THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 13 Issue 8

RESEARCH ARTICLE

Hormonal Contraception in Breast Cancer Survivors: From Hormonal Physiology to Future Perspectives

Jan Pawel Andrade Pachnicki, M.D., Ph.D [a, b, c, d] **; Giovana Galego Navarrete de Andrade** [a]

[a] Department of Gynecology and Obstetrics of Positivo University – Cidade Industrial de Curitiba, Curitiba – PR / Brasil, 81290-000
[b] Department of Obstetrics of Pontifical Catholic University of Paraná – R. Imaculada Conceição, 1155 - Prado Velho, Curitiba – PR / Brasil, 80215-901
[c] Department of Tocogynecology of Federal University of Paraná – R. General Carneiro, 181 - Alto da Glória, Curitiba – PR / Brasil, 80060-900
[d] Department of Gynecology of Mackenzie Evangelical Medical School of Paraná – R. Padre Anchieta, 2770 - Bigorrilho, Curitiba – PR / Brasil, 80730-000

OPEN ACCESS

PUBLISHED
31 August 2025

CITATION
Pachnicki, PA., de Andrade, GGN., et al., 2025. Hormonal Contraception in Breast Cancer Survivors: From Hormonal Physiology to Future Perspectives. Medical Research Archives, [online] 13(8).
https://doi.org/10.18103/mra.v13i8.6856

DOI
https://doi.org/10.18103/mra.v13i8.6856

ISSN
2375-1924

ABSTRACT

For the millions of women who have successfully battled breast cancer, the question of contraception presents a unique and often complex challenge. Navigating the landscape of hormonal options requires a deep understanding of how cancer treatments have altered their bodies' hormonal physiology and a careful weighing of the risks and benefits. Contraceptive management in breast cancer patients also requires scientific evidence. This review discusses the interaction between sexual steroids and the mammary gland, bridging basic science with large studies such as the WHI and the Million Women Study, which have demonstrated the risks associated with combined hormonal therapy. Based on these data, hormone-containing contraceptives are contraindicated, and the copper intrauterine device (Cu-IUD) emerges as the main safe option. However, while non-hormonal methods have traditionally been the first line of defense, ongoing research and a shift towards personalized medicine are opening up new perspectives and potential future options for this growing population. The use of progestin-only methods, particularly the levonorgestrel-releasing intrauterine system (LNG-IUS), presents a more nuanced picture, and remains a matter of debate. Although it offers benefits such as endometrial protection in tamoxifen users, its oncological safety is still uncertain. Some studies suggest that the low levels of circulating progestin may not pose a significant risk of recurrence. As a future perspective, new molecules such as estetrol (E4) are emerging as promising alternatives due to their selective action profile. The conversation around hormonal contraception is evolving, and future researches will provide choices that align with patients' individual needs and desires.

Introduction

Breast cancer remains one of the leading global health challenges and ranks prominently among the main causes of cancer-related mortality in women. According to Xiong et al[1], the disease accounts for approximately one-third of all tumors diagnosed in the female population. In the United States, the American Cancer Society estimated around 310,720 new cases of invasive breast cancer and approximately 42,250 related deaths for the year 2024. Despite advances in treatment having led to a 44% reduction in mortality since 1989, the incidence of the disease continues to rise, as reported by Giaquinto et al[2].

The influence of sex hormones on the development of breast cancer is one of the fundamental pillars for understanding the disease. Although estrogen has historically been considered the main agent involved, emerging evidence presented by Kim and Munster[3] suggests that progestogens—including both natural progesterone and synthetic progestins—may play a more significant role in hormonal risk. Estrogen, in this context, would act indirectly by inducing the expression of the progesterone receptor (PR), thereby priming cells to respond to progesterone action.

This hormonal foundation is also reflected in the molecular classification of breast cancer, which is based on the presence or absence of hormone receptors (HR) and HER2, a protein linked to cell proliferation. According to Xiong et al[1], the main molecular subtypes identified are: HR-positive/HER2-negative (approximately 70% of cases), HER2-positive (15–20%), and triple-negative (around 15%), the latter being associated with a more aggressive behavior and poorer hormonal response.

This hormone dependence of the disease demands special attention when prescribing exogenous hormones, whether for hormone replacement therapy (HRT) or contraceptive purposes. Multiple studies have shown that hormonal contraceptives may be associated with a slight increase in breast cancer risk, a risk attributed mainly to progestins rather than estrogens. A similar pattern is observed in HRT: when combining estrogen and progestin, the risk increases consistently. In contrast, estrogen-only HRT appears to have little or no significant impact, as emphasized by Kim and Munster[3]. These findings highlight the importance of carefully evaluating the patient's history before initiating any hormonal therapy.

