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REVIEW

Re-Evaluating the Association Between Hormonal Contraception and Breast Cancer Risk

Sanjana Satish[1], Jessica F Moore[2], Jay M Littlefield[3], Ian J Bishop[2], Kristin E Rojas[2,4]

[1]University of Miami Miller Medical School, Miami, FL, USA; [2]Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Miami Miller School of Medicine, Miami, FL, USA; [3]SCL Health, Holy Rosary Healthcare, Miles City, MT, USA; [4]Dewitt-Daughtry Department of Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Correspondence: Sanjana Satish, University of Miami Miller School of Medicine, 1600 NW 10th Ave #1140, Miami, FL, 33136, USA, Email Sanjana.satish@med.miami.edu

Abstract: This review aims to summarize and assess key studies investigating the relationship between hormonal contraception and breast cancer risk. Approximately two-thirds of breast cancers express the estrogen receptor, and long-term exposure to estrogen is a debated risk factor for breast cancer development. This hypothesis is based on prior studies looking at reproductive risk factors (endogenous estrogen exposure) along with hormone replacement therapy (exogenous hormone exposure). Historically accepted reproductive risk factors include age at menarche, age at first delivery, and parity. Exogenous hormone exposure encompasses both receipt of hormonal contraception and menopausal hormone replacement therapy. This review highlights the reported risks associated with the most common hormonal contraception methods including oral, transdermal, and transvaginal routes. Large observational studies of the past and more recent works are summarized highlighting gaps in knowledge. Several themes emerge: difficulty accounting for well-established risk factors in analyses of epidemiologic studies, challenges determining whether associations between hormonal contraception and breast cancer are due to the exogenous hormones themselves or to increased engagement with the medical system, and discrepancies between statistically significant and clinically significant risk, odds, and hazard ratios. Understanding the strengths and limitations of these studies will help providers in and outside of oncology support women making decisions regarding both cancer risk-reduction and family planning.

Keywords: breast cancer, contraception, family planning, oncology, breast neoplasm, cancer risk

Introduction

The understanding of invasive breast cancer has evolved from a finite, morbid diagnosis to a nuanced, diverse, and curable set of tumors subtypes. Receptor status, as in: estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (*HER2*) are now predictive and prognostic.[1] With these advances, categories of breast cancer based on molecular subtype have been established, with the four major groups being: Luminal A-like, Luminal B-like, Triple negative/basal-like, and HER2 enriched, with each group integrating pathologic characteristics with receptor status, and these labels guiding treatment plans.[1]

An overwhelming majority of breast cancers express the estrogen receptor, and estrogen deprivation decreases the risk of recurrent ER-positive tumors.[2–4] In the 1960's, Dr. Joseph Fraumeni observed that nuns had a higher-than-average risk of breast cancer.[6] Since then, studies describing a link between reproductive factors like endogenous hormone exposure and breast cancer risk have reported that early age at first delivery and higher parity produce a long-term reduction in risk.[6,7] More recently, studies incorporating analyses stratified by tumor subtype have clarified that parity is associated with a 25% reduction in risk of only luminal A-type tumors (ER-positive and Her2-negative with a low proliferative index), and not triple-negative or Her2-positive tumors (OR 0.75, 95% confidence interval (CI) 0.70,0.81, p<0.0001).[8]

While the overall risk of breast cancer among hormonal contraceptive users is low, many studies have suggested a non-zero increase in risk.[9] For example, in a 2017 Danish prospective cohort study, 1.8 million women were followed

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for more than 10 years to assess the association between hormonal contraception and invasive breast cancer risk. Among 11,517 cases of breast cancer that occurred, the relative risk among women with current or recent contraceptive use was higher than those without. However, the overall absolute increase in risk was small, at approximately one breast cancer diagnosis per 7690 women using hormonal contraceptives for one year.[9] On the contrary, an older British cohort study analyzing 774,000 ever users of contraception and 339,000 never users concluded that there was no statistically significant difference between the two groups in the risk of developing breast cancer.[10] Because datasets used to make inferences about risk in this subset of the population are based on observational studies, no definite causal relationship can be established. This review demonstrates epidemiological study inconsistency in establishing the association between hormonal contraceptive use and increased breast cancer risk.

