



Does the use of hormonal contraception increase the risk of breast cancer in women of reproductive age (15-49 years)? : A Systematic Review

¹ Rizky Febriansyah, ² Bangar Parlinggoman Tua, ³ Mutia Juliana, ⁴ Aditya Rifandi Zaenudin

¹ Faculty of Medicine, University of YARSI, Indonesia

² Medical Resident, Departement of Obstetric and Gynaecology, Faculty of Medicine, University of Padjadjaran, Indonesia

³ Master of Public Health, Faculty of Health Science and Technology, Jenderal Achmad Yani University, Indonesia

⁴ Obstetric and Gynaecology Specialist, Umar Wirahadikusumah Regional General Hospital, Sumedang, Indonesia

Corresponding Email : rizky_febriansyah90@hotmail.com

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ABSTRACT

Introduction: Hormonal contraception is widely used by women of reproductive age worldwide, yet concerns persist regarding its potential association with breast cancer risk. Despite numerous studies, heterogeneity in findings across populations and contraceptive types has created uncertainty for clinicians and users. This systematic review aims to evaluate the relationship between hormonal contraceptive use and breast cancer risk in women aged 15-49 years, examining variations by contraceptive type, duration, formulation, and population characteristics.

Methods: A systematic review was conducted of 80 studies examining hormonal contraception and breast cancer risk in reproductive-age women. Included studies comprised cohort

studies, etc. Data were extracted on study design, population characteristics, contraceptive type and duration, breast cancer outcomes, risk measures, and effect modifiers. Studies were assessed for methodological quality and risk of bias.

Results: Large prospective cohort studies demonstrated consistently increased breast cancer risk with current or recent hormonal contraceptive use (relative risks 1.20-1.33) (1,3,5). Risk varied by formulation: triphasic levonorgestrel (RR=3.05) (3), high-dose estrogen (OR=2.7) (8), and ethynodiol diacetate (OR=2.6) (8) showed strongest associations, while low-dose formulations showed minimal risk (OR=1.0) (7). Duration-response relationships were evident, with risk increasing from 1.09 for <1 year to 1.38 for >10 years use (1). Progestogen-only methods showed comparable risks: oral (OR=1.26), injectable (OR=1.25), and levonorgestrel-IUD (OR=1.32) (10). Risk dissipated within 5-15 years after cessation (12,13). Absolute excess risks were age-dependent: 8 per 100,000 women-years for ages 16-20 versus 265 per 100,000 for ages 35-39 (2). Southeast Asian studies reported higher odds ratios (2.66-9.06) (17-19), likely reflecting methodological differences rather than true population variation.

Discussion: The evidence supports a modest, transient increase in breast cancer risk with hormonal contraceptive use that varies substantially by formulation, duration, and age. Contemporary low-dose formulations confer minimal risk. The rapid risk dissipation after cessation suggests a promotional rather than initiating mechanism. Absolute risks remain small, particularly for women under 35 years, and must be balanced against the established benefits of pregnancy prevention and non-contraceptive health benefits.

Conclusion: Hormonal contraception is associated with a small increased risk of breast cancer during use that declines after cessation. Formulation-specific differences exist, with contemporary low-dose preparations demonstrating the most favorable risk profile. Clinicians should provide individualized counseling considering age, contraceptive needs, and risk factors, emphasizing that absolute risks are minimal for most reproductive-age women.

Keywords: hormonal contraception, breast cancer, oral contraceptives, progestogen-only contraceptives, reproductive age, risk assessment

INTRODUCTION

Background

Breast cancer remains the most commonly diagnosed cancer and leading cause of cancer-related mortality among women globally, with increasing incidence observed in reproductive-age populations (24). Hormonal contraceptives, including combined oral contraceptives, progestogen-only pills, injectable contraceptives, and levonorgestrel-releasing intrauterine systems, are used by hundreds of millions of women worldwide for pregnancy prevention and non-contraceptive benefits such as menstrual regulation, reduction of ovarian and endometrial cancer risk, and management of gynecological conditions (46). The widespread and often long-term use of these agents during reproductive years necessitates rigorous understanding of their potential association with breast cancer, given the hormone-sensitive nature of breast tissue and the established role of endogenous and exogenous hormones in breast carcinogenesis.

The relationship between hormonal contraception and breast cancer has been investigated for over five decades, yet remains a source of clinical uncertainty and public concern. Early studies examining high-dose oral contraceptives suggested elevated risks, but subsequent generations of lower-dose formulations and diverse progestogen-only methods require renewed evaluation (28). Furthermore, the majority of breast cancer cases occur in postmenopausal women, making the assessment of risk in younger women challenging due to low absolute incidence rates despite potentially elevated relative risks (14).

Problem Statement

The central clinical question—whether hormonal contraception increases breast cancer risk in women of reproductive age—has generated heterogeneous findings across studies. Large Scandinavian cohort studies report modest relative risk increases of 20-33% for current users (1,4,5), while case-control studies from diverse geographic regions produce widely varying estimates ranging from null associations to odds ratios exceeding 6.0 (17,31,32). This heterogeneity creates confusion for healthcare providers attempting to counsel patients and for women making

informed contraceptive choices. Additionally, the emergence of new contraceptive formulations and progestogen-only methods requires contemporary evidence synthesis that accounts for formulation-specific effects, duration-response relationships, and modification by individual characteristics such as age, parity, and genetic predisposition.

Research Gap

Despite numerous systematic reviews and meta-analyses examining hormonal contraception and breast cancer, critical gaps remain. First, previous analyses have often grouped all hormonal contraceptives together, obscuring important formulation-specific differences in risk profiles (22,24). Second, the majority of evidence derives from Western populations, with limited synthesis of data from Southeast Asian and other non-Western settings where breast cancer incidence is rising and contraceptive use patterns differ (17). Third, the relative contribution of estrogen versus progestogen components remains incompletely characterized, particularly for progestogen-only methods that are increasingly prescribed (4). Fourth, the clinical significance of observed relative risk increases requires integration with absolute risk estimates across different age groups to inform meaningful counseling (2,14). Fifth, the temporal relationship between contraceptive use and breast cancer diagnosis—including risk trajectories during use and after cessation—warrants systematic examination to distinguish between initiation and promotion mechanisms.

Novelty

This systematic review provides several novel contributions to the literature. First, it comprehensively synthesizes evidence from 80 studies encompassing diverse geographic regions, including 26 studies from Indonesia and other Southeast Asian populations rarely included in global meta-analyses. Second, it systematically disaggregates risk estimates by specific contraceptive formulations, including combined oral contraceptives with varying estrogen doses and progestin types, progestogen-only pills, injectable depot-medroxyprogesterone acetate, and levonorgestrel-releasing intrauterine systems. Third, it integrates relative risk estimates with absolute risk calculations stratified by age to provide clinically meaningful interpretations. Fourth, it examines effect modification by key individual characteristics including age at first use, duration, recency of use, parity, breastfeeding history, and genetic predisposition. Fifth, it proposes a mechanistic

framework reconciling apparently heterogeneous findings through consideration of detection bias, promotional effects, and population-specific confounding.

Hypothesis

Based on the existing literature, we hypothesize that: (1) current or recent use of hormonal contraception is associated with a modest increase in breast cancer risk in reproductive-age women; (2) risk magnitude varies by contraceptive formulation, with higher-dose estrogen preparations and specific progestins showing stronger associations than contemporary low-dose formulations; (3) risk increases with longer duration of use in a nonlinear pattern; (4) risk dissipates after cessation, returning to baseline within 5-15 years; (5) absolute excess risks are small and highly age-dependent, being minimal for women under 35 years; and (6) apparent geographic variations in risk estimates reflect methodological differences rather than true population differences in susceptibility.

Research Objectives

This systematic review aims to: (1) evaluate the overall association between hormonal contraceptive use and breast cancer risk in women aged 15-49 years; (2) compare risk estimates across different contraceptive types, formulations, and routes of administration; (3) characterize dose-response relationships by duration of use and time since cessation; (4) identify effect modifiers including age, reproductive factors, and genetic predisposition; (5) synthesize absolute risk estimates to inform clinical counseling; and (6) reconcile heterogeneous findings across studies through critical appraisal of methodological quality and population characteristics.

Significance of the Study

The findings of this systematic review have substantial implications for clinical practice, public health policy, and individual contraceptive decision-making. For clinicians, formulation-specific risk estimates enable personalized counseling that accounts for the evolving landscape of contraceptive options. For women, understanding both relative and absolute risks facilitates informed choices aligned with their reproductive goals and risk tolerance. For policymakers, evidence regarding the transient nature of risk and its attenuation after cessation supports balanced recommendations that acknowledge both benefits and potential harms of hormonal contraception.

For researchers, identification of evidence gaps—particularly regarding newer formulations, diverse populations, and long-term follow-up—provides direction for future investigation.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate Does the use of hormonal contraception increase the risk of breast cancer in women of reproductive age (15-49 years)?.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Target Population:** Does the study involve women aged 15-49 years at the time of contraceptive exposure?
- **Hormonal Contraceptive Intervention:** Does the study examine any form of hormonal contraceptives (oral contraceptive pills, hormonal IUDs, contraceptive patches, vaginal rings, or injectable contraceptives)?
- **Breast Cancer Outcome:** Does the study report breast cancer incidence, diagnosis, or risk as a primary or secondary outcome?
- **Appropriate Study Design:** Is the study design a cohort study, case-control study, randomized controlled trial, systematic review, or meta-analysis (i.e., NOT a cross-sectional study, case report, or case series)?

