 27434442]
34. Brinton LA, Scoccia B, Moghissi KS, et al. Long-term relationship of ovulation-stimulating drugs to breast cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2014; 23:584–593. [PubMed: 24700523]
35. Fei C, Deroo LA, Sandler DP, Weinberg CR. Fertility drugs and young-onset breast cancer: results from the Two Sister Study. *J Natl Cancer Inst*. 2012; 104:1021–1027. [PubMed: 22773825]
- 36*. Sergentanis TN, Diamantaras AA, Perlepe C, et al. IVF and breast cancer: a systematic review and meta-analysis. *Hum Reprod Update*. 2014; 20:106–123. Meta-analysis that included 8 cohort studies, with a total cohort size of 1,554,332 women, showing no increased risk of breast cancer with IVF treatment, but recommending longer follow up periods, comparisons with infertile women, and adjustment for various confounders before conclusive statements can be made. [PubMed: 23884897]
37. Reigstad MM, Larsen IK, Myklebust TA, et al. Risk of breast cancer following fertility treatment--a registry based cohort study of parous women in Norway. *Int J Cancer*. 2015; 136:1140–1148. [PubMed: 25042052]
38. Gennari A, Costa M, Puntoni M, et al. Breast cancer incidence after hormonal treatments for infertility: systematic review and meta-analysis of population-based studies. *Breast Cancer Res Treat*. 2015; 150:405–413. [PubMed: 25744295]
39. Stewart LM, Holman CD, Hart R, et al. In vitro fertilization and breast cancer: is there cause for concern? *Fertil Steril*. 2012; 98:334–340. [PubMed: 22633651]
40. Lerner-Geva L, Rabinovici J, Olmer L, et al. Are infertility treatments a potential risk factor for cancer development? Perspective of 30 years of follow-up. *Gynecol Endocrinol*. 2012; 28:809–814. [PubMed: 22475084]
41. Correa P, Chen VW. Endocrine gland cancer. *Cancer*. 1995; 75:338–352. [PubMed: 8001005]
42. Chaudhuri PK, Prinz R. Estrogen receptor in normal and neoplastic human thyroid tissue. *Am J Otolaryngol*. 1989; 10:322–326. [PubMed: 2817247]
43. Enewold L, Zhu K, Ron E, et al. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980–2005. *Cancer Epidemiol Biomarkers Prev*. 2009; 18:784–791. [PubMed: 19240234]
44. Modan B, Ron E, Lerner-Geva L, et al. Cancer incidence in a cohort of infertile women. *Am J Epidemiol*. 1998; 147:1038–1042. [PubMed: 9620047]

45. La Vecchia C, Ron E, Franceschi S, et al. A pooled analysis of case-control studies of thyroid cancer. III. Oral contraceptives, menopausal replacement therapy and other female hormones. *Cancer Causes Control*. 1999; 10:157–166. [PubMed: 10231164]
46. Althuis MD, Scoccia B, Lamb EJ, et al. Melanoma, thyroid, cervical, and colon cancer risk after use of fertility drugs. *Am J Obstet Gynecol*. 2005; 193:668–674. [PubMed: 16150258]
- 47*. Brinton LA, Moghissi KS, Scoccia B, et al. Effects of fertility drugs on cancers other than breast and gynecologic malignancies. *Fertil Steril*. 2015; 104:980–988. This is a subsequent follow up on a retrospective cohort study that followed 9,892 women through 2010, showing that clomiphene citrate treatment was significantly associated with melanoma and was not significantly associated with thyroid, lung, or colorectal cancer risks. [PubMed: 26232746]
48. Hannibal CG, Jensen A, Sharif H, Kjaer SK. Risk of thyroid cancer after exposure to fertility drugs: results from a large Danish cohort study. *Hum Reprod*. 2008; 23:451–456. [PubMed: 18065402]
- 49*. Spaan M, van den Belt-Dusebout AW, Burger CW, et al. Risk of Colorectal Cancer After Ovarian Stimulation for In Vitro Fertilization. *Clin Gastroenterol Hepatol*. 2016; 14:729–737. e725. Nationwide cohort study that included 19,158 women who received ovarian stimulation for IVF (IVF group) and 5,950 women who underwent non-IVF fertility treatments and evaluated for cancer risks as these were linked with the Netherlands Cancer Registry, with a median follow up of 21 years. IVF fertility treatment was not shown to be associated with colorectal cancer. [PubMed: 26687912]
- 50*. Spaan M, van den Belt-Dusebout AW, Schaapveld M, et al. Melanoma risk after ovarian stimulation for in vitro fertilization. *Hum Reprod*. 2015; 30:1216–1228. Same cohort study of [49] evaluating for the risk of melanoma. This study showed no increased risk of melanoma with IVF fertility treatment with a median follow up of 19 years. Despite the large cohort, the number of melanoma cases was small. [PubMed: 25743782]
51. Stewart LM, Holman CD, Finn JC, et al. Association between in-vitro fertilization, birth and melanoma. *Melanoma Res*. 2013; 23:489–495. [PubMed: 24048222]
52. Hannibal CG, Jensen A, Sharif H, Kjaer SK. Malignant melanoma risk after exposure to fertility drugs: results from a large Danish cohort study. *Cancer Causes Control*. 2008; 19:759–765. [PubMed: 18340541]
53. Calderon-Margalit R, Friedlander Y, Yanetz R, et al. Cancer risk after exposure to treatments for ovulation induction. *Am J Epidemiol*. 2009; 169:365–375. [PubMed: 19037008]

Table 1**Key Points**

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- Data on the association between use of fertility medications and cancer are limited and come principally from observational cohort and case-control studies with several methodological issues.
 - While infertility *per se* is a risk factor for a number of female cancers including breast, endometrial and invasive ovarian cancer, there are insufficient data to suggest a meaningful association between fertility medication use and these cancers.
 - Several studies have suggested a small increased risk of developing borderline ovarian cancer; however, the absolute increased risk is small and these indolent tumors have a favorable prognosis.
 - There is insufficient evidence to suggest an association between fertility medication use and cancers of the cervix, thyroid and colon or melanoma.
 - Additional studies with longer follow-up are needed to determine whether unique subgroups of women are at increased risk of developing cancer following fertility treatment.
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