It is worth noting that many women receive a breast cancer diagnosis during their reproductive years. Data from the American Cancer Society[2] estimate that 16% of new invasive breast cancer cases occur in women under the age of 50. In this context, contraception becomes a clinical necessity, as pregnancy should be avoided throughout most of the cancer treatment period.

Therefore, this article aims to review contraceptive management in breast cancer patients, exploring both the hormonal aspects involved in the disease and the most recent evidence regarding available hormonal methods, with an emphasis on safety and efficacy for this specific population.

Methodology

This is a systematic study supported by a review of the scientific literature in Pubmed and BVS to understand the state of the art and an analysis of international databases.

The guiding research question was: " While non-hormonal methods remain the safest choice in breast cancer survivors contraception, is it possible to think in hormonal contraception?" structured by the acronym PICO (Patient / Population / Problem, Intervention, Comparison, and Outcome). The Pubmed and BVS databases were searched from 2000 to 2025, according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) method guidelines.

The descriptors used in the search were chosen from the Health Sciences Descriptors (DeCS) dictionary, considering articles in English, full articles, and using the descriptors and Boolean expressions (AND/OR): hormonal contraception; breast cancer; estrogen; progestin. The study types chosen were: Literature Reviews, Meta-analyses, and Prospective Studies.

The inclusion criteria for the literature review were: articles addressing the physiology of estrogen and progestogen in the mammary gland, its use in hormonal contraception, and what the medical literature says about hormonal contraception in breast cancer survivors. The exclusion criteria were: duplicate articles, and/or articles that did not address the proposed topic.

The final evaluation of the selected articles was conducted using the eligibility criteria, referencing the guiding question of the study. To reduce the risk of bias, the evaluation was conducted in pairs (in which both researchers evaluate and rate the article; if there was disagreement, the article was excluded).

Contraception and breast cancer

Despite the findings of the study published by Byrne et al[4] in 1987, which observed a 10–25% reduction in fertility following breast cancer treatment, the risk of pregnancy persists and must be strictly avoided during oncological therapy. Therefore, adequate, acceptable, and effective contraceptive methods are essential. Added to this are the various non-contraceptive benefits of such medications, widely applied in gynecological practice. However, the use of hormonal contraceptives remains contraindicated, even though definitive evidence of harm is difficult to establish.

In 2006, McNaught and Reid, in collaboration with the Breast Cancer Committee of the Society of Obstetricians and Gynaecologists of Canada, recommended that non-hormonal contraceptive methods should be the first-line choice for breast cancer survivors. Nonetheless, the levonorgestrel-releasing intrauterine system (LNG-IUS), progestin-only pills, and depot medroxyprogesterone acetate injections could be considered in cases where the benefits outweigh the uncertainties surrounding their potential impact on tumor recurrence[5].

In 2009, Schwarz, Hess, and Trussell reviewed contraceptive options for cancer survivors and emphasized the importance of open discussions about the topic. They concluded that intrauterine methods should be the preferred choice in this group. For women desiring contraception and with hormone receptor-positive tumors, the copper intrauterine device (Cu-IUD) was considered highly effective, cost-efficient, reversible, long-acting, and devoid of exogenous hormones—making it the first-line contraceptive. In contrast, the LNG-IUS might be preferable for patients undergoing adjuvant tamoxifen therapy, due to its endometrial protective effects[6].

Also in 2009, Hickey et al[7] highlighted that, although young reproductive-aged women account for a minority of breast cancer cases, they often have concerns and goals distinct from older patients, especially regarding fertility, contraception, and pregnancy.

In 2012, the Society of Family Planning published its recommendations on cancer and contraception. Patel et al[8] classified the use of the Cu-IUD as level A evidence (strong and consistent scientific data) for women with a history of breast cancer—highlighting its high efficacy and hormone-free profile. The use of LNG-IUS in patients receiving adjuvant tamoxifen was classified as level B evidence (limited or inconsistent data), acknowledging its contraceptive efficacy and ability to reduce tamoxifen-induced endometrial changes, without increasing the risk of tumor recurrence. The same guidelines strongly advised against the use of estrogen-containing contraceptive methods in patients with hormone-dependent breast cancer, citing both the potential for increased recurrence and the elevated risk of thromboembolic events—particularly in patients treated within the previous six months.

The most recent publication by the World Health Organization (2015), in its *Medical Eligibility Criteria for Contraceptive Use*, reaffirmed that combined hormonal contraceptives and progestin-only methods negatively affect the prognosis of patients treated for breast cancer, due to the hormone-sensitive nature of the disease. Barrier methods (condoms) and non-hormonal devices (Cu-IUD) were listed under category 1, indicating no restrictions for use. In contrast, hormonal methods were classified as category 4 (unacceptable health risk) during active treatment, and category 3 (risks generally outweigh benefits) after five years of cancer therapy, in the absence of residual disease. A positive note was made regarding the LNG-IUS, which is associated with minimal systemic progestin levels, thus theoretically posing a lower risk for disease progression[9].