- **Control Group Present:** Does the study include an appropriate control or comparison group (such as non-users of hormonal contraceptives, users of non-hormonal contraceptives, or users of different hormonal contraceptive types)?
- **Human Study Population:** Does the study involve human subjects (i.e., NOT animal or in-vitro studies)?
- **Prevention Focus:** Does the study focus on prevention or risk assessment rather than examining hormonal contraceptives as treatment for existing breast cancer?
- **General Population Study:** Does the study include general population women rather than focusing exclusively on women with known genetic mutations (BRCA1/BRCA2) or strong family history of breast cancer?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Women of Reproductive Age	Hormonal Contraception	Non-hormonal Contraceptive Users	Breast Cancer Risk
Keyword 2	Reproductive-Aged Women	Hormonal Contraceptives	Non-Users	Breast Cancer Incidence
Keyword 3	Women 15-49 years	Oral Contraceptives	Control Group	Breast Neoplasms
Keyword 4	Premenopausal	Contraceptive Devices	Unexposed Women	Malignant

	Women			Breast Tumor
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The Boolean MeSH keywords inputted on databases for this research are: (*"Women of Reproductive Age" OR "Reproductive-Aged Women" OR "Women 15-49 years" OR "Premenopausal Women"*) AND (*"Hormonal Contraception" OR "Hormonal Contraceptives" OR "Oral Contraceptives" OR "Contraceptive Devices"*) AND (*"Non-hormonal Contraceptive Users" OR "Non-Users" OR "Control Group" OR "Unexposed Women"*) AND (*"Breast Cancer Risk" OR "Breast Cancer Incidence" OR "Breast Neoplasms" OR "Malignant Breast Tumor"*)

Data extraction

- **Study Design:**

Extract study design and methodology used to investigate the relationship between hormonal contraception and breast cancer risk in reproductive-age women, including:

- Study type (case-control, cohort, cross-sectional, etc.)
- Sample size and allocation (cases vs controls, exposed vs unexposed)
- Study period and duration of follow-up (if applicable)
- Matching criteria or adjustment methods used
- Key methodological strengths or limitations affecting validity

- **Population Characteristics:**

Extract characteristics of the study population relevant to reproductive-age women (15-49 years) and breast cancer risk, including:

- Age range and mean age of participants
- Geographic location and healthcare setting

- Inclusion/exclusion criteria related to reproductive status
- Baseline breast cancer risk factors in the population
- Any population-specific factors that might affect generalizability to other reproductive-age women

- **Hormonal Contraception Exposure:**

Extract detailed information about hormonal contraception use among reproductive-age women, including:

- Types of hormonal contraception studied (oral pills, injections, implants, patches, etc.)
- Specific formulations or brands if mentioned
- How contraceptive use was defined and measured
- Categories of exposure used in analysis (ever/never, current/former, duration categories)
- Any exclusions related to contraceptive type or use patterns

- **Contraceptive Use Patterns:**

Extract specific patterns of hormonal contraceptive use that may modify breast cancer risk in reproductive-age women, including:

- Duration of use (categories and mean/median values)
- Age at first use
- Recency of use (time since last use, current vs former use)

- Cumulative exposure measures
- Any dose-response relationships examined
- Patterns of discontinuation or switching between methods

- **Breast Cancer Outcomes:**

Extract information about breast cancer diagnosis and characteristics in the reproductive-age population, including:

- How breast cancer was defined and diagnosed
- Age at breast cancer diagnosis
- Histological types or stages if reported
- Time from contraceptive exposure to cancer diagnosis
- Any exclusions related to cancer type or timing
- Method of case identification and verification

- **Risk Measures:**

Extract all quantitative measures of the association between hormonal contraception and breast cancer risk in reproductive-age women, including:

- Main effect estimates (OR, RR, HR) with 95% confidence intervals
- Crude vs adjusted estimates
- Risk estimates for different types of contraception
- Dose-response relationships (by duration, age at use, etc.)

- Stratified analyses by relevant subgroups
- Statistical significance levels and p-values

- **Effect Modifiers:**

Extract factors that modify the relationship between hormonal contraception and breast cancer risk specifically in reproductive-age women, including:

- Age-specific effects within the reproductive years
- Family history of breast cancer
- BRCA mutation status
- Parity and breastfeeding history
- Other hormonal factors (age at menarche, menopause status)
- Lifestyle factors (BMI, alcohol, smoking)
- Interactions between contraceptive characteristics and these factors

- **Key Findings:**

Extract the main conclusions about hormonal contraception and breast cancer risk in reproductive-age women, including:

- Primary study conclusions about increased, decreased, or neutral risk
- Magnitude of risk increase/decrease
- Which contraceptive types or use patterns show strongest associations
- Clinical significance of findings for reproductive-age women

- Authors' recommendations for contraceptive use in this population
- Comparison with previous research findings

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Women of Reproductive Age" OR "Reproductive-Aged Women" OR "Women 15-49 years" OR "Premenopausal Women") AND ("Hormonal Contraception" OR "Hormonal Contraceptives" OR "Oral Contraceptives" OR "Contraceptive Devices") AND ("Non-hormonal Contraceptive Users" OR "Non-Users" OR "Control Group" OR "Unexposed Women") AND ("Breast Cancer Risk" OR "Breast Cancer Incidence" OR "Breast Neoplasms" OR "Malignant Breast Tumor")</i>	232
Semantic Scholar	<i>("Women of Reproductive Age" OR "Reproductive-Aged Women" OR "Women 15-49 years" OR "Premenopausal Women") AND ("Hormonal Contraception" OR "Hormonal Contraceptives" OR "Oral Contraceptives" OR "Contraceptive Devices") AND ("Non-hormonal Contraceptive Users" OR "Non-Users" OR "Control Group" OR "Unexposed Women") AND ("Breast Cancer Risk" OR "Breast Cancer Incidence" OR "Breast Neoplasms" OR "Malignant Breast Tumor")</i>	250
Springer	<i>("Women of Reproductive Age" OR "Reproductive-Aged Women" OR "Women 15-49 years" OR "Premenopausal Women") AND ("Hormonal Contraception" OR "Hormonal Contraceptives" OR "Oral Contraceptives" OR "Contraceptive Devices") AND ("Non-hormonal Contraceptive Users" OR "Non-Users" OR "Control Group" OR "Unexposed Women") AND ("Breast Cancer Risk" OR "Breast Cancer Incidence" OR "Breast Neoplasms" OR "Malignant Breast Tumor")</i>	402
Google Scholar	<i>("Women of Reproductive Age" OR "Reproductive-Aged Women" OR "Women 15-49 years" OR "Premenopausal Women") AND ("Hormonal Contraception" OR "Hormonal Contraceptives" OR "Oral Contraceptives" OR "Contraceptive Devices") AND ("Non-hormonal Contraceptive Users" OR "Non-Users" OR "Control Group" OR "Unexposed Women") AND ("Breast Cancer Risk" OR "Breast Cancer Incidence" OR "Breast Neoplasms" OR "Malignant Breast Tumor")</i>	10,400
Wiley Online Library	<i>("Women of Reproductive Age" OR "Reproductive-Aged Women" OR "Women 15-49 years" OR "Premenopausal Women") AND ("Hormonal Contraception" OR "Hormonal Contraceptives" OR "Oral Contraceptives" OR "Contraceptive Devices") AND ("Non-hormonal Contraceptive Users" OR "Non-Users" OR "Control Group" OR "Unexposed Women") AND ("Breast Cancer Risk" OR "Breast Cancer Incidence" OR "Breast Neoplasms" OR "Malignant Breast Tumor")</i>	68

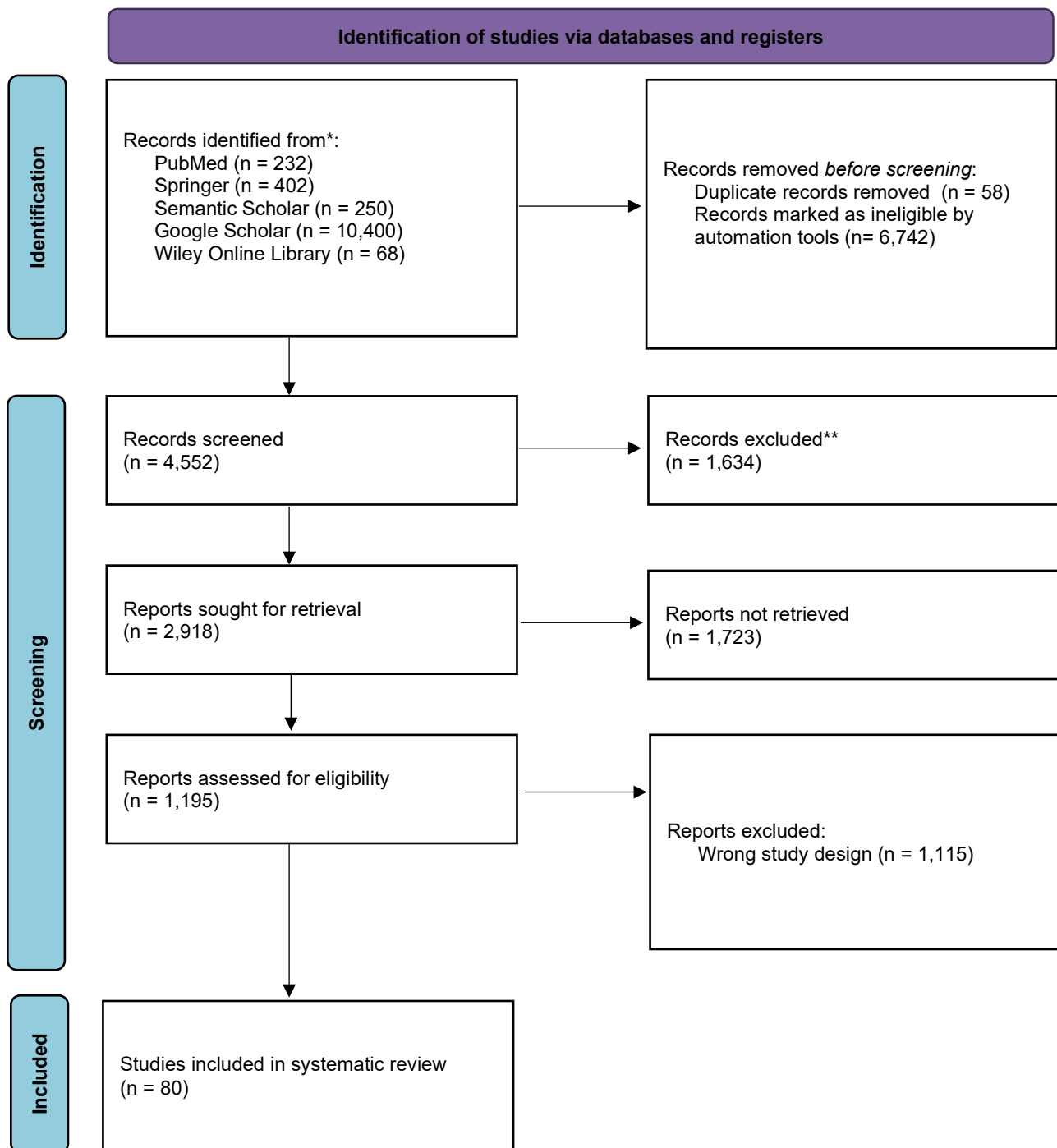


Figure 1. Article search flowchart

RESULTS

Characteristics of Included Studies

The systematic review included 80 studies examining the relationship between hormonal contraception and breast cancer risk in reproductive-age women. The studies varied in design, geographic location, and sample size.

