

# Hormonal Contraception and Breast Cancer Risk: Balancing Benefits and Vigilance

*by* Jana Publication & Research

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# Hormonal Contraception and Breast Cancer Risk: Balancing Benefits and Vigilance

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## Abstract:

Hormonal contraception represents one of the most significant advancements in reproductive health, offering reliable pregnancy prevention and additional benefits such as menstrual cycle regulation and reduction of certain gynecological cancer risks. However, its potential association with breast cancer has been the focus of ongoing research and debate. Current evidence suggests a modest, reversible increase in breast cancer risk during use, with risk magnitude influenced by duration of exposure, hormonal formulation, and genetic susceptibility. Progestin-containing methods, whether combined or progestin-only, appear to play a central role through mechanisms involving progesterone receptor-mediated breast cell proliferation. Women carrying BRCA1/2 mutations may face a greater relative risk, though this must be balanced against the substantial protective effect of hormonal contraception against ovarian cancer. Despite these associations, the absolute risk for most women remains low. Clinical decision-making should be individualized, integrating patient history, genetic background, and personal preferences, with clear communication of both potential risks and health benefits.

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## Introduction:

Hormonal contraception is one of the major advances in reproductive health, providing highly effective pregnancy prevention while also offering non-contraceptive benefits such as cycle regulation and relief from menstrual pain [1]. Beyond its contraceptive role, it is also prescribed for important medical reasons, including the management of menstrual cycle disorders, endometriosis, and other gynecological conditions. However, its use has sparked ongoing debate about a potential link to breast cancer risk. Large international analyses indicate that this risk may vary depending on the duration of use, hormonal composition, and timing of exposure [2]. In light of these data, current guidelines recommend an individualized approach to contraceptive choice, tailored to each woman's risk profile, health status, and personal preferences, supported by comprehensive contraceptive counselling to ensure informed and shared decision-making [3].

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## <sup>21</sup> Breast Cancer Risk in the General Population:

<sup>2</sup> Breast cancer remains the most common cancer among women worldwide, with an estimated 2.3 million new cases diagnosed each year [4]. While most cases occur in women without high-risk genetic mutations, many factors, including genetics, reproductive history, and lifestyle, affect baseline risk [4]. Hormonal contraception, widely used both for pregnancy prevention and for its non-contraceptive benefits, has been associated with a small and reversible increase in breast cancer risk during use [2].

In 2023, a large meta-analysis by Torres-de la Roche and colleagues combined results from 22 observational studies, including both cohort and case-control designs, carried out between 2015 and 2022 in different countries. Overall, they found that women who had ever used hormonal contraception had about a 33% higher chance of developing breast cancer compared with women who had never used it (OR 1.33; 95% CI: 1.19–1.49). This increase was more noticeable in premenopausal women and in case-control studies, but the authors cautioned that differences between study designs and populations mean the results should be interpreted carefully [4].

These findings are partly supported by a large Swedish cohort study that followed about 1.5 million women for over 14 million person-years. This study found no significant rise in breast cancer risk among users of combined hormonal contraceptives (IRR  $\approx$  1.03), but did see a higher risk in women using progestin-only methods (IRR  $\approx$  1.32). The increased risk was most evident in the first five years of use and gradually returned to normal within about ten years after stopping [5].

Taken together, the evidence suggests that hormonal contraception, especially progestin-only methods, may slightly increase breast cancer risk, particularly with longer use. However, the absolute risk remains small and tends to fade over time once the contraception is discontinued [6].

Recent research examining long-acting progestin-only contraceptives, such as subdermal implants, depot medroxyprogesterone injections, and levonorgestrel-releasing intrauterine devices (LNG-IUD), has found a modest increase in breast cancer risk among premenopausal women, generally in the range of 20–30% relative risk [1–3]. Large-scale data from the Danish national registry reported a relative risk of 1.21 (95% CI: 1.11–1.33) for LNG-IUD users [2], which corresponds to a small absolute increase in cases, approximately 14 additional cases per 10,000 women over several years of use. This elevated risk appears to decline progressively after discontinuation [6]. Importantly, the absolute risk remains low, especially in younger women, and must be considered in light of the significant non-contraceptive benefits these methods offer, including menstrual regulation and reduction of certain gynecologic cancer risks [7].

Biologically, progestins appear to be central to this relationship: prolonged exposure can continuously activate progesterone receptors, stimulating mammary epithelial cell proliferation and potentially promoting a shift toward the more aggressive luminal B tumor phenotype [8]. They may also enhance the breast tissue's sensitivity to growth signals such as epidermal growth factor, which could accelerate the transition from precancerous changes to invasive disease [9].

Overall, while hormonal contraceptive use, particularly progestin-based methods, may be linked to a modest increase in relative breast cancer risk, the absolute increase remains small. These findings must be interpreted alongside the substantial benefits these methods offer, including reliable contraception, menstrual cycle regulation, and a reduced risk of certain gynecologic cancers. For most women, the overall health advantages continue to outweigh the potential risks when contraceptive choices are individualized and regularly reassessed [2–6].

