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Progestin and Breast Cancer Risk: A Systematic Review

Marsha Samson, MSPH, MHSA[1,2,3], **Nancy Porter, MS**[1,2,3], **Olubunmi Orekoya, MD, MPH**[1,3], **James R. Hebert, ScD**[1,2,3], **Swann Arp Adams, PhD**[1,2,3], **Charles L. Bennett, MD, PhD**[4], and **Susan E. Steck, PhD**[1,2]

[1]Department of Epidemiology and Biostatistics, University of South Carolina, SC, USA

[2]Cancer Prevention and Control Program, University of South Carolina, SC, USA

[3]Arnold School of Public Health, University of South Carolina, Columbia, SC, USA

[4]College of Pharmacy, University of South Carolina, Columbia, SC, USA

Abstract

Purpose—This systematic review summarizes research on the use of progestin and breast cancer risk. Although mainly used for contraception, progestin can help treat menstrual disorders, and benign breast, uterine and ovarian diseases. Breast cancer is the leading site of new, non-skin, cancers in females in the United States, and possible factors that may modulate breast cancer risk need to be identified.

Methods—ProQuest (Ann Arbor, MI) and PubMed-Medline (US National Library of Medicine, Bethesda MD, USA) databases were used to search for epidemiologic studies from 2000–2015 that examined the association between progestin and breast cancer. Search terms included epidemiologic studies + progesterone or progestin or progestogen or contraceptive or contraceptive agents + breast cancer or breast neoplasms. A total of six studies were included in the review.

Results—Five of the six studies reported no association between progestin-only formulations (including norethindrone oral contraceptives, depot medroxyprogesterone acetate, injectable, levonorgestrel system users, implantable and intrauterine devices) and breast cancer risk. Duration of use was examined in a few studies with heterogeneous results.

Conclusion—Unlike studies of other oral contraceptives, studies indicate that progestin-only formulations do not increase the risk of breast cancer, although the literature is hampered by small sample sizes. Future research is needed to corroborate these findings, as further understanding of synthetic progesterone may initiate new prescription practices or guidelines for women's health.

Corresponding author: Marsha Samson, MSPH, MHSA, Phone: 786-877-7287, msamson@email.sc.edu, Address: 915 Greene Street, 2nd Floor #10, Columbia, SC, 29208.

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Experiments comply with the current laws of the United States.

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Keywords

contraception; risk; pharmacoepidemiology; breast cancer; progestin; progesterone; progestogen

Background

Worldwide, breast cancer is accountable for the plurality of cancer deaths among females [1]. Breast cancer is a hormonally-dependent disease wherein estrogen has been implicated as a primary carcinogen involved in breast cancer etiology [2]. In recent years, the use of estrogen + progestin-containing products has been carefully monitored due to possible estrogen-related adverse events, which has led to alterations in the recommended use of estrogen [3–5]. The popularity of combined estrogen + progestin birth control pill use has influenced the amount of research in this area [6]; there are numerous studies assessing the potential risk of breast cancer among combined oral contraceptive (OC) users but few focus on non-estrogen containing formulations [e.g., injectable, progestin-only pill, intrauterine device (IUD)] despite their increased use in the past thirty years [7,8].

Women are prescribed progestin for menstrual disorders, contraception, and benign breast, uterine or ovarian diseases [8,9]. Despite the increase of progestin-only products, many studies exclude progestin-only users due to the small sample size [10,11] or the infrequency of use compared to combined OCs [6]. More research needs to be done to understand the effects of naturally occurring progesterone and the compound's synthetic form, progestin. The paucity of literature related to exogenous progestin has limited our understanding of the hormone in relation to breast cancer risk. A previous review by the International Agency for Research on Cancer (IARC) monograph published in 1999 indicated that there was inadequate evidence for the relationship between progestogen-only contraceptives and breast cancer [12]. Other studies suggest that the biologic action may vary depending on the administration route (e.g., oral, parenteral) and the particular dose used [13]. This review was undertaken to help elucidate the scientific literature on the safety of using progestin-only products to aid researchers, clinicians, and women in making a more informed decision in relation to progestin-only drugs.