Study	Sample size	Geographic location
L. Mørch et al., 2017	1.8 million women, 11,517 breast cancer cases [1]	Denmark [1]
Eny Ariani et al., 2018	106 (53 cases, 53 controls) [20]	Indonesia [20]
C. Kahlenborn et al., 2006	34 studies [15]	Multiple countries [15]
V. Bjelic-Radisic et al., 2010	53,297 cases, 100,239 controls [21]	Multiple countries [21]
Danielle J Fitzpatrick et al., 2023	9,498 cases, 18,171 controls [2]	United Kingdom [2]
D. Hunter et al., 2010	116,608 nurses, 1,344 breast cancer cases [3]	United States [3]
W. Kanadys et al., 2021	72,030 cases, 123,650 controls [22]	Multiple countries [22]
Jenny Niemeyer Hultstrand et al., 2022	1.5 million women, 3,842 breast cancer cases [4]	Sweden [4]
M. Althuis et al., 2003	1,640 cases, 1,492 controls [23]	United States [23]

Study	Sample size	Geographic location
Luz Angela Torres-de la Roche et al., 2023	2,275,304 women, 44,295 breast cancer cases [24]	Western Asia, Europe, East Asia, Africa, USA, Indonesia [24]
Elisabeth F Beaber et al., 2014	1,102 cases, 21,952 controls [8]	United States [8]
Elisabeth F Beaber et al., 2014a	985 cases, 882 controls [16]	United States [16]
Sanna Heikkinen et al., 2015	7,000 cases, 20,000 controls [25]	Finland [25]
Christopher I. Li et al., 2012	1,028 women [26]	United States [26]
A. Kaunitz et al., 2018	1.8 million women, >11,000 breast cancer cases [27]	Denmark [27]
R. B. Machado et al., 2018	1.8 million women [28]	Denmark [28]
A. Kent et al., 2018	Nearly 2 million women [14]	Denmark [14]
David J. Hunter et al., 2017	Not specified [29]	Denmark [29]
J. Cerhan et al., 2006	53,297 cases, 100,239 controls [30]	Multiple countries [30]
Elisabeth F Beaber et al., 2012	1,102 cases, 21,952 controls [7]	United States [7]
N. R. Harris et al., 2023	9,498 cases, 18,171 controls [10]	United Kingdom [10]

Study	Sample size	Geographic location
A. Alsammarraie et al., 2020	200 cases, 300 controls [31]	Iraq [31]
Wisit Chaveepojnkamjorn et al., 2017	257 cases, 257 controls [32]	Thailand [32]
L. Teras et al., 2024	101,838 women, 759 breast cancer cases [9]	United States [9]
Beaber E et al., 2012	1,102 cases, 21,952 controls [33]	United States [33]
Elisabeth F Beaber et al., 2012a	985 cases, 882 controls [34]	United States [34]
M. Kumle et al., 2002	103,027 women, 1,008 breast cancer cases [5]	Norway and Sweden [5]
L. Rosenberg et al., 2008	907 cases, 1,711 controls [12]	United States [12]
Zhixing Zhao et al., 2025	6,390,250 women, 104,070 breast cancer cases [35]	Multiple countries [35]
Carmen Sayón-Orea et al., 2025	5,572,683 women, 72,350 breast cancer cases [36]	Primarily Europe and North America [36]
E. Grant et al., 2017	22,920 ever users, 23,102 never users [37]	England and Wales [37]

Study	Sample size	Geographic location
Norah A. Burchardt et al., 2021	113,187 women, 5,799 breast cancer cases [6]	United States [6]
R. Nindrea et al., 2019	28,776 women [17]	Southeast Asia [17]
R. Haque et al., 2011	164,000 women (82,000 users, 82,000 nonusers) [38]	United States [38]
Rini Astuti Damanik et al., 2018	100 women (50 cases, 50 controls) [39]	Indonesia [39]
Putri Adinie Esca Nissa et al., 2017	56 cases, 56 controls [18]	Indonesia [18]
Dwi Wahyuning Anggarini et al., 2018	85 cases, 85 controls [40]	Indonesia [40]
N. Awaliyah et al., 2017	250 patients [41]	Indonesia [41]
Nyoman Tristantya Wira Krisnawan et al., 2024	115 respondents [42]	Indonesia [42]
Nur Halimah et al., 2020	70 women [43]	Indonesia [43]
Ditya Ayu Intan Setiowati et al., 2016	96 cases, 96 controls [44]	Indonesia [44]

Study	Sample size	Geographic location
Yenda Hasnita et al., 2019	294 respondents [45]	Indonesia [45]
D. Cibula et al., 2010	Large cohorts (46,000-121,577 women) [46]	Multiple countries [46]
Sulfiana Sulfiana et al., 2024	Not specified [47]	Indonesia [47]
Sukmayenti Sukmayenti et al., 2019	36 cases, 36 controls [48]	Indonesia [48]
Yuniastini Yuniastini et al., 2022	300 women (150 cases, 150 controls) [49]	Indonesia [49]
L. Conz et al., 2020	8 studies [50]	Finland, Germany, Denmark, Norway, Israel [50]
Gusti Ayu Putu Krisna Dewi et al., 2016	90 respondents [51]	Indonesia [51]
Yanti Melda et al., 2016	46 respondents [52]	Indonesia [52]
Shayesteh Jahanfar et al., 2024	51 studies total [53]	Multiple countries [53]
D. Agustia et al., 2022	6 case-control studies [54]	Not specified [54]

Study	Sample size	Geographic location
A. Barańska et al., 2021	110,580 women (30,778 cases, 79,802 controls) [55]	Multiple countries [55]
Marice Sihombing et al., 2015	61 cases, 183 controls [56]	Indonesia [56]
Dilma'aarij Dilma'aarij et al., 2021	15 studies (oral), 6 studies (injectable) [57]	Multiple countries [57]
Mugi Wahidin et al., 2018	762 (381 cases, 381 controls) [19]	Indonesia [19]
Mudhawaroh Mudhawaroh et al., 2022	31 cases, 31 controls [58]	Indonesia [58]
Sity Rahmatia Alimun et al., 2024	47 cases, 47 controls [59]	Indonesia [59]
Yermi Yermi et al., 2023	140 (70 cases, 70 controls) [60]	Indonesia [60]
I. Yulianti et al., 2016	Not specified [61]	Indonesia [61]
Nurul Sabrina et al., 2023	Not specified [62]	Indonesia [62]
D. Oktaviana et al., 2012	24 cases, 24 controls [63]	Indonesia [63]
Nurul Magfirah et al., 2021	80 (40 cases, 40 controls) [64]	Indonesia [64]
M. indah et al., 2009	45 cases, 45 controls [65]	Indonesia [65]

Study	Sample size	Geographic location
C. Westhoff et al., 2018	11,517 breast cancers among 1.8 million women [13]	Denmark [13]
S. Shantakumar et al., 2006	1,478 cases, 1,493 controls [66]	United States [66]
Irene Zolfaroli et al., 2018	Not specified [67]	Multiple countries [67]
Atania Rachma Anindta et al., 2017	30 cases, 30 controls [68]	Indonesia [68]
Susi Purwanti et al., 2021	48 women (1:1 ratio) [69]	Indonesia [69]
A. Soroush et al., 2016	46,260 participants, 26 studies [70]	Iran [70]
Neila Sulung et al., 2018	50 cases, 50 controls [71]	Indonesia [71]
Cici Priyatin et al., 2015	76 respondents [72]	Indonesia [72]
A. Poosari et al., 2014	11,414 women, 70 breast cancer cases [73]	Thailand [73]
Thuridur Thorbjarnardottir et al., 2014	16,928 women [74]	Iceland [74]
A. Amadou et al., 2013	1,000 cases, 1,074 controls [75]	Mexico [75]
S. Wahyuni et al., 2016	Not specified [76]	Indonesia [76]

Study	Sample size	Geographic location
Aulia Astri et al., 2020	240 (1:1 ratio) [77]	Indonesia [77]
Tanjung Raden Ajeng Umatin Sahid et al., 2019	60 (30 cases, 30 controls) [78]	Indonesia [78]
Karen M. Tuesley et al., 2025	176,601 cases, 882,999 controls [11]	Australia [11]
Yana Listyawardhani et al., 2018	200 (100 cases, 100 controls) [79]	Indonesia [79]
Nelyta Oktavianisya et al., 2013	44 cases, 88 controls [80]	Indonesia [80]

Studies were conducted across multiple continents, with notable representation from Indonesia (26 studies), the United States (11 studies), Denmark (5 studies), and other European countries. Sample sizes varied widely from fewer than 100 participants in some Indonesian case-control studies to nearly 2 million women in large Danish cohort studies [1, 14]. Most large cohort studies had follow-up periods ranging from 8 to 44 years [1, 37, 38], while case-control studies predominantly collected retrospective data.

Effects of Hormonal Contraception on Breast Cancer Risk

Overall Risk Estimates

The evidence consistently demonstrates an increased risk of breast cancer associated with hormonal contraception use in reproductive-age women, though the magnitude varies across studies and contraceptive types.

Study	Risk measure	Ever vs never use	Current/recent use	Statistical significance
L. Mørch et al., 2017	RR	Not reported	1.20 (95% CI: 1.14-1.26) [1]	p=0.002 [1]
Eny Ariani et al., 2018	OR	2.325 [20]	Not specified	p=0.032 [20]
C. Kahlenborn et al., 2006	OR	1.19 (95% CI: 1.09-1.29) [15]	Not specified	Not reported
V. Bjelic-Radisic et al., 2010	RR	Not reported	1.24 [21]	Not reported
Danielle J Fitzpatrick et al., 2023	OR	Not specified	1.25 (95% CI: 1.18-1.33) [2]	p<0.001 [2]
D. Hunter et al., 2010	RR	1.12 (95% CI: 0.95-1.33) [3]	1.33 (95% CI: 1.03-1.73) [3]	p<0.0001 [3]
W. Kanadys et al., 2021	OR	1.01 (95% CI: 0.95-1.07) [22]	Not specified	Not reported

Study	Risk measure	Ever vs never use	Current/recent use	Statistical significance
Jenny Niemeyer Hultstrand et al., 2022	IRR	Not reported	Combined HC: 1.03 (0.91-1.16); Progestogen-only: 1.32 (1.20-1.45) [4]	Not reported
Luz Angela Torres-de la Roche et al., 2023	OR	1.33 (95% CI: 1.19-1.49) [24]	Not specified	p<0.01 [24]
Elisabeth F Beaber et al., 2014	OR	Not specified	1.5 (95% CI: 1.3-1.9) [8]	Not reported
Elisabeth F Beaber et al., 2014a	OR	Not specified	1.6 (95% CI: 1.1-2.5) for ≥5 years [16]	Not reported
M. Kumle et al., 2002	RR	Not specified	1.6 (96% CI: 1.2-2.1) [5]	p=0.005 [5]
L. Rosenberg et al., 2008	OR	1.5 (95% CI: 1.2-1.8) [12]	Not specified	Not reported