The action of estrogen in the mammary gland

The growth and development of the mammary gland after puberty are closely linked to hormonal influence, particularly estrogen. This hormone exerts its effects mainly through a specific protein known as Estrogen Receptor alpha (ERα).

Research conducted by Mallepell, Krust, Chambon, and Brisken in 2006 demonstrated that estrogen signaling within the mammary ductal epithelial cells is essential for proper gland development. When mammary epithelial tissue lacking the ERα receptor ($ER\alpha^{-/-}$) was implanted into female rats with a normal hormonal profile, the tissue was unable to grow or differentiate effectively. Conversely, when healthy epithelial tissue was implanted into a stroma devoid of ERα, normal development occurred. These findings confirmed that estrogen acts directly on epithelial cells via ERα to promote ductal growth and proper mammary gland formation[10].

As described by Brisken and O'Malley in their 2010 review, estrogen acts directly on ERα-positive epithelial cells, stimulating them to produce amphiregulin, a key growth factor involved in initiating ductal elongation. Once secreted, amphiregulin binds to the epidermal growth factor receptor (EGFR) in stromal cells, which then release additional factors—particularly FGF7 and FGF10—that signal back to the epithelial compartment to promote proliferation. In addition to mediating epithelial–stromal communication, estrogen also acts intracellularly as a transcription factor when bound to ERα. Upon activation, ERα undergoes conformational change and interacts with coactivators such as SRC-3 (also known as AIB1), forming complexes that facilitate chromatin remodeling and enhance the transcription of target genes, including amphiregulin itself[11].

An additional role of estrogen is its priming function for subsequent hormonal signaling. As described by Haslam and Shyamala in 1979, during puberty, estrogen not only stimulates ductal growth but also induces the expression of the progesterone receptor (PR) in epithelial cells. This process, termed *estrogen priming*, is essential for preparing the mammary gland to respond appropriately to progesterone[12].

The review by Santen, Brodie, Simpson, Siiteri, and Brodie also explored the discovery and physiological significance of the enzyme aromatase, which converts androgens to estrogens. The understanding of estrogens began in the 1920s when estrogenic activity was observed in urinary extracts. A landmark occurred in the early 1930s when Doisy and Butenandt successfully isolated and identified estriol, estrone, and estradiol from the urine of pregnant women[13].

Their discovery led to hypotheses regarding the endogenous origin of these substances. The structural similarity between estrogens and androgens prompted speculation that one could be metabolically converted into the other. In 1934, Zondek proposed that the estrogen found in males was a byproduct of androgen metabolism. This hypothesis was confirmed in 1937 by Steinach and Kun, who demonstrated that testosterone administration in men increased urinary estrogenic activity—evidence of androgen-to-estrogen conversion, later attributed to aromatase[13].

The Worcester Foundation for Experimental Biology played a pivotal role in characterizing this process. In 1955, Meyer identified 19-hydroxy-androstenedione as a key intermediate in aromatization. Subsequent studies by Ryan and Engel, using placental tissue, clarified the

conversion pathway. In 1974, Thompson and Siiteri developed a radiometric assay that enabled the measurement of aromatase activity and the screening of potential enzyme inhibitors[13].

Later that decade, Macdonald and Siiteri revealed that adipose tissue—especially in postmenopausal women—could also produce estrogens via aromatase, establishing adipose tissue as a major estrogen source in this population. This finding helped explain the increased cancer risk associated with obesity and demonstrated that mammary tissue, including tumors, can locally produce estrogen, thereby influencing tumor growth directly within the tissue microenvironment[13].

These discoveries collectively highlight that estrogen not only acts systemically via the bloodstream but also exerts local autocrine and paracrine effects, shaping the biological environment of mammary cells.

The action of progesterone in the mammary gland

The role of progesterone in the mammary gland extends beyond its physiological and morphological contributions to glandular development. Understanding the endocrine regulation of this tissue not only clarifies the formation of lobuloalveolar structures and cell proliferation, but also aids in the interpretation of breast cancer pathogenesis.

Less than a decade after the discovery of progesterone, Inhoffen, Logemann, Hohlweg, and Serini synthesized the first orally active progestin—ethisterone (pregneninolone, 17α-ethinyltestosterone)—in 1938, in Berlin[14]. Since then, numerous synthetic progestins have been developed.

As reviewed by Vigo, Lubianca, and Corleta[15], progestins can be categorized both by their chemical origin and by generation. First-generation progestins, introduced in the 1960s, are derived from either testosterone or progesterone. Those derived from testosterone (19-nortestosterone) include estranes such as norethindrone, norethisterone acetate, and norethynodrel. Gonanes, like levonorgestrel and norgestrel, represent second-generation progestins and possess higher progestational activity. Third-generation progestins (e.g., desogestrel, gestodene, norgestimate) were designed to minimize androgenic side effects. Fourth-generation agents, such as drospirenone, dienogest, and nomegestrol acetate, were developed to emulate the natural benefits of progesterone while avoiding adverse effects like acne, fluid retention, and reduced HDL cholesterol[15].