In this systematic review, we performed a thorough review of the literature on progestin-only drugs and breast cancer published since 1999 to present an overview of the hormonal risk caused by synthetic progesterone for breast carcinogenesis. The objective of this systematic review was to evaluate the peer-reviewed literature and determine if there is an association between progestin-only containing drugs and breast cancer.

Methods

Epidemiologic studies of synthetic progesterone (progestin) and breast cancer risk were selected from PubMed-Medline, OVID and ProQuest using the following combinations of search terms: progesterone and cancer, progestin and cancer, progestogen and cancer, progesterone-only contraceptive and breast cancer, progestin contraceptive and breast cancer, progestogen-only contraceptive and breast cancer, progesterone and neoplasm, progestin and neoplasm, progestogen and neoplasm, progesterone-only contraceptive and

neoplasm, progestin contraceptive and neoplasm, progestogen-only contraceptive and neoplasm, progestin OC breast cancer, progestin-only contraceptive, and progesterone congeners adverse effects. MeSH was used through PubMed to identify progestin, progesterone, and progestogen-related articles.

The search was restricted to female breast cancer studies that were published after 1999 and written in English or French. Case-control studies of progestin-only contraceptives and breast cancers that were systematically reviewed previously by the International Agency for Research on Cancer (IARC) monograph were excluded [12]. Titles and abstracts of searched articles were reviewed and of the selected papers, reference lists were searched and no additional articles were identified. We restricted our search to studies that assessed typical exposures to progesterone (i.e., injections, implants, OCs). Endocrinological studies, literature reviews, reports, and studies focusing on hormone replacement therapy were excluded. In addition, studies addressing OCs were excluded if progestin-only pills were not included in the manuscript. The estrogen component of the formulation could be the primary focus of the paper, but risk estimates of progestin-only pills had to be included (Figure 1). The protocol used was created in accordance with the PRISMA Statement [14]. All studies were evaluated using STROBE recommendations [15].

Information about study design, location, study participants, exposure and outcome assessment, confounding, and main findings were extracted (Table 1) from each study. The term “progestin” has been used to replace all progesterone synthetic names, such as progestogen, progesterone, and progestagen.

Results

The initial search identified 3,332 articles. Of these, 3,307 were excluded as not relevant, based on thorough review of titles and abstract, and 25 were preselected for further evaluation. Of the 25, 19 of those articles did not fulfill the inclusion criteria (Figure 1).Thus, only six articles published between 2000 and 2015 (three case-control and three cohort studies) were selected [16–21]. The selected studies were conducted in North America (n=2), Europe (n=3), and South Africa (n=1). In total, these studies included 217,355 women and 12,189 cases of breast cancer.

Injectable and Implantable Progestin-only

Two case-control studies evaluated the association of injectable progestin-only contraceptives (IPCs) and implantable progestin contraceptives and breast cancer risk.

Strom et al. used the Women’s Contraceptive and Reproductive Experiences (CARE) study to identify primary invasive breast cancers (n= 4,575) among black and white users of progestin-based injectable and implantable contraceptives in the Metropolitan areas of Georgia, Michigan, California, Philadelphia and Washington. Exposure to contraceptive injections were higher among women who were younger, premenopausal, and black; previously used an OC, and of lower socioeconomic status (SES). Adjusting for confounders did not affect the results; there was no significant increase in breast cancer risk for pre-and post-menopausal women who had been exposed to injections or implants compared to

women who had never been exposed to progestin [18]. Compared to women who had never used a contraception injection, there was a non-significant reduced risk among women who currently used IPCs (OR= 0.7; 95% CI: 0.4–1.3), and no association among women who initiated use in the 5 years preceding the reference date (OR= 0.9; 95% CI: 0.5–1.4) and women whose first use was between the ages of 25–35 (OR= 0.9; 95% CI: 0.6–1.3). However, first use before age 25 years was associated with a non-significant increased risk (OR= 1.3; 95% CI: 0.7–2.3) [18].