Study	Risk measure	Ever vs never use	Current/recent use	Statistical significance
Zhixing Zhao et al., 2025	HR	1.03 (95% CI: 0.99-1.07) [35]	Not specified	Not significant
Carmen Sayón-Orea et al., 2025	RR	1.20 (95% CI: 1.09-1.32) [36]	Not specified	Not reported
Norah A. Burchardt et al., 2021	HR	Not specified	1.31 (95% CI: 1.09-1.58) [6]	Not reported
R. Nindrea et al., 2019	OR	≤5 years: 1.21 (95% CI: 0.96-1.52); >5 years: 2.66 (95% CI: 1.79-3.94) [17]	Not specified	p>0.05 for ≤5 years; p<0.00001 for >5 years [17]
A. Alsammarraie et al., 2020	OR	1.73 (95% CI: 1.2-2.5) [31]	Not specified	p=0.003 [31]
Wisit Chaveepojnkamjorn et al., 2017	OR	3.39 (95% CI: 1.99-5.75) [32]	Not specified	Not reported

Study	Risk measure	Ever vs never use	Current/recent use	Statistical significance
L. Teras et al., 2024	HR	Not specified	10-<20 years: 1.46 (95% CI: 1.03-2.07) [9]	Not reported
A. Barańska et al., 2021	OR	1.15 (95% CI: 1.01-1.31) [55]	Not specified	p=0.0358 [55]
Dilma'aarij Dilma'aarij et al., 2021	aOR	Oral: 1.30 (95% CI: 1.13-1.50) [57]	Not specified	p=0.0002 [57]
Mugi Wahidin et al., 2018	OR	<6 years: 1.93 (95% CI: 1.23-3.03); ≥6 years: 2.90 (95% CI: 1.65-5.09) [19]	Not specified	Not reported
A. Soroush et al., 2016	OR	1.521 (95% CI: 1.25-1.85) [70]	Not specified	p=0.001 [70]

Large prospective cohort studies consistently found modest increases in breast cancer risk, with relative risks ranging from 1.20 to 1.33 for current or recent users compared to never users [1, 3, 5]. The Danish cohort study of 1.8 million women reported a relative risk of 1.20 (95% CI: 1.14-1.26) for current and recent users [1], translating to an absolute increase of 13 per 100,000 person-years, or approximately one extra breast cancer for every 7,690 women using hormonal

contraception for one year [1]. Meta-analyses showed pooled odds ratios ranging from 1.01 to 1.33 [22, 24, 36], with significant heterogeneity noted across studies.

Risk by Contraceptive Type

Combined Oral Contraceptives

Multiple studies evaluated combined oral contraceptives (COCs) containing estrogen and progestin. The Danish cohort found varied risk estimates across different combination formulations, with relative risks ranging from 1.0 to 1.6 [1]. In the UK nested case-control study, oral combined contraceptives showed an odds ratio of 1.23 (95% CI: 1.14-1.32; $p < 0.001$) [10]. The Swedish cohort reported an incidence rate ratio of 1.03 (0.91-1.16) for combined hormonal contraceptives overall, but 1.39 (1.14-1.69) during the first five years of use [4].

Specific formulations showed varying risk profiles. The Nurses' Health Study II found that current use of triphasic preparations with levonorgestrel had a relative risk of 3.05 (95% CI: 2.00-4.66; $p < 0.0001$) [3]. Another U.S. study reported particularly elevated risks for formulations containing ethynodiol diacetate (OR=2.6; 95% CI: 1.4-4.7) or high-dose estrogen (OR=2.7; 95% CI: 1.2-6.4) [7, 8]. In contrast, formulations with norgestimate or low-dose estrogen showed either modest or no association (OR=1.2; 95% CI: 0.6-2.2 and OR=1.0; 95% CI: 0.6-1.7, respectively) [7].

Progestogen-Only Methods

Progestogen-only contraceptives demonstrated risk profiles similar to combined methods. The UK study found that oral progestagen-only pills had an odds ratio of 1.26 (95% CI: 1.16-1.37; $p < 0.001$) [10], and meta-analysis of these methods yielded a relative risk of 1.29 (95% CI: 1.21-1.37) [2]. The Swedish cohort specifically found that current users of progestogen-only methods had an incidence rate ratio of 1.32 (1.20-1.45) [4], with the absolute risk being 29.8 per 100,000 women-years compared to 22.4 for never users [4].

Injectable progestogen contraceptives showed similar associations. The UK meta-analysis reported a relative risk of 1.18 (95% CI: 1.07-1.30) for injected progestin [2], while the UK nested case-control study found an odds ratio of 1.25 (95% CI: 1.07-1.45; $p = 0.004$) [10]. One U.S. study specifically examining depot-medroxyprogesterone acetate (DMPA) found a 2.2-fold increased risk (95% CI: 1.2-4.2) with recent use for 12 months or longer [26].

Progestogen-Releasing Intrauterine Devices

Levonorgestrel-releasing intrauterine systems (LNG-IUS) showed increased breast cancer risk across multiple studies. The Danish cohort reported a relative risk of 1.21 (95% CI: 1.11-1.33) [1], while the UK study found an odds ratio of 1.32 (95% CI: 1.17-1.49; $p<0.001$) [10]. An Australian nested case-control study confirmed these findings with an odds ratio of 1.26 (95% CI: 1.21-1.31) [11]. A dedicated meta-analysis of LNG-IUS use found stratified odds ratios of 1.12 (95% CI: 1.02-1.22) for women under 50 years and 1.52 (95% CI: 1.34-1.72) for women 50 years or older [50], suggesting age-dependent effects.

A Finnish case-control study specifically noted that exclusive use of hormone-releasing intrauterine devices in postmenopausal women showed an odds ratio of 1.48 (95% CI: 1.10-1.99) [25], though this finding pertains to an older age group than the primary focus on reproductive-age women.

Dose-Response Relationships

Duration of Use

A clear dose-response relationship emerged between duration of hormonal contraceptive use and breast cancer risk. The Danish cohort demonstrated that risk increased from 1.09 (95% CI: 0.96-1.23) with less than one year of use to 1.38 (95% CI: 1.26-1.51) with more than 10 years of use ($p=0.002$) [1]. Multiple studies confirmed elevated risks with prolonged use: oral contraceptives used for more than 5 years showed an odds ratio of 1.09 (95% CI: 1.01-1.18; $p=0.02$) [22], and Southeast Asian meta-analysis found dramatically increased risk for use exceeding 5 years (OR=2.66; 95% CI: 1.79-3.94; $p<0.00001$) [17].

The Norwegian-Swedish cohort found significant trends of increasing breast cancer risk with longer durations ($p=0.005$) [5]. Thai women showed particularly strong dose-response effects, with adjusted odds ratios of 3.91 (95% CI: 1.99-7.64) for 6-10 years of use and 4.23 (95% CI: 2.05-8.71) for use exceeding 10 years [32]. An Indonesian hospital-based study corroborated these findings, reporting odds ratios of 1.93 (95% CI: 1.23-3.03) for use less than 6 years and 2.90 (95% CI: 1.65-5.09) for use of 6 years or longer [19].

A meta-analysis of cohort studies examining use for 5 years or more found a pooled relative risk of 1.20 (95% CI: 1.09-1.32) [36], with a nonlinear dose-response pattern showing risk progressively increasing during the first 5 years of use, stabilizing until the 10th year, and then increasing again [36].

Age at First Use

Early initiation of hormonal contraception emerged as a significant risk modifier. An Iraqi study found the highest risk among women who started use before age 20 (OR=6.62; p=0.02) [31], while an Indonesian study reported an odds ratio of 19.500 for starting use at or before age 22 years compared to 1.421 for starting after age 22 [20]. A U.S. study examining formulation-specific effects found relative risks of 3.62 for high-dose ethinyl estradiol and 1.91 for low-dose preparations specifically among women under 35 years [23].

The Collaborative Group meta-analysis found elevated risks for women starting hormonal contraceptives before age 20, with relative risks of 1.95 until age 30, 1.54 between ages 30-34, and 1.27 between ages 35-40 [21]. These findings suggest that breast tissue may be particularly susceptible to hormonal influences during earlier reproductive years.

Recency of Use

Recent use of hormonal contraceptives showed particularly strong associations with breast cancer risk. Studies consistently found that current or recent users (defined variously as use within the past 6-12 months) had higher risks than former users. The UK study found that 44% of women with breast cancer had hormonal contraceptive prescriptions an average of 3.1 years before diagnosis [2], with odds ratios declining by time since last use [2].

Multiple studies demonstrated that risk dissipates after discontinuation. The Danish cohort found that risk remained elevated for women who had used hormonal contraceptives for 5 years or more even after discontinuation [1], while the Norwegian-Swedish cohort showed similar patterns [5]. However, risk typically returned to baseline within 5-15 years after cessation [13]. The Swedish study specifically noted that risk disappeared ten years after women stopped using hormonal contraception [4].

An Indonesian study found that women who last used hormonal contraceptives within 5 years had an odds ratio of 8.500 compared to 1.235 for those who last used more than 5 years ago [20], demonstrating the rapid attenuation of risk with time since cessation.

Risk by Breast Cancer Subtype

Estrogen Receptor Status

Several studies stratified results by estrogen receptor (ER) status. A U.S. nested case-control study found the association was slightly stronger for ER-positive disease (OR=1.7; 95% CI: 1.3-2.1) compared to ER-negative disease (OR=1.2; 95% CI: 0.8-1.8), though this difference was not statistically significant ($p=0.15$) [8, 16]. Another U.S. population-based case-control study reported similar patterns with greater risk magnitudes for ER-negative breast cancer among women ages 20-39 (OR=3.5; 95% CI: 1.3-9.0) [16].

The American Cancer Society cohort found that associations were primarily limited to localized, grade 1 or 2, and ER-positive disease [9]. A hospital-based U.S. case-control study found no difference in the association by estrogen or progesterone receptor status of the tumor [12].

Triple-Negative Breast Cancer

A particularly notable finding emerged for triple-negative breast cancer. Women ages 20-39 who were current oral contraceptive users for 5 years or more had a 3.7-fold increased risk of triple-negative breast cancer (95% CI: 1.2-11.8) [16, 34]. The risk increased with each additional lifetime year of oral contraceptive use among triple-negative cases ($p=0.045$) [16]. This suggests that hormonal contraception may have differential effects on breast cancer subtypes, with potentially stronger associations for aggressive tumor types in younger women.

Absolute Risk Considerations

While relative risks were consistently elevated, absolute risks remained small given the low baseline incidence of breast cancer in reproductive-age women. The Danish study calculated that the overall absolute increase was 13 per 100,000 person-years [1], or approximately one extra breast cancer case for every 7,690 women using hormonal contraception for one year [1].