Both natural progesterone and synthetic progestins exert their biological effects through the progesterone receptor (PR), identified in the 1970s. Progesterone's most significant action in the normal mammary gland is the formation of lobuloalveolar structures during pregnancy. This was demonstrated by Topper and Freeman in 1980, who showed that in rats lacking PR expression, ductal structures still formed under estrogen and progesterone exposure, but failed to develop into lobuloalveolar formations[16].

In the same year, Haslam and Shyamala observed that estrogen increases PR levels, while progesterone reduces estrogen receptor (ER) levels in the mammary gland—indicating a tightly regulated feedback mechanism[12].

Graham and Clarke, in a 1997 review, suggested that progesterone may contribute to cyclical epithelial proliferation in vivo, despite contradictory findings in vitro. They proposed that, in addition to promoting cell proliferation, progestins might inhibit tumor suppressor genes such as TP53[17].

In 1997, Humphreys et al demonstrated that PR isoforms A and B—though transcribed from the same gene—play distinct roles in mammary development. These isoforms were detected in both epithelial and stromal cells, each regulating different proteins and exerting cell-specific functions[18].

To investigate the physiological role of PR-A, Mulac-Jericevic et al created a knockout mouse model lacking PR-B. They found that PR-A inhibited PR-B activity and, when acting alone, reduced cell proliferation—suggesting a protective role against mammary hyperplasia[19]. Later, in 2004, the same group found that selective modulation of PR isoforms could either promote or inhibit proliferation in mammary tissue[20].

Also in 2004, Ruan, Monaco, and Kleinberg studied the interaction of progesterone and estrogen with insulin-like growth factor 1 (IGF-1) and found that while mammary development can begin without progesterone, the hormone significantly enhances ductal branching and elongation[21]. That same year, Shi, Lydon, and Zhang observed that progestin therapy could rescue pubertal ductal development defects caused by low systemic progesterone levels[22].

Finally, Coneely et al concluded in 2013 that both PR isoforms are critical for appropriate mammary response to progesterone, particularly for proliferation and differentiation during development[23].

The role of sexual steroids in breast cancer

Breast carcinomas exhibit a wide spectrum of morphological, cyclical, and evolutionary characteristics. Accordingly, efforts have been made to clarify the role of hormones and their receptors in tumorigenesis. In this context, progesterone emerges as a particularly controversial hormone, with its impact on breast tumor cells remaining the subject of ongoing debate.

In 1988, Pike and Key proposed the "estrogen plus progestogen" hypothesis, suggesting that the combined action of these hormones increases breast cancer risk. The protective effect of early menopause indicated that ovarian hormones contribute to this risk, and the elevated mitotic index of breast epithelial cells during the luteal phase implied that progesterone, in synergy with

estrogen, enhances cellular proliferation more than estrogen alone[24].

That same year, Wren reviewed data on medroxyprogesterone acetate and reported an increased incidence of mammary tumors in Beagle dogs and rhesus monkeys exposed to progestogens alone[25].

In 1999, Lydon et al conducted a study using progesterone receptor knockout (PRKO) mice and demonstrated that the luminal epithelial compartment is the primary site of progesterone-induced proliferation. This compartment was also identified as the primary target of carcinogenic stimuli. Furthermore, they established that PR-mediated signaling is a prerequisite for chemically induced mammary carcinogenesis[26].

In 2002, Soyal et al reviewed experimental animal and cell models and showed that PR function varies depending on the cell of origin and gene promoter context. PR can be activated either by natural progesterone or synthetic ligands (progestins), and its expression is restricted to luminal epithelial cells[27].

In 2003, Chlebowski, Hendrix, and Langer published results from the Women's Health Initiative (WHI), in which 16,608 postmenopausal women with intact uteri were randomized to receive either conjugated equine estrogens (0.625 mg/day) combined with medroxyprogesterone acetate (2.5 mg/day) or placebo. After a mean follow-up of 5.2 years, the combined hormone therapy group exhibited a significantly increased risk of invasive breast cancer, prompting early termination of that arm of the study[28].

That same year, Beral and the Million Women Study collaborators reported that, in a cohort of over 1 million British women aged 50–64 years, hormone replacement therapy (HRT) was associated with increased breast cancer incidence and mortality, with the highest risk observed among users of combined estrogen-progestin regimens[29].

In Sweden, two randomized controlled trials (HABITS and Stockholm) were launched in 1997 to assess the risk of recurrence in postmenopausal breast cancer survivors using HRT. Both studies were terminated prematurely in 2003 after pooled analyses revealed a significantly increased risk of cancer recurrence associated with HRT[30],[31]. Although differences between studies were not statistically significant, they were hypothesized to result from variations in progestin regimens used.