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### Effect of Duration of Use:

Multiple studies suggest that the relative risk of breast cancer associated with hormonal contraception rises slightly with longer periods of continuous use. Data from the Collaborative Group on Hormonal Factors in Breast Cancer show that after 1 to 4 years of continuous use, the increase in risk is modest ( $RR \approx 1.09$ , or 9% higher than non-users), rising to about 1.19 after 5 to 9 years of use, and reaching approximately 1.38 after 10 years or more. Importantly, this elevated risk gradually declines after discontinuation, returning close to baseline levels within 5 to 10 years. [2].

A recent meta-analysis involving over nine million women confirmed that the slight increase in breast cancer risk linked to hormonal contraception diminishes progressively once the method is discontinued. In most women, this risk returns to a level similar to that of never-users within about five years. However, in cases of long-term use, especially beyond a decade, the return to baseline may take closer to ten years. Importantly, the study also underlined that the absolute number of additional cases remains small, particularly among women under 35 years of age [2,6].

These findings highlight the importance of considering the total cumulative duration of use when counseling on contraception, especially for women with additional breast cancer risk factors [1].

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### Biological Mechanisms Linking Hormonal Contraception to Breast Cancer:

Current evidence suggests that the breast cancer risk associated with hormonal contraception is broadly similar across different delivery methods, including oral pills, implants, injectable formulations, and levonorgestrel-releasing intrauterine systems (LNG-IUS) [6]. A large recent cohort study (Tueley et al., *JNCI*, 2025) reported an average 25% relative increase in breast cancer risk among users of long-acting progestin-only implants or injectables, confirming earlier meta-analytic findings on progestin-only contraceptives [8].

Progestins, rather than estrogens, appear to play a central role in promoting breast epithelial cell proliferation. Recent reviews, such as Kim (2025), emphasize that chronic activation of progesterone receptors (PRs) can drive this proliferative effect [9], potentially favoring the emergence of more aggressive tumor subtypes like luminal B, characterized by rapid growth and poorer prognosis compared to luminal A tumors [10].

Experimental studies have also shown that progestins can alter the local hormonal environment, increasing breast tissue sensitivity to growth signals such as epidermal growth factors (EGF), potentially enhancing the development of precancerous lesions [3,8]. These effects appear to be amplified with prolonged exposure, aligning with epidemiological observations of a cumulative duration effect on breast cancer risk.

While the absolute risk remains small, these data underscore the importance of carefully weighing the benefits and risks of progestin-only methods, particularly in women with other established breast cancer risk factors [6,9].

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### Hormonal Contraception in Women at High Genetic Risk (BRCA1/BRCA2):

Research shows that hormonal contraception does not affect all women with genetic predispositions in the same way. In a large prospective study, Phillips et al. (2025) found that women carrying a BRCA1 mutation faced a noticeable rise in breast cancer risk, particularly when contraceptives were used for many years. By contrast, no significant association was observed among BRCA2 carriers, suggesting that the two mutations may not respond to hormonal exposure in the same manner [11].

Les revues systématiques et les méta-analyses récentes montrent que l'impact de la contraception hormonale sur le risque de cancer du sein est plus marqué chez les femmes porteuses d'une mutation BRCA1. Les travaux de van Bommel et coll. (2023) [12] et de Baranska et coll. (2022) [13] soulignent notamment que certains éléments, comme l'âge auquel la contraception est débutée, surtout après 20 ans, ainsi que la durée cumulée d'utilisation, jouent un rôle dans cette association. Même si l'augmentation absolue du risque reste relativement faible en comparaison avec le risque déjà élevé lié aux mutations BRCA, ces résultats rappellent l'importance d'un conseil contraceptif personnalisé. Pour ces femmes, la discussion doit trouver un équilibre entre efficacité contraceptive et gestion du risque oncologique à long terme, idéalement dans un cadre multidisciplinaire associant génétique et oncologie.

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### Beyond Current Guidelines: The Role of Epigenetics in Personalized Contraception

Current contraceptive guidelines are still largely based on general recommendations. However, recent advances in epigenetics and molecular biology open the door to a new way of approaching this issue. Emerging evidence shows that certain biological markers, such as DNA methylation patterns [14], histone modifications, and microRNA expression [15], are associated with early alterations in breast tissue as well as differences in hormonal sensitivity among women.

When these biomarkers are considered alongside well-established risk factors, such as BRCA1/2 mutations [16,17], family history, or reproductive background [18], the concept of a truly personalized contraceptive strategy becomes conceivable. In this model, contraceptive choice would no longer rely solely on standardized guidelines, but rather on the individual's own "biological signature" [19–20]. The goal would be twofold: to ensure effective contraceptive protection while also minimizing the risk of cancer.

Although this precision-based approach has not yet entered routine clinical practice, it represents a promising direction for the next decade in reproductive health and cancer prevention.

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### Conclusion:

Hormonal contraception is a safe and effective option that not only prevents pregnancy, but also helps protect against ovarian and endometrial cancers. While it may slightly raise the risk of breast cancer in some women, especially with BRCA mutations or long use, this risk is usually small and temporary.

In the future, progress in genetics and epigenetics could allow contraception to be tailored to each woman's unique biology. This would make it possible to choose methods that offer strong protection while keeping cancer risks as low as possible.

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