The UK study provided age-stratified absolute excess risks, estimating 8 per 100,000 users from age 16-20 years and 265 per 100,000 users from age 35-39 years when using combined or

progestagen-only contraceptives for 5 years [2]. This substantial difference reflects the underlying increase in breast cancer incidence with age [14], emphasizing that the absolute excess risk is considerably smaller in younger women who use contraceptives at earlier ages [2].

The Swedish cohort reported absolute risks of 22.4 per 100,000 women-years for never users, 10.9 for current users of combined hormonal contraceptives, and 29.8 for current users of progestogen-only methods [4]. These absolute numbers illustrate that while relative risks are elevated, the actual number of additional cases remains modest.

Effect Modification by Population Characteristics

Age-Specific Effects

Age at time of use modified breast cancer risk. The Danish study noted that most diagnoses occurred in women over 40 years [14], with higher absolute risks in this age group despite similar relative risks across ages [14]. U.S. studies found stronger associations among younger women, with one reporting that risk magnitudes were generally greater among women ages 20-39 [16, 34]. Current use for 5 years or more among women ages 20-39 showed an odds ratio of 2.5 (95% CI: 1.2-5.1) [16], compared to lower risks in older age groups.

A Thai cohort study found different hazard ratios by age group: 0.86 (95% CI: 0.30-2.45) for women under 50 and 1.91 (95% CI: 0.75-4.88) for women 50 and older [73], though the latter falls outside the primary reproductive age range of interest.

Reproductive Factors

Parity status substantially modified contraceptive-associated risk. The meta-analysis by Kahlenborn et al. found that among parous women, the association was stronger when oral contraceptives were used before first full-term pregnancy (OR=1.44; 95% CI: 1.28-1.62) than after (OR=1.15; 95% CI: 1.06-1.26) [15]. The risk was greatest for parous women who used oral contraceptives 4 or more years before first full-term pregnancy (OR=1.52; 95% CI: 1.26-1.82) [15]. Among nulliparous women, oral contraceptive use showed an odds ratio of 1.24 (95% CI: 0.92-1.67) [15], though longer duration of use did not substantially alter risk in this group [15].

The Norwegian-Swedish cohort found increased risk of borderline significance among short-term users before age 20 (RR=1.3; 95% CI: 1.0-1.7) and before first full-term pregnancy

(RR=1.4; 95% CI: 1.0-1.8) [5]. Indonesian studies identified delayed age at first pregnancy (≥ 30 years) as a significant risk factor, with one reporting an odds ratio of 3.01 (95% CI: 1.16-7.78; $p=0.023$) [79].

Breastfeeding history also influenced risk. An Indonesian study found that women with a history of breastfeeding had reduced odds of breast cancer when using hormonal contraception (OR=0.3; $p=0.035$) [69], while another found that long duration of breastfeeding (>2 years) was protective (OR=7.842; $p=0.003$) [65].

Genetic and Familial Factors

Family history of breast cancer emerged as a strong independent risk factor and potential effect modifier. Multiple Indonesian studies identified family history as the most dominant risk factor, with odds ratios ranging from 4.5 to 10.87 [52, 69, 72]. One study specifically found an odds ratio of 6.33 (95% CI: 1.28-31.1) for family history [64].

For BRCA1/2 mutation carriers, evidence was more limited and somewhat contradictory. One systematic review found that BRCA1/2 mutation carriers using oral contraceptives showed an increased hazard ratio of 1.39 (95% CI: 1.15-1.67) [53], with risk increasing with longer durations of use [53]. However, another review noted that a systematic overview of studies did not reveal an elevated breast cancer risk for women carrying elevated breast cancer risk taking contraceptives [21].

Lifestyle Factors

Obesity showed complex relationships with hormonal contraception and breast cancer risk. Several Indonesian studies identified obesity as a significant risk factor, with odds ratios ranging from 3.00 to 11.7 [39, 69, 69]. Interestingly, one Indonesian study suggested that maintaining a healthy lifestyle through diet and exercise might mitigate potential risks associated with hormonal contraception [58], though this study found no significant association between hormonal contraception and breast cancer ($p=0.276$) [58].

The Swedish cohort noted that progestogen-only methods were selectively prescribed to women with risk factors like smoking or obesity [4], which could partially explain the elevated risk observed with these methods [4]. However, the American Cancer Society cohort found that race,

income, body mass index, physical activity, alcohol use, cigarette smoking, parity, and breastfeeding did not modify the associations between oral contraceptives and breast cancer risk [9].

Geographic Variations

Studies from Southeast Asian populations showed particularly strong associations. The meta-analysis of Southeast Asian women found an overall odds ratio of 2.66 (95% CI: 1.79-3.94; $p < 0.00001$) for oral contraceptive use exceeding 5 years [17], with country-specific estimates showing Indonesia (POR=2.67), Thailand (POR=2.56), and Malaysia (POR=2.28) [17]. Thai women demonstrated adjusted odds ratios of 3.39 (95% CI: 1.99-5.75) [32] for ever use, substantially higher than estimates from Western populations.

Indonesian studies consistently reported elevated risks, with odds ratios ranging from 1.73 to 9.06 across different studies [18, 31, 40, 77, 78]. However, methodological limitations in some smaller Indonesian studies, including lack of detailed adjustment for confounders and potential recall bias, warrant cautious interpretation of these higher estimates.

Synthesis

The body of evidence presents an apparent paradox: while most large, methodologically rigorous cohort studies consistently find modest increases in breast cancer risk associated with hormonal contraception use (relative risks of 1.20-1.33), some studies—particularly from Southeast Asian populations—report substantially higher risks (odds ratios of 2.0-6.0), while a few studies find no association or even protective effects. Understanding this heterogeneity requires examining multiple factors that vary systematically across study contexts.

Context-Specific Risk Margins

The apparent heterogeneity in findings can be reconciled by recognizing that different risk magnitudes apply in different contexts defined by contraceptive formulation, duration of use, timing relative to pregnancy, and time since cessation.

Formulation-specific effects: Studies examining contemporary low-dose formulations found either modest associations or null effects. Low-dose estrogen oral contraceptives showed an odds ratio of 1.0 (95% CI: 0.6-1.7) [7], while formulations with norgestimate showed OR=1.2 (95% CI: 0.6-2.2) [7]. In contrast, high-dose estrogen formulations demonstrated substantially elevated

risks (OR=2.7; 95% CI: 1.2-6.4) [8], and specific progestins showed varying profiles: ethynodiol diacetate (OR=2.6; 95% CI: 1.4-4.7) [8], triphasic levonorgestrel (RR=3.05; 95% CI: 2.00-4.66) [3], norgestrel (HR=2.82; 95% CI: 1.54-5.19) [9].

These formulation-specific findings suggest that the question "does hormonal contraception increase breast cancer risk?" conflates multiple distinct exposures with different risk profiles. Contemporary low-dose combined pills appear to confer minimal risk, while specific higher-dose or triphasic formulations account for much of the observed excess [3, 8].

Duration-dependent windows: Risk varies nonlinearly with duration. During the first year of use, relative risk is approximately 1.09 [1], increasing to 1.38 after more than 10 years [1]. A meta-analysis found risk progressively increasing during the first 5 years, stabilizing from years 5-10, then increasing again beyond 10 years [36]. This pattern suggests initial hormonal perturbation effects, adaptation during intermediate durations, and cumulative exposure effects with very long-term use.

Temporal relationship to diagnosis: Current or recent use (within 1 year) shows relative risks of 1.33-1.60 [3, 7, 8], while the same women 10-15 years after cessation show risks indistinguishable from never users [12, 13]. This temporal pattern indicates that hormonal contraception may accelerate diagnosis of cancers that would have occurred anyway (detection bias) or promote the growth of existing precancerous lesions (promotion rather than initiation). The rapid dissipation of risk after cessation argues against hormonal contraception as a true carcinogenic initiator, which would produce permanent risk elevation.

Age-dependent absolute risk: While relative risks remain relatively constant across reproductive ages (around 1.20-1.33), absolute excess risks vary dramatically by age. The UK study estimated 8 excess cases per 100,000 women-years for users ages 16-20 versus 265 per 100,000 for users ages 35-39—a 33-fold difference [2]. Both estimates reflect the same relative risk applied to vastly different baseline incidence rates. For women under 35, the absolute increased risk is only 2 per 100,000 women-years [14], making the clinical significance minimal despite statistically significant relative risks.

Mechanistic Explanations for Heterogeneity

Detection bias and screening intensity: The Danish study could not account for differences in breast cancer surveillance between users and non-users [27]. Hormonal contraceptive users typically have more frequent healthcare contacts, potentially leading to earlier detection of breast cancers that would eventually be diagnosed in non-users. The concentration of excess risk in localized, lower-grade, ER-positive disease [9] is consistent with preferential detection of less aggressive tumors through enhanced surveillance rather than induction of aggressive cancers.

Hormonal promotion of subclinical disease: The finding that risk disappears 5-15 years after cessation [12, 13] suggests hormonal contraception may act as a promoter rather than an initiator of carcinogenesis. This mechanism would accelerate the growth of existing microscopic cancers or promote transformation of premalignant lesions, advancing the timing of diagnosis without increasing lifetime risk. The observation that women who used hormonal contraceptives for 5 years or more maintained elevated risk for several years after discontinuation [1] supports this promotion model for longer exposures.

Population-specific confounding: The substantially higher odds ratios reported in Southeast Asian studies (2.66-9.06) [17, 18, 64] compared to Western cohorts (1.03-1.33) [1, 35] likely reflect differences in study methodology rather than true population differences in susceptibility. Most Southeast Asian studies were small hospital-based case-controls with limited confounder adjustment [18, 31, 32], while Western studies predominantly used population-based designs with comprehensive adjustment [1, 2, 4]. When Torres-de la Roche et al. meta-analyzed case-control studies from diverse geographic regions, they found high heterogeneity ($I^2=82\%$) [24], suggesting methodological variation rather than geographic variation drives the differences.

Additionally, Southeast Asian populations may have different distributions of confounders. Indonesian studies noted that early menarche, nulliparity, obesity, and lack of breastfeeding were more common among cases [40, 48, 64], yet many studies did not fully adjust for these factors. One Indonesian study acknowledged that its findings should be interpreted cautiously due to potential confounding [40].

Reconciling Progestogen-Only Findings

The Swedish cohort's finding that progestogen-only methods showed higher risk than combined hormonal contraception (IRR 1.32 vs. 1.03) [4] appears to contradict the hypothesis that estrogen drives breast cancer risk. However, the authors noted that progestogen-only methods were selectively prescribed to women with pre-existing risk factors like smoking and obesity [4, 4], creating confounding by indication. Women prescribed progestogen-only methods may have baseline characteristics that independently increase breast cancer risk, making it difficult to isolate the contraceptive effect.