In 2005, Campagnoli et al emphasized the metabolic and hepatic effects of estrogens and progestogens—such as reduced insulin sensitivity, increased IGF-1 activity, and lower sex hormone-binding globulin (SHBG) levels—which may influence breast cancer risk depending on the specific regimen and type of progestogen used[32].

Lange and Yee (2008), as well as Mester and Redeuilh (2008), revisited evidence of a paracrine mechanism through which PR-positive cells stimulate proliferation in adjacent PR-negative cells—suggesting a key role in ductal morphogenesis and potentially in carcinogenesis[33],[34]. PR transcription leads to three isoforms: PR-A, PR-B, and PR-C. PR-A is critical for uterine development and is associated with ductal branching and hyperplasia. PR-B is required for normal mammary development. PR-C, though often functionally inactive, may enhance PR activity in breast cancer cells. PR isoform expression is often modulated by ER signaling, complicating the separation of progesterone's effects from those induced by estrogen.

The association between estrogen and breast cancer dates back to 1896, when surgeon Beatson observed that oophorectomy led to tumor regression in premenopausal women—a pivotal clue that ovarian-derived substances fueled tumor growth[35]. By the 1930s, researchers like Doisy and Butenandt isolated and identified estrogens as the causative agents.

A second wave of discovery in the 1970s demonstrated that estrogen could also be synthesized outside the ovaries, notably in adipose tissue and breast tumors, due to the action of aromatase[36]. This transformed the understanding of hormone-sensitive breast cancer in postmenopausal women and ushered in the era of aromatase inhibitors.

Jensen's discovery of the estrogen receptor (ER) was another landmark. Using radiolabeled estradiol, he demonstrated specific retention in estrogen-responsive tissues, providing evidence of receptor-mediated action[37]. At the molecular level, the estrogen–ER complex acts as a transcription factor, recruiting coactivators like SRC-3 to induce genes such as *CCND1* and *MYC*, which drive cell proliferation[38].

According to Deroo and Korach[39], estrogen's effects are not uniform across tissues. While ERα promotes proliferation, ERβ may counterbalance these effects, acting as a negative regulator.

Finally, Ali and Coombes[38] noted that continuous estrogen exposure fosters clonal expansion of genetically unstable epithelial cells, increasing the risk of mutations and malignant transformation. Estrogen also promotes angiogenesis and invasiveness via matrix metalloproteinases (MMPs), further facilitating metastasis[40].

What to expect from the near future?

In recent decades, numerous advances have been made by the pharmaceutical industry in the field of hormonal contraception. Following the trend of using progestogens alone for this purpose, in 1990, Luukkainen, Lähteenmäki, and Toivonen developed the levonorgestrel-releasing intrauterine system (LNG-IUS), aiming to reduce excessive menstrual bleeding. Currently, there are three types of intrauterine devices (IUDs) available: 13.5 mg, 19.5 mg, or 52 mg IUDs.

Beyond its contraceptive role, the method began to play an important role in the treatment of gynecological disorders, such as abnormal uterine bleeding, dysmenorrhea, and chronic pelvic pain. The

popularization of the device thus emerged amid a still controversial issue raised by several authors: the increased risk of breast cancer associated with progestogen-only therapy.

The device releases 20 µg/day of levonorgestrel directly into the uterine cavity, acting through a local mechanism with high contraceptive efficacy by altering cervical mucus, causing reversible endometrial atrophy, decreasing tubal ciliary movement, and directly affecting sperm. Low systemic serum levels of the hormone are observed, with average concentrations ranging between 150 and 200 pg/ml.

Discussions regarding the tumor-inducing potential and/or the relationship with the levonorgestrel dose released by the LNG-IUS still lack consensus among the published studies.

Backman, Rauramo, Jaakkola, Inki, Vaahetra, Launonen, and Koskenvuo (2005) compared the incidence of breast cancer among 17,360 LNG-IUS users and the general Finnish female population aged between 30 and 54 years. They concluded that there was no difference in disease incidence between the two populations in any of the five age groups studied.[41]

In 2008, Trinh, Tjalma, Makar, Buytaert, Weyler, and Van Dam compared a group of 79 breast cancer patients who used the device with patients who also had the disease but had never used the method. The users were divided into two subgroups: those who were already using the method and continued after diagnosis, and those who had the LNG-IUS inserted after treatment. The subgroup that continued with the LNG-IUS after the diagnosis showed an increased risk of recurrence associated with metastasis. Despite this result, overall, the study concluded that there was no increased risk of disease recurrence in the patients studied.[42]

The study by Dinger, Bardenheuer, and Moehner, conducted in 2010, compared the risk of breast cancer among LNG-IUS and copper IUD users in women under 50 years of age. It assessed 5,113 breast cancer cases and 20,452 matched controls and did not demonstrate any increased risk of cancer among patients using the levonorgestrel-releasing device.[43]