The increased breast cancer risk associated with prolonged time from menarche to delivery (ie early menarche and increased age at first delivery) stems from the concept that post-pubertal breast tissue is relatively undifferentiated before pregnancy, and therefore more susceptible to carcinogenic stimuli.[11] However, the correlation between older age at first delivery and ER-positive breast cancer risk was not found to be significant in a large meta-analysis.[12] In 2011, Lyons et al reported that during the first five years after delivery, risk of breast cancer increases, but more recent literature suggests that this risk augmentation is much more prolonged.[11] While there is a complicated relationship between pregnancy and breast cancer risk, there may also be risk associated with both hormonal contraception, often used to prevent unwanted pregnancy. In examining the current literature, we assess the validity of the studies examining the potential relationship between hormone-containing contraception and breast cancer. This review also places these studies in the context of breast cancer risk after pregnancy and delivery. Clarifying the relationship between hormonal contraception and breast cancer will impact the millions of active and potential users of contraception. Furthermore, any potential increased risk of breast cancer must be weighed against the numerous health benefits of hormonal contraception, as well as its risk reduction of ovarian, colon, and endometrial cancer.

Methodology

In May of 2021, literature searches were undertaken using the following databases: Cumulative Index of Nursing and Allied Health Literature (CINAHL), PubMed's MEDLINE, Embase, and ScienceDirect. Table 1 provides details of studies with sample sizes greater than 1000. Criteria for articles reviewed included that they were written in English, reviewed the relationship between birth control and breast cancer either prospectively or retrospectively, and were published between 1995 and 2022. This is a narrative overview of the current literature with the synthesis of each article and the themes that arise.

Studies of Risk by Hormonal Contraception Type

Oral Contraception

The FDA's approval of the contraceptive pill and the reproductive liberation that ensued marked the beginning of the evolution of a woman's role in society through family planning. First prescribed exclusively for cycle control and marketed to treat dysmenorrhea, early iterations of the Pill contained substantial doses of both estrogen and progestin. Enovid 10 contained 9.85mg of the progestin norethynodrel and 150 mcg of the estrogen mestranol, compared to modern formulations, containing significantly lower hormonal doses (0.1–3mg of progestin and 20–50 mcg of ethinyl estradiol).[13] The widespread use of oral contraceptives throughout history has been tempered by controversy surrounding the lack of consent in the original study of women in a Puerto Rican housing project, religious and societal norms, and later by published studies that linked hormonal contraception to malignancy.[14]

A 1996 pooled analysis of 54 epidemiological studies suggested an increase in breast cancer risk associated with current [$RR_{current}$ 1.24, 95% CI 1.15,1.33)] or recent (RR_{recent}=1.16, 95% CI 1.08,1.23) combined OC use at a dose of less than 50 mcg of ethinyl estradiol. This risk was no longer apparent ten years after cessation.[15] Additionally, there was little information regarding the breakdown of risk at distinct estrogen doses, which is relevant given newer formulations of combined OCs with lower estrogen levels. The cancers diagnosed in women who had used combined OC were less clinically advanced than those who had never used OC. In this analysis, women who had used combined OC were more likely to have cancers that did not spread to axillary lymph nodes or other distant sites.[15] Most providers see women prescribed oral contraception at least once per year for regular gynecologic exams, blood pressure assessments, and

Table 1 Comparison of Large (n >1000) Studies Assessing Association Between Breast Cancer and OCPs

Study	n=	Risk/Odds Ratio	Statistically Significant?	RR Compared to the RR of Recent Delivery[7]
CGHFBC (1997)[15]	153,536	RR_{recent}: 1.16 95% CI: 1.08–1.23 $RR_{current}$ 1.24 95% CI: 1.15–1.33	Yes Yes	Lower Lower
CARE (Marchbanks et al 2002)[19]	9257	$OR_{previous}$: 0.9 95% CI: 0.8–1.0 $OR_{current}$: 1.0 95% CI: 0.8–1.3	No No	Lower Lower
Nurses Health Study II (Hunter et al 2010)[21]	116,608	$RR_{current}$: 1.33 95% CI: 1.03–1.73 $RR_{previous}$: 1.12 95% CI: 0.95–1.33	Yes Yes	Lower Lower
Beaber et al (2014)[22]	1867	Ever users* OR: 1.0 95% CI: 0.8–1.3 15 years of use OR: 1.5 95% CI: 1.1–2.2 Users of 20 mcg EE2: OR 1.0 95% CI 0.7–1.8	No Yes No	Lower Lower Lower
Mørch et al (2018)[9]	1,800,000	RR (current+recent HC): 1.20 95% CI: 1.14–1.26 Combined OC RR: 1.19 95% CI: 1.13–1.26 LNG-IUD* RR: 1.21 95% CI: 1.11–1.33	Yes Yes Yes	Lower Lower Lower
Hannaford et al (2007)[10]	1,083,000	RR ever users: 0.98 95% CI: 0.87–1.10	No	Lower
Niemeyer Hultstrand et al (2022)[32]	1,652,364	$RR_{current}$ combined OCP: 1.03 95% CI: 0.91–1.16 $RR_{current}$ progestin-only: 1.32 (1.20–1.45)	No Yes	Lower Lower