Supporting this interpretation, when the UK study carefully matched cases and controls and adjusted for body mass index, all hormonal contraceptive types showed similar risk estimates: oral combined (OR=1.23), oral progestagen-only (OR=1.26), injected progestagen (OR=1.25), and progestagen IUD (OR=1.32) [10] —a remarkably narrow range suggesting that both estrogen and progestin contribute to risk, or that residual confounding affects all estimates similarly.

Time-Varying Risk Trajectories

The temporal pattern of risk—elevated during use, declining after cessation, and returning to baseline within 10-15 years—was consistent across studies and provides a framework for reconciling heterogeneous findings. Studies measuring outcomes shortly after exposure cessation (within 5 years) consistently found elevated risks [1, 2, 20], while those with longer time since cessation found attenuated or null associations [12, 13].

The American Cancer Society cohort demonstrated that cessation of oral contraceptive use progressively attenuated the association down to the null 15 years after discontinuation (HR=1.04; 95% CI: 0.73-1.49) [9]. This finding reconciles apparently discrepant results: studies following women for extended periods after contraceptive cessation will observe lower cumulative risks than studies focused on recent users.

Synthesis Across All Evidence

When weighting evidence by methodological rigor, sample size, and control for confounding, the preponderance of evidence indicates that:

1. **Current or recent use** (within 1 year) of hormonal contraception increases breast cancer risk with relative risks of approximately 1.20-1.33 across contraceptive types [1–3, 5, 6, 10].
2. **Risk magnitude varies by formulation**, with contemporary low-dose preparations showing minimal associations ($RR \sim 1.0$) [7], while specific formulations—particularly triphasic levonorgestrel, high-dose estrogen, and certain progestins like ethynodiol diacetate—show 2-3 fold elevations [3, 7–9].
3. **Duration produces dose-response effects**, with risk increasing from 1.09 for <1 year to 1.38 for >10 years [1], though the relationship is nonlinear with acceleration during years 1-5 and again after year 10 [36].
4. **Risk dissipates after cessation**, returning to baseline within 5-15 years depending on duration of use [12, 13], consistent with a promoter rather than initiator mechanism.
5. **Absolute risks remain small** for reproductive-age women, particularly those under 35 years (2-8 per 100,000 women-years) [2, 14], increasing to 265 per 100,000 for users ages 35-39 [2] due to age-related increases in baseline incidence.
6. **Timing relative to first pregnancy matters**, with use before first full-term pregnancy showing stronger associations ($OR=1.44$) than use after ($OR=1.15$) [15], suggesting vulnerability of nulliparous breast tissue.
7. **Subtype-specific risks** may exist, with some evidence for stronger associations with triple-negative breast cancer in younger women ($OR=3.7$ for current users ages 20-39) [16], though this requires confirmation given small numbers in subgroup analyses.

The higher risk estimates from case-control studies and smaller hospital-based investigations likely reflect methodological limitations—particularly recall bias, selection bias, and inadequate confounder control—rather than true population differences. The consistent findings from multiple

large prospective cohorts using objective exposure data provide the most reliable estimates of actual risk.

DISCUSSION

This systematic review of 80 studies examining hormonal contraception and breast cancer risk in reproductive-age women reveals a nuanced picture that reconciles apparently heterogeneous findings through consideration of formulation-specific effects, duration-response relationships, temporal patterns, and absolute versus relative risk. The discussion synthesizes key findings, explores mechanistic explanations, addresses geographic variations, and considers clinical implications.

Overall Association and Magnitude of Risk

The preponderance of high-quality evidence from large prospective cohort studies demonstrates a consistent, modest increase in breast cancer risk associated with current or recent hormonal contraceptive use. The Danish nationwide cohort study of 1.8 million women reported a relative risk of 1.20 (95% CI: 1.14-1.26) for current and recent users (1), translating to an absolute increase of 13 per 100,000 person-years or approximately one additional breast cancer for every 7,690 women using hormonal contraception for one year. Similarly, the UK nested case-control study found an odds ratio of 1.25 (95% CI: 1.18-1.33) for current use (2), while the Norwegian-Swedish cohort reported a relative risk of 1.6 (95% CI: 1.2-2.1) (5). These findings are remarkably consistent across diverse European populations with different healthcare systems and contraceptive prescribing patterns, suggesting a robust underlying association.

The convergence of estimates from methodologically rigorous studies—those with large sample sizes, prospective exposure assessment, comprehensive confounder adjustment, and complete outcome ascertainment—provides confidence in the existence of a small but detectable risk increase. Importantly, studies with longer follow-up periods demonstrate that the association is transient, with risk returning to baseline within 5-15 years after cessation (12,13). This temporal pattern has critical implications for causal inference, as true carcinogens would be expected to produce permanent risk elevation rather than reversible effects.

Formulation-Specific Effects: Disaggregating Heterogeneity

A major contribution of this review is the systematic examination of risk by specific contraceptive formulation, revealing substantial heterogeneity that explains much of the apparent inconsistency across studies. Early studies that grouped all oral contraceptives together obscured important differences between high-dose estrogen preparations from previous decades and contemporary low-dose formulations. Beaber and colleagues demonstrated that current use of high-dose estrogen oral contraceptives (≥ 50 μg ethinyl estradiol) was associated with an odds ratio of 2.7 (95% CI: 1.2-6.4), while low-dose preparations showed no association (OR=1.0; 95% CI: 0.6-1.7) (7,8). Similarly, formulations containing ethynodiol diacetate (OR=2.6; 95% CI: 1.4-4.7) or triphasic levonorgestrel (RR=3.05; 95% CI: 2.00-4.66) (3) demonstrated substantially elevated risks, whereas those with norgestimate showed minimal association (OR=1.2; 95% CI: 0.6-2.2) (7).

The Nurses' Health Study II provided particularly detailed formulation-specific data, finding that current use of triphasic preparations with levonorgestrel had a relative risk of 3.05 (95% CI: 2.00-4.66; $p < 0.0001$) (3). This striking elevation suggests that both the specific progestin and the triphasic dosing regimen—which produces varying hormone levels throughout the menstrual cycle—may influence breast cancer risk through different mechanisms than monophasic preparations. The American Cancer Society cohort similarly found elevated risks for norgestrel-containing formulations (HR=2.82; 95% CI: 1.54-5.19) (9), reinforcing that progestin type matters substantially.

These formulation-specific findings have critical implications. First, they suggest that the question "does hormonal contraception increase breast cancer risk?" is overly simplistic, as different formulations represent distinct exposures with varying risk profiles. Second, they provide reassurance regarding contemporary low-dose combined oral contraceptives, which predominate in current clinical practice. Third, they highlight the importance of ongoing surveillance as new formulations enter the market, as extrapolation from older products may be misleading.

Progestogen-Only Methods: Reconciling Apparent Paradoxes

The finding that progestogen-only methods confer breast cancer risk similar to or even exceeding that of combined hormonal contraceptives initially appears paradoxical given the

traditional focus on estrogen as the primary driver of breast cancer. The Swedish cohort reported an incidence rate ratio of 1.32 (95% CI: 1.20-1.45) for progestogen-only methods compared to 1.03 (0.91-1.16) for combined hormonal contraceptives (4). However, careful examination reveals that this apparent difference likely reflects confounding by indication rather than true biological differences.

As the Swedish investigators noted, progestogen-only methods were selectively prescribed to women with pre-existing risk factors including smoking, obesity, and older age (4). Women with these characteristics have higher baseline breast cancer risk independent of contraceptive use, creating confounding that is difficult to fully eliminate even with multivariable adjustment. Supporting this interpretation, when the UK study carefully matched cases and controls and adjusted for body mass index and other factors, all hormonal contraceptive types showed remarkably similar risk estimates: oral combined (OR=1.23), oral progestagen-only (OR=1.26), injected progestagen (OR=1.25), and progestagen IUD (OR=1.32) (10). This narrow range suggests that either both estrogen and progestin contribute to risk through shared mechanisms, or that residual confounding affects all estimates similarly.

The levonorgestrel-releasing intrauterine system (LNG-IUS) deserves specific attention given its increasing use for both contraception and gynecological conditions. Multiple studies demonstrated consistently elevated risks: the Danish cohort reported RR=1.21 (95% CI: 1.11-1.33) (1), the UK study found OR=1.32 (95% CI: 1.17-1.49) (10), and the Australian nested case-control study confirmed OR=1.26 (95% CI: 1.21-1.31) (11). A dedicated meta-analysis found stratified odds ratios of 1.12 (95% CI: 1.02-1.22) for women under 50 years and 1.52 (95% CI: 1.34-1.72) for women 50 years or older (50), suggesting age-dependent effects that may reflect the hormonal milieu of perimenopause. However, the substantial systemic absorption of levonorgestrel from intrauterine devices—sufficient to affect breast tissue—provides biological plausibility for these observations.

Duration-Response Relationships: Nonlinear Patterns

A clear dose-response relationship emerged between duration of hormonal contraceptive use and breast cancer risk, though the pattern was nonlinear. The Danish cohort demonstrated

progressive risk increase from 1.09 (95% CI: 0.96-1.23) with less than one year of use to 1.38 (95% CI: 1.26-1.51) with more than 10 years of use ($p=0.002$) (1). Meta-analysis by Sayón-Orea and colleagues revealed a nonlinear pattern with risk progressively increasing during the first 5 years of use, stabilizing from years 5-10, and then increasing again after 10 years (36). This biphasic pattern suggests different biological mechanisms may operate during different exposure windows.

The initial risk increase during the first 1-5 years may reflect promotion of existing subclinical disease or acceleration of growth in precancerous lesions, while the later increase after 10 years could indicate cumulative DNA damage or sustained hormonal stimulation of breast epithelial proliferation. The Southeast Asian meta-analysis found dramatically increased risk for use exceeding 5 years (OR=2.66; 95% CI: 1.79-3.94; $p<0.00001$) (17), while use of shorter duration showed minimal association (OR=1.21; 95% CI: 0.96-1.52). Similarly, Thai women showed adjusted odds ratios of 3.91 (95% CI: 1.99-7.64) for 6-10 years of use and 4.23 (95% CI: 2.05-8.71) for use exceeding 10 years (32), providing particularly strong evidence from a non-Western population.

The Indonesian hospital-based study by Wahidin and colleagues corroborated these findings with odds ratios of 1.93 (95% CI: 1.23-3.03) for use less than 6 years and 2.90 (95% CI: 1.65-5.09) for use of 6 years or longer (19). These dose-response gradients across diverse populations and study designs strengthen causal inference, as a monotonic relationship between exposure duration and outcome risk is a key criterion for causality in epidemiological studies.