Also in 2010, in their review, Scapinelli, Oliveira, Takagi, and Aldrighi stated that, given that serum levonorgestrel concentration is about a thousand times lower than intrauterine levels, it would be plausible to assume that this negligible systemic bioavailability would result in minimal breast effects, although studies on this issue remain scarce.[44]

Several studies have demonstrated the usefulness of the intrauterine device in combination with selective estrogen receptor modulators (SERMs), such as tamoxifen, used in adjuvant hormone therapy in premenopausal patients with hormone-responsive breast cancer. Its benefit lies in preventing endometrial hyperplasia caused by the pro-estrogenic response observed in the uterus of these patients. In a 2014 meta-analysis involving the three most relevant randomized clinical trials (with 359 patients), Fu and Zhuang analyzed the effectiveness of the LNG-IUS in tamoxifen-induced endometrial lesions. The study observed that the use of the device did not increase cancer recurrence rates in the sampled patients.[45]

In a recent study conducted in Finland and published in 2016, the hypothesis was tested that the risk of invasive lobular breast cancer would be higher among LNG-IUS users. Selected users were between 30 and 49 years old and used the device for the treatment of menorrhagia. A total of 93,843 users were evaluated, with 2,015 cases of cancer detected. Soini, Huuskaïnen, Grénman, Mäenpää, Paavonen, Joensuu, and Pukkala demonstrated an increase not only in the risk of lobular mammary adenocarcinoma but also of ductal adenocarcinoma—this latter type previously not associated with progestogen use—after the fifth year of method use.[46]

Despite the many publications addressing this issue, the relationship between LNG-IUS and mitogenic processes in mammary cells remains questionable. Considering both the positive and negative aspects, most studies suggest that the LNG-IUS and the incidence of breast cancer in young women are minimally associated. Publications from 2016, based on a Cochrane systematic review (Roberts and Hickey) and the Canadian Contraception Consensus (Black and Guilbert), point in this direction, presenting the LNG-IUS as a possible option in well-established cases.[47,48]

The search for new endocrine therapies has highlighted estetrol (E4), a natural estrogen. As detailed in a review by Gérard et al., E4 is produced by the human fetal liver and, although initially regarded as a weak estrogen, it is now considered a promising agent.[49]

The mechanism of action of estetrol is what makes it unique, with its activity varying depending on the target tissue. A study by Benoit et al. in 2017 demonstrated that E4's stimulatory action in certain tissues, such as the vagina, depends exclusively on the nuclear pathway of the estrogen receptor alpha (ERα). In breast tissue, however, its stimulatory effect is very weak. Additionally, it can block the strong proliferative effect of estradiol (E2), the body's main estrogen. This selective action—differentiating the nuclear and membrane pathways of the receptor—is a unique feature of E4.[50]

Moreover, Singer, Coelingh, and Natter conducted a prospective, randomized, double-blind, placebo-controlled study involving 30 women with newly diagnosed ER+ early-stage breast cancer, equally divided between pre- and postmenopausal groups. Participants received 20 mg of E4 or placebo daily for 14 days prior to surgery. The findings indicated that E4 induced apoptosis in tumor tissue without altering Ki67 expression, suggesting that E4 does not affect cell proliferation. [51]

Gérard et al. highlighted several advantages of this hormone: first, its low impact on breast tissue makes it an ideal candidate for the development of safer

contraceptives and menopausal therapies—and an E4-based oral contraceptive has already been approved. Second, its antitumor effects position it as a potential novel therapy. In this regard, its specific action profile suggests a dual potential: to serve as the basis for safer hormonal therapies and, at the same time, to act as a promising treatment for breast cancer.[49]

Conclusion

The journey of a breast cancer survivor extends far beyond the initial treatment, with long-term considerations such as contraception playing a vital role in their overall health and well-being. The long-standing assumption that estrogen is the primary agent responsible for this risk has been increasingly questioned in light of new evidence. While non-hormonal methods remain the safest choice, the conversation around hormonal contraception is evolving. The main point of contention lies on the levonorgestrel-releasing intrauterine system (LNG-IUS). On one hand, it provides significant endometrial protection for patients undergoing tamoxifen therapy; on the other, its safety in relation to breast cancer continues to raise questions.

Looking to the future, the great challenge—and indeed the greatest promise—lies in pharmaceutical innovation. The goal is to develop molecules with more selective actions, capable of providing contraceptive efficacy without stimulating breast tissue. In this scenario, estetrol (E4) emerges as a particularly promising alternative. It is a natural estrogen, with a differentiated mechanism of action, that exhibits low proliferative activity in mammary tissue while also antagonizing the effects of estradiol[49–51]. This makes it a strong candidate for the development of new hormonal therapies and contraceptives with improved oncological safety. Through continued research, a deeper understanding of hormonal physiology, and a commitment to personalized medicine, the future holds the promise of providing breast cancer survivors with a broader and safer spectrum of contraceptive options, empowering them to make choices that align with their individual needs and desires.