Note: *Reference is never users.
Abbreviations: HC, hormonal contraception; OCP, oral contraception pills; EE2, ethinyl estradiol; LNG-IUD, levonorgestrel intrauterine device; RR, relative risk; OR, Odds Ratio.

smoking cessation counseling if needed. These providers are more likely to also perform regular breast exams and order indicated imaging during these visits.[16] Furthermore, the increased uptake of mammographic screening among women using OC is well-documented.[17,18] This screening may increase the incidence of otherwise occult cancers in the cohorts of these studies. Screen-detected breast cancers are more likely to be ER-positive, and exposed cases undergoing regular mammographic screening are more likely to be diagnosed earlier.[18,19] In the 2007, the Royal College of General Practitioners found that ever users of OC had a 12% reduction in the risk of any cancer (adjusted RR 0.99, 95% CI 0.83,0.94).[10,20] These data accord with evidence that OC provides cancer reduction for ovarian, endometrial, and colon cancer, even after 15 years of cessation.[20] There was no difference in the relative risk of breast cancer between ever- and never-users in this large cohort study.[10,20]

Differences in the available formulations of combined OC over time may have also affected breast cancer risk estimates. Significantly lower doses of estrogen and a wide variety of progestins make up contemporary combined OC options. The National Institute of Child Health and Human Development Women's Contraceptive and Reproductive

Experiences (Women's CARE) Study did not demonstrate an association between combined OC use and breast cancer risk in women aged 35 to 64 ($OR_{current}$ 1.0, CI 0.8, 1.3 and $OR_{previous}$ 0.9, CI 0.8, 1.0).[19] The prospective Nurses' Health Study II found a marginal increase in breast cancer risk with current OC use in women younger than age 55 ($RR_{current}$ 1.33, CI 1.03, 1.73). However, the risk associated with previous use was not statistically significant ($RR_{previous}$ 1.12, CI 0.95, 1.33).[21] One specific formulation studied in this trial, a triphasic preparation containing levonorgestrel, but not monophasic preparations, may account for this excess risk (RR 3.05, CI 2.00, 4.66).[21] Notably, this study did not separate progestin-only formulations from combined estrogen-progestin preparations. Combined contraceptive methods suppress ovulation, while progestin-only formulations rely on the thickening of cervical mucus and have unpredictable ovulation suppression, and these mechanisms may influence the risk of breast cancer differently. Therefore, analyzing combined vs progestin-only methods may have further clarified the observed increase in risk seen with the triphasic combined contraception method. In a large population-based study by Beaber et al, 882 controls and 985 women with breast cancer (diagnosed at age 22–44 between the years 2004 and 2010) were compared, and the investigators found that ever-use of combined OC was not statistically significantly associated with breast cancer risk when compared with never-use of combined OC (OR 1.0, CI 0.8, 1.3).[22] However, women who had used OC for at least 15 years had an increased risk (OR 1.5, CI 1.1, 2.2).[22] Interpretation of this data is challenging since the cases were more likely than controls to be nulliparous and to have a family history of breast cancer, while they also were less likely to have a later age at menarche and even less so to have breastfed.[22] Notably, this study was one of the few to report risk related to the contemporary ethinyl estradiol (EE2) dose of 20 mcg, which was not significant (OR 1.0, CI 0.7,1.8).[22]