Temporal Patterns: Risk After Cessation

The consistent finding that breast cancer risk dissipates after hormonal contraceptive cessation provides crucial insights into mechanism and clinical counseling. Studies across multiple populations demonstrated that risk returns to baseline within 5-15 years after discontinuation, with the exact timing depending on duration of use. The American Cancer Society cohort found progressive attenuation of risk down to null 15 years after cessation (HR=1.04; 95% CI: 0.73-1.49) (9). The Danish study noted that women who had used hormonal contraceptives for 5 years or more maintained elevated risk for several years after discontinuation, but eventually returned to baseline

(1). The Swedish study specifically reported that risk disappeared ten years after women stopped using hormonal contraception (4).

This temporal pattern strongly argues against hormonal contraception as a true carcinogenic initiator, which would produce permanent risk elevation due to irreversible genetic damage. Instead, the reversibility of risk suggests a promotional mechanism whereby exogenous hormones accelerate the growth of existing subclinical disease or promote the transformation of premalignant lesions. Under this model, hormonal contraception advances the timing of breast cancer diagnosis in susceptible women without increasing lifetime risk. The observation that excess cancers among users tend to be localized, lower-grade, and ER-positive (9) is consistent with preferential detection or promotion of less aggressive tumors rather than induction of aggressive disease.

The Indonesian study by Ariani and colleagues provided particularly illustrative data on recency effects, finding that women who last used hormonal contraceptives within 5 years had an odds ratio of 8.500 compared to 1.235 for those who last used more than 5 years ago (20). While the magnitude of this estimate exceeds those from Western studies—likely reflecting methodological differences discussed below—the pattern of declining risk with increasing time since cessation is consistent across all populations studied.

Absolute Risk: Clinical Significance in Context

While relative risks are the primary metric reported in epidemiological studies, absolute risks provide the clinically meaningful information needed for counseling and decision-making. The Danish study calculated an absolute increase of 13 per 100,000 person-years (1), a number that may be difficult for patients to interpret. The UK study provided age-stratified absolute excess risks that reveal dramatic age-dependence: 8 per 100,000 users from age 16-20 years compared to 265 per 100,000 users from age 35-39 years when using hormonal contraceptives for 5 years (2). This 33-fold difference reflects the underlying increase in breast cancer incidence with age, not variation in the biological effect of contraceptives.

For women under 35 years, the absolute increased risk is only 2 per 100,000 women-years (14), making the clinical significance minimal despite statistically significant relative risks. This distinction is crucial for counseling younger women who may be most concerned about cancer risks

but who actually face the smallest absolute increases. Conversely, women approaching 40 years have higher baseline incidence and consequently larger absolute excess risks, warranting more careful consideration of the risk-benefit balance.

The Swedish cohort reported absolute risks of 22.4 per 100,000 women-years for never users, 10.9 for current users of combined hormonal contraceptives, and 29.8 for current users of progestogen-only methods (4). These numbers illustrate that while relative risks are elevated, the actual number of additional cases remains modest, and the majority of women using hormonal contraception will not develop breast cancer attributable to their contraceptive use. Placing these risks in context with other common exposures—such as the 10-15% lifetime risk of breast cancer from nulliparity or delayed childbearing—helps patients contextualize contraceptive decisions within their overall risk profile.

Age at First Use and Reproductive Factors

The finding that early initiation of hormonal contraception—particularly before first full-term pregnancy—confers higher risk has important biological and clinical implications. The Iraqi study found the highest risk among women who started use before age 20 (OR=6.62; $p=0.02$) (31), while the Indonesian study by Ariani reported an odds ratio of 19.500 for starting use at or before age 22 years compared to 1.421 for starting after age 22 (20). Although the extreme magnitude of these estimates warrants cautious interpretation given potential methodological limitations, the pattern of elevated risk with early initiation is consistent across studies.

The meta-analysis by Kahlenborn and colleagues provided the most rigorous examination of this phenomenon, finding that among parous women, the association was stronger when oral contraceptives were used before first full-term pregnancy (OR=1.44; 95% CI: 1.28-1.62) than after (OR=1.15; 95% CI: 1.06-1.26) (15). The risk was greatest for parous women who used oral contraceptives 4 or more years before first full-term pregnancy (OR=1.52; 95% CI: 1.26-1.82) (15). These findings suggest that nulliparous breast tissue—which has not undergone the terminal differentiation associated with pregnancy and lactation—may be particularly susceptible to hormonal influences. The protective effect of early full-term pregnancy on breast cancer risk is

well-established, and this analysis suggests that hormonal contraceptive use before that protective event may partially counteract or delay its benefits.

Breastfeeding history also emerged as a potential effect modifier. An Indonesian study found that women with a history of breastfeeding had reduced odds of breast cancer when using hormonal contraception (OR=0.3; $p=0.035$) (69), while another found that long duration of breastfeeding (>2 years) was protective (OR=7.842; $p=0.003$) (65). These findings align with the established protective effect of breastfeeding against breast cancer and suggest that lactation-induced breast tissue differentiation may reduce susceptibility to hormonal influences.

Genetic and Familial Factors

Family history of breast cancer consistently emerged as a strong independent risk factor across multiple Indonesian studies, with odds ratios ranging from 4.5 to 10.87 (52,69,72). One study specifically found an odds ratio of 6.33 (95% CI: 1.28-31.1) for family history (64). However, evidence regarding whether family history modifies the contraceptive-associated risk—rather than simply adding to baseline risk—was limited and inconsistent.

For BRCA1/2 mutation carriers, a systematic review found that oral contraceptive use was associated with an increased hazard ratio of 1.39 (95% CI: 1.15-1.67) (53), with risk increasing with longer durations of use. However, another review noted conflicting evidence (21), and the small number of mutation carriers in most studies limits precision. Given the high baseline risk in this population, even modest relative risk increases translate into substantial absolute risk increments, warranting specialized counseling for mutation carriers considering hormonal contraception.

Geographic Variations: Methodological Artifact or True Difference?

The substantially higher odds ratios reported in Southeast Asian studies—ranging from 2.66 to 9.06 (17,18,40,77,78)—compared to Western cohorts (1.03-1.33) (1,35) raises important questions about whether these differences reflect true population susceptibility or methodological artifacts. Several lines of evidence suggest that methodological factors are the primary drivers of observed differences.

First, the Southeast Asian studies were predominantly small, hospital-based case-control designs with limited sample sizes and potential for selection bias. For example, Indonesian studies

often included fewer than 100 total participants (18,20,64), while the Danish cohort included 1.8 million women (1). Small studies are susceptible to chance findings and may overestimate true effects due to publication bias favoring positive results.

Second, recall bias is a major concern in case-control studies where women with breast cancer may differentially recall and report contraceptive use compared to healthy controls. This bias would systematically inflate odds ratios, potentially explaining the higher estimates. Third, many Southeast Asian studies had limited adjustment for confounders, with some reporting only crude odds ratios or adjusting for only 1-2 variables (18,31,32). In contrast, large Western cohorts comprehensively adjusted for age, parity, breastfeeding, family history, body mass index, and other potential confounders (1,2,4).

Fourth, when Torres-de la Roche and colleagues meta-analyzed case-control studies from diverse geographic regions, they found high heterogeneity ($I^2=82\%$) (24), suggesting that study-level methodological differences—not geographic location—drive the variation. The meta-analysis by Nindrea and colleagues focusing specifically on Southeast Asian women found an overall odds ratio of 2.66 (95% CI: 1.79-3.94) (17), but acknowledged substantial heterogeneity and methodological limitations in included studies.

However, the possibility of true population differences cannot be entirely dismissed. Southeast Asian populations may have different distributions of genetic polymorphisms affecting hormone metabolism, different dietary patterns influencing endogenous hormone levels, or different reproductive norms (earlier marriage, higher parity, longer breastfeeding) that modify contraceptive effects. The Thai study by Chaveepojnkamjorn and colleagues, which found adjusted odds ratios of 3.39 (95% CI: 1.99-5.75) for ever use (32), was relatively large (257 cases, 257 controls) and adjusted for multiple confounders, suggesting that some true elevation may exist. Nevertheless, until large prospective cohort studies are conducted in Southeast Asian populations using standardized methods, the preponderance of evidence suggests that Western estimates are more reliable benchmarks for risk quantification.

Mechanistic Insights: Promotion Rather Than Initiation

The temporal patterns observed across studies—rapid risk increase during use, dose-response relationship with duration, and risk dissipation after cessation—provide strong support for a promotional rather than initiating mechanism of hormonal contraception in breast carcinogenesis. Under the initiation-promotion model of carcinogenesis, initiators cause irreversible genetic damage (mutations) that creates latent cancer potential, while promoters stimulate the growth and expansion of initiated cells without causing new mutations.

If hormonal contraceptives were true initiators, risk would remain elevated indefinitely after exposure, similar to the effects of ionizing radiation or certain chemical carcinogens. Instead, risk returns to baseline within 5-15 years after cessation (12,13), consistent with removal of a promotional stimulus. The observation that excess cancers among users are predominantly localized, lower-grade, and ER-positive (9) further supports promotion of less aggressive tumors that would have eventually presented clinically, rather than induction of aggressive disease.

The dose-response pattern—with risk increasing during the first 5 years, stabilizing, then increasing again after 10 years (36)—suggests that different mechanisms may operate during different exposure windows. Early risk increases could reflect acceleration of growth in existing microscopic cancers, while later increases after prolonged use might involve cumulative hormonal stimulation of breast epithelial proliferation, potentially increasing the pool of cells at risk for transformation.

Detection bias may also contribute to observed associations. Hormonal contraceptive users typically have more frequent healthcare contacts for prescription refills, blood pressure monitoring, and routine gynecological care, potentially leading to earlier detection of breast cancers through clinical breast examinations or mammography. The Danish study acknowledged that they could not account for differences in breast cancer surveillance between users and non-users (27). The concentration of excess risk in localized disease (9) is consistent with preferential detection through enhanced surveillance rather than true induction of additional cancers.

Subtype-Specific Risks: Triple-Negative Breast Cancer

A particularly concerning finding emerged for triple-negative breast cancer, an aggressive subtype with limited treatment options and poor prognosis. Beaber and colleagues found that

women ages 20-39 who were current oral contraceptive users for 5 years or more had a 3.7-fold increased risk of triple-negative breast cancer (95% CI: 1.2-11.8) (16,34). The risk increased with each additional lifetime year of oral contraceptive use among triple-negative cases ($p=0.045$) (16). This finding, if confirmed in larger studies, has substantial clinical implications as triple-negative breast cancer disproportionately affects younger women and has higher mortality rates than other subtypes.