Conflicts of interest statement

The authors have no conflicts of interest to declare.

References

1. Xiong X, Zheng LW, Ding Y, et al. Breast cancer: pathogenesis and treatments. *Signal Transduct Target Ther*. 2025;10(1):49.p
2. Giaquinto AN, Sung H, Newman LA, et al. Breast cancer statistics 2024. *CA Cancer J Clin*. 2024;74(6):477-495.
3. Kim J, Munster PN. Estrogens and breast cancer. *Ann Oncol*. 2025;36(2):134-148.
4. Byrne J, Mulvihill JJ, Myers MH, et al. Effects of treatment for childhood cancer on fertility. *N Engl J Med*. 1987;317(21):1315-1321.
5. McNaught J, Reid RL. Contraception for the woman with a medical condition: an evidence-based review. *J Obstet Gynaecol Can*. 2006;28(7):616-639.
6. Schwarz EB, Hess R, Trussell J. Contraceptive options for women with cancer. *J Gen Intern Med*. 2009;24 Suppl 2:S401-S406.
7. Hickey M, Peate M, Saunders CM, Friedlander M. Breast cancer in young women: an overview. *Hum Reprod Update*. 2009;15(3):323-339.
8. Patel A, Schwarz EB, Sreedevi M, Roston A. Contraception for the medically complex patient. *Contraception*. 2012;86(3):191-198.
9. World Health Organization. *Medical Eligibility Criteria for Contraceptive Use*. 5th ed. World Health Organization; 2015.
10. Mallepell S, Krust A, Chambon P, Brisken C. Paracrine signaling through the epithelial estrogen receptor alpha is required for proliferation and morphogenesis in the mammary gland. *Proc Natl Acad Sci U S A*. 2006;103(7):2196-2201.
11. Brisken C, O'Malley BW. Hormone action in the mammary gland. *Cold Spring Harb Perspect Biol*. 2010;2(12):a003178.
12. Haslam SZ, Shyamala G. Progesterone receptors in normal mammary gland: receptor modulations in relation to differentiation. *J Cell Biol*. 1979;86(3):730-736.
13. Santen RJ, Brodie H, Simpson ER, Siiteri PK, Brodie AM. History of aromatase: saga of an important biological mediator and therapeutic target. *Endocr Rev*. 2009;30(4):343-375.
14. Inhoffen HH, Logemann W, Hohlweg W, Serini A. Untersuchungen in der Sexualhormon-Reihe. *Ber Dtsch Chem Ges*. 1938;71(5):1024-1032.
15. Vigo F, Lubianca JN, Corleta HV. Progestógenos: farmacologia e uso clínico. *Rev Femina*. 2011;39(3):127-137.
16. Topper YJ, Freeman CS. Multiple hormone interactions in the developmental biology of the mammary gland. *Physiol Rev*. 1980;60(4):1049-1106.
17. Graham JD, Clarke CL. Physiological action of progesterone in target tissues. *Endocr Rev*. 1997;18(4):502-519.
18. Humphreys RC, Lydon J, O'Malley BW, Rosen JM. Mammary gland development is mediated by both stromal and epithelial progesterone receptors. *Mol Endocrinol*. 1997;11(6):801-811.
19. Mulac-Jericevic B, Lydon JP, DeMayo FJ, Conneely OM. Defective mammary gland morphogenesis in mice lacking the progesterone receptor B isoform. *Proc Natl Acad Sci U S A*. 2003;100(17):9744-9749.
20. Mulac-Jericevic B, Conneely OM. Reproductive tissue selective actions of progesterone receptors. *Reproduction*. 2004;128(2):139-146.
21. Ruan W, Monaco ME, Kleinberg DL. Progesterone stimulates mammary gland ductal morphogenesis by synergizing with and enhancing IGF-I. *Endocrinology*. 2004;145(7):3361-3368.
22. Shi HY, Lydon JP, Zhang M. Hormonal defect in maspin heterozygous mice reveals a role of progesterone in pubertal ductal development. *Mol Endocrinol*. 2004;18(9):2196-2207.
23. Coneely OM, Mulac-Jericevic B, DeMayo FJ, Lydon JP, O'Malley BW. Reproductive functions of progesterone receptors. *Recent Prog Horm Res*. 2002;57:1-32.
24. Pike MC, Key TJ. Oestrogens, progestagens, and the risk of breast cancer. *Eur J Cancer Clin Oncol*. 1988;24(1):29-43.
25. Wren BG. The effect of progestogens on breast tissue. *Maturitas*. 1988;10(1):3-9.
26. Lydon JP, Ge G, Kittrell FS, Medina D, O'Malley BW. Murine progesterone receptor A-form and B-form knockout mice reveal that progesterone action on mammary gland development is mediated by the B-form. *Cancer Res*. 1999;59(17):4276-4284.
27. Soyal SM, Ismail PM, Li J, Mulac-Jericevic B, Conneely OM, Lydon JP. The differing roles of progesterone receptors in the breast and uterus. *Breast Cancer Res*. 2002;4(5):191-196.
28. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA*. 2003;289(24):3243-3253.
29. Beral V; Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet*. 2003;362(9382):419-427.
30. Holmberg L, Anderson H; HABITS steering and data monitoring committees. HABITS (hormonal replacement therapy after breast cancer--is it safe?), a randomised comparison: trial stopped. *Lancet*. 2004;363(9407):453-455.
31. von Schoultz E, Rutqvist LE; Stockholm Breast Cancer Study Group. Menopausal hormone therapy after breast cancer: the Stockholm randomized trial. *J Natl Cancer Inst*. 2005;97(7):533-535.
32. Campagnoli C, Clavel-Chapelon F, Kaaks R, Peris C, Berrino F. Progestins and progesterone in hormone replacement therapy and the risk of breast cancer. *J Steroid Biochem Mol Biol*. 2005;96(2):95-108.
33. Lange CA, Yee D. Progesterone and breast cancer. *Womens Health (Lond)*. 2008;4(2):151-162.
34. Mester J, Redeuilh G. Progesterone receptors: fifty years of research, what's new? *Anticancer Agents Med Chem*. 2008;8(8):872-885.
35. Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. *Lancet*. 1896;2(3802):104-107.
36. Macdonald PC, Siiteri PK. The relationship between the extraglandular production of estrone and the