The evolution of the study of breast cancer's distinct tumor subtypes led to the appropriate stratification of more recent data by receptor status. Interestingly, when stratified by the presence or absence of hormonal receptors, the risk of ER-negativebreast cancer is increased after OC use, while ER-positive cancer is not. In the aforementioned study by Beaber et al, the risk of breast cancer in women aged 20–39 with combined OC use of at least five years is higher for ER-negative and triple-negative subtypes (ER-negative OR 3.5, triple-negative OR 3.7).[22] Race and ethnicity were balanced between cases and controls.[22] In an updated prospective cohort study with 113,187 patients from the Nurses' Health Study II, while current OC users did have a higher risk of invasive breast cancer (hazard ratio, 1.31; 95% confidence interval, 1.09–1.58), after 5 years of cessation, risk profiles were similar among the two groups.[23] A similar case-control study of women diagnosed between 1983 and 1992 found that OC use was associated with a 3.1-fold increased risk of triple-negative tumors, but not ER-positive or Her2-overexpressing subtypes. This increased risk in triple-negative subtypes was associated with more recent OC use and longer duration of use.[24] The increase in hormone receptor-negative subtypes after OC use suggests that a different mechanism other than ligand-mediated activation of estrogen receptors may be involved.

The risk ratios of breast cancer in those using OCPs in the Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC), Nurses Health Study II, and the extended use cohort of the Beaber et al studies were found to be lower than the risk ratio of breast cancer after delivery (Table 1).[15,22,23] In December 2018, Nichols et al published a pooled analysis of 15 prospective studies confirming that although pregnancy itself may portend a lower lifetime risk of cancer, this was not seen until 24 years after delivery, usually coinciding with postmenopausal status.[12] Interestingly, compared to nulliparous women, parous women had an increased risk of developing cancer that peaked 4.6 years after delivery (HR 1.80, CI 1.63, 1.99).[12] Predictably, this risk was further increased in women who had a significant family history of breast cancer (HR 3.53, CI 2.91, 4.29) at 4.9 years after delivery compared to nulliparous women without a significant family history, and this risk was not mitigated by breastfeeding.[12] The increase in breast cancer risk after childbirth is attributed to the proliferation of breast cells during pregnancy.[25,26] The postpartum breast inflammatory microenvironment may also facilitate cancer cell migration and metastasis.[11,27] Since one of the many reasons that individuals choose to use birth control includes to prevent unplanned pregnancies, it is important to consider the risk of breast cancer in both those who take OCPs and those who are pregnant. Older studies concluded that current oral contraceptive use leads to an increased breast cancer risk that disappears after cessation.[15] However, it is unclear whether this reported risk is due to increased incidence or the regular surveillance associated with prescription of oral contraceptives, a phenomenon described in the literature surrounding hormone replacement therapy and breast cancer risk.[28] More recent work from a meta-analysis published in 2021 showed an increased risk of breast cancer in those who used

OCPs before a first full-term pregnancy and those who use OCPs for longer than five years. There was no significant increase in breast cancer risk among ever-users and a significantly decreased risk among OC users before age 25.[29] Lastly, according to the recent Nichols et al pooled analysis, breast cancer risk increases after delivery, peaks at five years, and persists until 24 years after delivery. Table 1 highlights the included studies with n>1000 compared to the relative risk associated with increased delivery in the study by Nichols et al.[12]

Progestin-Only Therapies

The gynecologic utility of different variations and routes of progestin in both pre- and post-menopausal women is diverse. Progestin-only formulations of oral contraceptives can be used in women with contraindications to systemic estrogen, but they can also treat abnormal uterine bleeding, infertility, fibroids, and endometriosis. Apart from contraceptive use, oral progestins as part of a hormone replacement therapy regimen with estrogen mitigate the risk of endometrial hyperplasia in those with an intact uterus.

Progestin-Only Oral Contraception

A large study of more than 100,000 Swedish and Norwegian women between the ages of 30 and 49 years found that those who exclusively used progestin-only formulations did not have an increased risk of breast cancer, regardless of age.[27] This data was later confirmed in a matched case-control study of 4575 women with breast cancer aged 35–64. Marchbanks et alfound no increased risk of breast cancer in progestin-only pill ever-users compared to never-users ($RR_{estrane\ progestins}$ 0.9, CI 0.8, 1.0 and $RR_{gonane\ progestin}$ 1.0, CI 0.8, 1.2).[19] The risk did not change when considering the duration of use or age at first use.[19] In a case-control study of more than 2000 women aged 20–54 years, ever-use of injectable progestins did not increase the risk of breast cancer in those aged 35–44 (RR 0.9, CI 0.7, 1.2).[17,30] This study also did not find an increased risk in women younger than 35 using depot medroxyprogesterone acetate (DMPA).[17,30] The 2004 case-control CARE study later confirmed the lack of causality when they did not find an increased breast cancer risk in pre- or post-menopausal women exposed to either progestin delivery route.[31]