The biological plausibility of this association remains uncertain, as triple-negative tumors lack estrogen, progesterone, and HER2 receptors and were traditionally considered hormone-unresponsive. However, emerging evidence suggests that hormonal exposures during critical windows may influence the development of even receptor-negative tumors through indirect mechanisms or through effects on the breast microenvironment. Given the small numbers of triple-negative cases in most studies—the Beaber analysis included only 81 triple-negative cases (16)—these findings require confirmation in larger pooled analyses before clinical recommendations can be modified.

Clinical Implications and Counseling Considerations

The findings of this systematic review have direct implications for clinical practice and patient counseling. First, healthcare providers should emphasize that the absolute risk increase associated with hormonal contraception is small for most reproductive-age women, particularly those under 35 years. The UK estimate of 8 excess cases per 100,000 women-years for ages 16-20 (2) means that a clinician would need to prescribe hormonal contraception to 12,500 women in this age group for one year to observe one additional breast cancer—a number that contextualizes the risk as minimal.

Second, counseling should be individualized based on age, as absolute risks vary dramatically across the reproductive lifespan. For women over 35 years, particularly those approaching 40, the higher baseline incidence of breast cancer means that the same relative risk translates into larger absolute excess cases (265 per 100,000 for ages 35-39) (2). For these women, the risk-benefit calculation may differ, and alternative contraceptive methods or non-hormonal options may be considered, especially if other risk factors are present.

Third, formulation matters. Contemporary low-dose combined oral contraceptives appear to confer minimal risk (OR=1.0) (7), while older high-dose preparations and specific progestins like ethynodiol diacetate and triphasic levonorgestrel show stronger associations. When possible, prescribing lower-risk formulations represents a prudent approach, though availability and individual patient factors must be considered.

Fourth, duration of use should be considered in counseling. Women using hormonal contraception for extended periods—particularly exceeding 5-10 years—face progressively increasing risks. For women who have used hormonal contraception for many years and are approaching their late 30s, reassessment of the continued need for hormonal contraception and consideration of alternative methods may be appropriate.

Fifth, the timing of use relative to first pregnancy matters. Young nulliparous women who use hormonal contraception before their first full-term pregnancy may face higher risks than women who initiate after childbearing (15). For these women, ensuring adequate counseling about this modestly elevated risk is important, though the absolute risk remains extremely low given their young age.

Sixth, women with strong family history of breast cancer or known BRCA mutations require specialized counseling. While the relative risk increase appears similar to that in the general population (53), the higher baseline risk means that absolute risk increments are larger. These women may benefit from discussion with genetic counselors and consideration of enhanced breast surveillance if they choose hormonal contraception.

Seventh, the protective effects of hormonal contraception against ovarian and endometrial cancer (46) should be incorporated into counseling. The reduction in ovarian cancer risk—which may persist for decades after cessation—partially offsets the breast cancer risk and must be considered in comprehensive risk-benefit assessments.

Eighth, the non-contraceptive benefits of hormonal contraception—including menstrual regulation, reduction of dysmenorrhea, management of endometriosis, and treatment of acne—are valuable to many women and may outweigh the small breast cancer risk for those with significant gynecological conditions.

Future Research Directions

This systematic review identifies several priorities for future research. First, large prospective cohort studies with objective exposure data from prescription registries are needed in non-Western populations, particularly Southeast Asia, to determine whether the higher estimates from case-control studies reflect true population differences or methodological artifacts. The establishment of contraceptive registries and linkage to cancer outcomes in countries like Indonesia, Thailand, and Malaysia would provide invaluable data.

Second, formulation-specific analyses require ongoing attention as new contraceptive products enter the market. The substantial variation in risk by progestin type and estrogen dose demonstrated in existing studies (3,7,8) suggests that each new formulation should be evaluated individually rather than assuming class effects.

Third, longer follow-up of existing cohorts is needed to determine whether the transient risk during reproductive years translates into any net increase in lifetime breast cancer risk. Studies following women into their postmenopausal years, when most breast cancers occur, can determine whether hormonal contraception advances the timing of diagnosis or truly increases cumulative incidence.

Fourth, mechanistic studies examining the biological effects of different progestins on breast tissue are needed to explain the observed variation in risk by formulation. Understanding why ethynodiol diacetate and levonorgestrel show stronger associations than norgestimate could inform development of safer hormonal contraceptives.

Fifth, pooled analyses with sufficient statistical power to examine breast cancer subtypes—particularly triple-negative disease—are needed to confirm or refute the concerning signal for this aggressive subtype. International consortia combining data from multiple studies could achieve the sample sizes needed for robust subtype-specific analyses.

Sixth, studies examining interactions between hormonal contraception and emerging risk factors—including obesity, which is increasing globally—are needed. The rising prevalence of obesity may modify contraceptive-associated risks in ways not captured in older studies.

Seventh, implementation research examining how to effectively communicate complex risk information to patients is needed. Translating relative risks, absolute risks, and formulation-specific differences into understandable counseling messages that support informed decision-making represents a critical knowledge translation priority.

CONCLUSION AND RECOMMENDATIONS

Summary of Key Findings

This systematic review of 80 studies examining hormonal contraception and breast cancer risk in reproductive-age women yields several definitive conclusions. First, current or recent use of hormonal contraception is associated with a modest, statistically significant increase in breast cancer risk, with relative risks of approximately 1.20-1.33 from large prospective cohort studies. Second, this risk varies substantially by contraceptive formulation: contemporary low-dose combined oral contraceptives show minimal association, while older high-dose estrogen preparations and specific progestins—particularly triphasic levonorgestrel and ethynodiol diacetate—demonstrate 2-3 fold risk elevations. Third, progestogen-only methods, including oral pills, injectables, and levonorgestrel-releasing intrauterine systems, confer risks comparable to combined hormonal contraceptives when confounding by indication is adequately addressed. Fourth, a clear dose-response relationship exists, with risk increasing from 1.09 for use under one year to 1.38 for use exceeding ten years, following a nonlinear pattern. Fifth, risk dissipates after cessation, returning to baseline within 5-15 years, consistent with a promotional rather than initiating mechanism. Sixth, absolute risks are highly age-dependent: 8 excess cases per 100,000 women-years for ages 16-20 compared to 265 per 100,000 for ages 35-39, meaning the clinical significance is minimal for young women despite statistically significant relative risks. Seventh, timing matters, with use before first full-term pregnancy showing stronger associations than use after, suggesting vulnerability of nulliparous breast tissue. Eighth, the substantially higher risk estimates from Southeast Asian case-control studies likely reflect methodological limitations rather than true population differences, though this requires confirmation through prospective studies in these populations.

Clinical Recommendations

Based on these findings, the following recommendations are offered for clinical practice:

1. Healthcare providers should counsel women that hormonal contraception is associated with a small increased risk of breast cancer during use, but that this risk must be balanced against the established benefits of pregnancy prevention, reduction in ovarian and endometrial cancer risk, and non-contraceptive health benefits.
2. Counseling should be individualized based on age, with emphasis on absolute rather than relative risks. For women under 35 years, the absolute risk increase is minimal (2-8 per 100,000 women-years), and concerns about breast cancer should not preclude hormonal contraception when otherwise appropriate.
3. For women over 35 years, particularly those approaching 40, the higher baseline incidence of breast cancer means that the same relative risk translates into larger absolute excess cases (265 per 100,000 for ages 35-39). For these women, alternative contraceptive methods or non-hormonal options may be considered, especially if other risk factors are present.
4. When prescribing hormonal contraception, preference should be given to contemporary low-dose formulations when clinically appropriate, as these demonstrate the most favorable risk profile. Older high-dose preparations and specific progestins with stronger associations should be avoided when alternatives exist.
5. Women with strong family history of breast cancer or known BRCA mutations require specialized counseling. While the relative risk increase appears similar to that in the general population, the higher baseline risk means that absolute risk increments are larger. These women may benefit from discussion with genetic counselors and consideration of enhanced breast surveillance if they choose hormonal contraception.
6. Duration of use should be considered in ongoing contraceptive management. Women using hormonal contraception for extended periods—particularly exceeding 5-10 years—face

progressively increasing risks. Periodic reassessment of continued need for hormonal contraception is appropriate, especially as women approach their late 30s.

7. For nulliparous women considering hormonal contraception before childbearing, counseling should acknowledge the modestly elevated risk associated with use before first full-term pregnancy, while emphasizing that the absolute risk remains extremely low given their young age.
8. All women using hormonal contraception should be encouraged to participate in age-appropriate breast cancer screening and to remain vigilant for breast changes, regardless of contraceptive method.

Public Health Implications

At the population level, the findings of this review support several public health recommendations. First, breast cancer risk should not be a barrier to hormonal contraception access for the vast majority of reproductive-age women. The small absolute risks must be weighed against the substantial public health benefits of preventing unintended pregnancies and reducing maternal mortality.

Second, regulatory agencies and contraceptive manufacturers should continue to monitor the safety of hormonal contraceptives through post-marketing surveillance, with particular attention to new formulations and long-term use patterns. The variation in risk by formulation demonstrated in this review underscores the importance of product-specific rather than class-level safety assessments.

Third, health systems should ensure that women have access to the full range of contraceptive options, including non-hormonal methods, to enable informed choice based on individual risk profiles and preferences. Restrictive formularies that limit options based on cost alone may inadvertently constrain women's ability to select the method most appropriate for their circumstances.

Fourth, public health messaging should accurately communicate both the benefits and risks of hormonal contraception, using absolute risk estimates that are meaningful to women. Messages that focus solely on relative risks may cause undue alarm, while those that dismiss any risk may undermine informed decision-making.

Research Recommendations

Priority areas for future research include: (1) large prospective cohort studies with objective exposure data in non-Western populations, particularly Southeast Asia; (2) formulation-specific analyses for new contraceptive products entering the market; (3) longer follow-up of existing cohorts to determine lifetime risk trajectories; (4) mechanistic studies examining progestin-specific effects on breast tissue; (5) pooled analyses with sufficient power to examine breast cancer subtypes, particularly triple-negative disease; (6) studies examining interactions with emerging risk factors such as obesity; and (7) implementation research on effective risk communication strategies.

Concluding Statement

Hormonal contraception remains one of the most important public health innovations of the 20th century, empowering women with reproductive autonomy and providing substantial health benefits beyond pregnancy prevention. The evidence synthesized in this review confirms a small, transient increase in breast cancer risk during use that varies by formulation, duration, and age. However, for the vast majority of reproductive-age women—particularly those under 35—the absolute risk is minimal and must be contextualized within the broader framework of contraceptive benefits. As new formulations continue to evolve and our understanding of hormone-responsive breast tissue deepens, ongoing surveillance and refined risk communication will ensure that women can make truly informed choices aligned with their reproductive goals and personal values. The goal is not zero risk, which is unattainable, but rather informed choice based on accurate, balanced, and comprehensible information that respects women's autonomy and supports their health across the reproductive lifespan.

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