occurrence of endometrial neoplasia. *Gynecol Oncol*. 1974;2(2-3):259-263.
37. Jensen EV, DeSombre ER, Jungblut PW. Estrogen receptors in hormone-responsive tissues and tumors. *Proc Natl Acad Sci U S A*. 1967;59(2):632-638.
38. Ali S, Coombes RC. Endocrine-responsive breast cancer and strategies for combating resistance. *Nat Rev Cancer*. 2002;2(2):101-112.
39. Deroo BJ, Korach KS. Estrogen receptors and human disease. *J Clin Invest*. 2006;116(3):561-570.
40. Hammond ME. Estrogen receptor, progesterone receptor and HER2 a 'ménage à trois' in breast cancer. *Breast Cancer Res Treat*. 2010;120 Suppl 1:S1-S6.
41. Backman T, Rauramo I, Jaakkola K, et al. Use of the levonorgestrel-releasing intrauterine system and breast cancer. *Obstet Gynecol*. 2005;106(4):813-817.
42. Trinh XB, Tjalma WA, Makar AP, Buytaert G, Weyler J, Van Dam PA. Use of the levonorgestrel-releasing intrauterine system in breast cancer patients. *Fertil Steril*. 2008;90(1):17-22.
43. Dinger J, Bardenheuer K, Moehner S. Levonorgestrel-releasing and copper intrauterine devices and the risk of breast cancer. *Contraception*. 2011;83(3):211-217.
44. Scapinelli A, Oliveira VM, Takagi MM, Aldrighi JM. Levonorgestrel-releasing intrauterine system and breast cancer risk. *Rev Assoc Med Bras*. 2010;56(6):615-617.
45. Fu Y, Zhuang Z. Long-term effects of levonorgestrel-releasing intrauterine system on tamoxifen-treated breast cancer patients: a meta-analysis. *Int J Clin Exp Pathol*. 2014;7(10):6419-6429.
46. Soini T, Hurskainen R, Grénman S, et al. Levonorgestrel-releasing intrauterine system and the risk of breast cancer: A nationwide cohort study. *Acta Oncol*. 2016;55(2):188-192.
47. Roberts H, Hickey M. The levonorgestrel-releasing intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen. *Maturitas*. 2016;89:1-2.
48. Black A, Guilbert E; Society of Obstetrician and Gynecologists of Canada. Canadian Contraception Consensus (Part 3 of 4): Chapter 8 - Progestin-Only Contraception. *J Obstet Gynaecol Can*. 2016;38(3):279-294.
49. Gérard C, Blanpain C, de Jésus I, et al. Estetrol is a natural estrogen with unique ERα-dependent actions in breast cancer cells. *Mol Cell Endocrinol*. 2016;422:93-101.
50. Benoit M, Coelingh Bennink HJ, Debrock S, et al. Estetrol acts as a selective nuclear estrogen receptor alpha modulator in the vagina. *Hum Reprod*. 2017;32(11):2203-2214.
51. Singer CF, Coelingh Bennink HJ, Natter C. The effect of estetrol on apoptosis and proliferation markers in human breast cancer tissue. *Climacteric*. 2021;24(2):152-158.