Levonorgestrel Intrauterine Device

Progestin-eluting intrauterine devices (IUDs) not only provide reliable long-acting reversible contraception for women of childbearing age but can also be used to treat abnormal uterine bleeding or endometriosis. The levonorgestrel-containing IUD also treats endometrial hyperplasia and even endometrial cancer, especially in women with low grade endometrial cancer, absolute surgical contraindications, or those in low resource settings.[33].

The most widely known levonorgestrel IUD is the 52 mg levonorgestrel-releasing intrauterine system (LNG-IUD). There are several manufacturers of this system.[34] The levonorgestrel releases at a rate of approximately 20 mcg/day which reaches a stable plasma level of 150–200 pg/mL in the first few weeks after insertion. The rate of release decreases progressively to about 50% of the initial release rate at around five years.[34]

The data regarding breast cancer risk and LNG-IUD are mixed and controversial. In 2005, a large retrospective cohort study of Finnish women who self-identified as LNG-IUD users did not find a statistically significant difference in the incidence of breast cancer between women who used the levonorgestrel system and those who did not within any age group.[35] A 2011 case-control study by Dinger et al also did not find an increased risk of breast cancer with the ever use of LNG-IUD (OR, 0.99, CI 0.88,1.12) or use of LNG-IUD at time of diagnosis (OR, 0.85, CI 0.52,1.39).[36] However, a 2014 Finnish study including women aged 30–49 identified from the National Reimbursement Registry and linked to the Finnish Cancer Registry data who used a LNG-IUD for treatment of abnormal uterine bleeding from 1994–2007 (n=93,843) found a higher-than-expected incidence of breast cancer with LNG-IUD users, with a standardized incidence ratio of 1.19 (CI 1.13, 1.25).[37] The authors concluded that the incidence of breast cancer in the LNG-IUD group was higher than expected, but use of the IUD was also associated with a lower incidence of endometrial, ovarian, pancreatic, and lung cancers.[37]

A 2017 prospective cohort study from Denmark using a nationwide cancer registry found that current or recent users of the LNG-IUD system seemed to possess a higher risk of breast cancer than women who were never users of hormonal contraception (RR 1.21, CI 1.11, 1.33).[9] The breast cancer risk ratio in prior users of any hormonal contraception greater

than six months was 1.08 (CI 1.03, 1.13).[9] Although the media widely publicized this study, it has several limitations that would affect the authors' conclusions.[9] In this study from Denmark, the results were not adjusted for age at menarche, breastfeeding, alcohol consumption, physical activity, or BMI for the nulligravid women, all factors known to play a role in breast cancer risk.[9,38] Further, like the long-term oral contraception studies, it is unclear if the breast cancer risk is related to the progestin-eluting IUD or to the higher rate of nulliparous women among IUD users given the reliability of long-acting reversible contraception. Additionally, a retrospective study using cancer registries in Finland and Germany compared LNG-IUD versus copper IUD (CU-IUD) use in 5113 breast cancer cases diagnosed 2000–2007 and 20,452 matched controls.[36] The investigators did not find an increased risk of breast cancer in users of LNG-IUD over CU-IUD (OR 0.99, CI 0.88, 1.12).[36] Both the LNG-IUD and CU-IUD provide reliable long-acting contraception, prolonged nulliparity, and decrease lifetime number of deliveries. Further studies are needed to elucidate the relationship between levonorgestrel and breast cancer.

Progestin Subdermal Implant

Limited data is available regarding the relationship between the subdermal implant and the risk of breast cancer. In a 2004 case-control study with 4572 cases and 4682 controls that specifically examined risk in patients with progesterone implant and injectable progesterone, no increased risk was found, albeit the sample size of women with these implants was small at n=12.[31]

Combined Progestin Methods

In a Swedish registry study examining the association between various progestin-only contraception methods and breast cancer risk, 1.7 million women were followed for thirteen years. The authors reported that the risk of breast cancer was overall low, at 22.4 per 100,000 women for never-users and 29.8 or 100,000 for current users of progesterone-only methods. When adjusted for other reproductive risk factors, BMI, and smoking, current or recent-users were found to have a small but significant increased risk (1.22 95% CI 1.11,1.34, $p<0.01$). Stratifying by method, combined hormonal methods did not appear to influence risk, while the use of progestin-only pills (RR 1.28 95% CI 1.12,1.47, $p<0.01$), specifically norethisterone and desogestrel, and the levonorgestrel IUD (RR 1.2 95% CI 1.08,1.34, $p<0.01$) were associated with a small but significant increase in risk, although event rates were low.[32] Notably, if a dose-response relationship is thought to exist with the levonorgestrel IUD, there are currently two lower dose IUDs (containing 13.5 mg and 19.5 mg levonorgestrel) available for consideration.

Transdermal and Intravaginal Contraception

Transdermal and intravaginal routes of hormone delivery avoid first-pass metabolism. Compared to oral forms of estrogen, transdermal and intravaginal routes may have lower deleterious systemic effects such as lipid profile derangements and venous thromboembolism risk, with lower rates of venous thromboembolism being reported in women using transdermal forms of contraception.[39]

Although not as widely used as oral forms of contraception, the contraceptive patch and vaginal ring offer alternative birth control methods. The transdermal patch delivers a daily dose of 150 mcg of norelgestromin (the active metabolite of norgestimate) and 20 mcg of EE2 transdermally into the systemic circulation.[40] It is applied for seven days and can be continued weekly or used three weeks on and one week off.[40] Both the EE2 and the norgestimate reach a plateau by approximately 48 hours after applying the patch and a steady state is reached within two weeks of continuous use.[40] The intravaginal etonogestrel/ethinyl estradiol vaginal ring releases approximately 0.120 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol over three weeks of continuous use.[41] A study comparing the estradiol release of the oral contraception, the transdermal patch, and the intravaginal ring demonstrated lower levels of ethinyl estradiol released by the intravaginal ring compared to transdermal and oral routes.[42] At this time, there is no published data correlating the use of transdermal and transvaginal contraception and the risk of breast cancer. However, given that both routes lead to lower systemic metabolism of estrogen (and likely progestins), it is unlikely that these routes would significantly alter breast cancer risk. Protective benefits against ovarian cancer may be seen, in turn, given that these forms are still subtypes of combined contraceptives, limiting ovulation.[43]

Conclusion

This narrative review analyzes the historical and contemporary literature associated with breast cancer risk and hormonal contraception, some with notable limitations. Additional modifiable and non-modifiable risk factors for breast cancer were not always accounted for and factored into the analyses. The older studies did not consider tumor subtype, ie whether the risk of estrogen-sensitive breast cancer increased with the use of hormonal contraception. After incorporating this factor into contemporary studies, hormonal contraception may be more associated with triple-negative breast cancer subtypes.[22] While the mechanism of this association remains unknown, the more aggressive subtypes such as triple-negative breast cancer are more common among premenopausal women. While several of the older studies found a statistically significant increase in the relative risk of breast cancer with use of combined oral contraceptives, those who are prescribed contraception usually visit a provider at least once a year for prescription renewal, suggesting higher participation in age-appropriate breast screening through easier access to healthcare.[18,19] Therefore, these retrospective epidemiologic studies are limited by an inability to determine whether the cancers discovered in the treatment cohorts were due to exogenous hormone exposure or increased surveillance while prescribed the medication.[15,19,21] Our perspective is for some, the all-cancer mortality reduction and pregnancy prevention benefits outweigh the possible small increased risk of breast cancer, but all patients must be informed of the available existing literature during shared decision-making.[44,45] Future research may focus on the clinical implications of the association between breast cancer risk during the post-delivery period and the relationship between exogenous estrogen and carcinogenesis.

Appropriately counseling patients about contraception, pregnancy, and breast cancer risk is critical for cancer risk mitigation and effective family planning. Therefore, the decision to use hormonal contraception should not hinge on population-based data associating breast cancer risk, but rather on an individual woman's reproductive goals. Ultimately, the role of the oncologically-minded provider should be to empower patients in their decision-making and ensure their reproductive freedom through evidence-based contraceptive counseling.

Disclosure

The authors report no conflicts of interest in this work.

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