Women with less than 6 months of contraceptive injection use had a non-significant decreased risk compared to never users (OR= 0.6; 95% CI: 0.4–1.0). Furthermore, risk was not significantly increased among women with more than 24 months of injection use compared to never users (OR= 1.4; 95% CI: 0.8–2.5) or among women using implantable contraceptives. However, among progestin-only users of injectable and implantable contraceptives, there was a statistically significant increase in risk with prolonged use (> 6 months) (P=0.03) [18]. Strom et al. explained that the significantly increased risk was attenuated when short-term users were excluded from the analysis and that the decreased risk in short-term users compared to long-term users may have skewed the results. This finding suggests that compared to short-term users who have a decreased risk of breast cancer, prolonged use is associated with an increased risk of disease. However, there was no increased risk with long-term use compared to never users.

Shapiro et al. reported similar findings among black and mixed-race women aged 20–54 years in South Africa [17]. The study excluded white women due to their low exposure to IPCs; 87% of cases were biracial and 13% black. Sixty-six percent of cases used IPCs compared to 71% of never users. Among women aged less than 35 years and those aged 35–44 years, there was no effect between ever use of IPC and risk of breast cancer [(RR= 1.1; 95% CI: 0.5–2.4) and (RR=1.1; 95% CI: 0.7–1.6), respectively for ‘ever use’ compared to ‘never use’)]. The risk was non-significantly decreased among IPC users age 45–54 (RR= 0.8; 95% CI: 0.7–1.1) compared to never users. Overall there was no significant association between total breast cancer risk and any use of IPCs (RR= 0.9; 95% CI: 0.7–1.2); however, an increased risk of breast cancer was observed among current users of IPC aged 35–44 (RR=2.3; 95% CI: 1.3–4.1) compared to never users. All calculations were based on unconditional multiple logistic regression models; controls were frequency matched to cases in a ratio of 4:1 for race/ethnicity, decade of age, and area of residence.

IPCs, principally depot medroxyprogesterone acetate (DMPA), were not associated with an increased overall risk of breast cancer (RR= 0.9; 95% CI: 0.7–1.2) when excluding women with past combined OC use compared to never users. There was no evidence that IPCs cause an increase in breast cancer risk five years after exposure had been discontinued, or that it increased the risk of breast cancers occurring in younger women. Furthermore, this study did not support an increased risk among users who were exposed to the substance at a young age [17].

Levonorgestrel-Releasing Intrauterine System

Backman et al. linked women who self-identified as levonorgestrel system users (n=17, 360) in a large post-marketing study on intrauterine system to the Finnish Cancer Registry to

determine breast cancer incidence rates. These rates were compared to the general Finnish female population using Finnish Cancer Registry data from 1998 to examine the relationship between breast cancer and the use of levonorgestrel-releasing intrauterine system. [19]. Among women 40–54 years of age, breast cancer incidence was non-significantly higher in the average Finnish population than the levonorgestrel system users; however, the reverse was seen among women 30–39 years of age. Nevertheless, there was no significant difference in breast cancer risk between levonorgestrel system users and the average Finnish female population in any of the age groups (Table 1). Furthermore, there was no association between length of time since insertion (up to 10 years) and breast cancer incidence in any of the age groups [19].

Oral Progestin

Oral contraceptives—The majority of studies examining the relationship between OCs and breast cancer are focused among women using combined OCs, though a few studies have examined use of progestin-only pills as well. Using a matched case-control study design, Marchbanks et al. examined the risk of breast cancer among women aged 35–64 (n=11, 938) by OC formulation. Progestin-only pill use was not associated with risk of breast cancer among current and previous users compared to never users (RR= 0.9; 95% CI: Not Provided). Any, current, or former use; duration of use; age at first use; and interval since last use did not alter the risk of breast cancer [16].

Kumle et al., in a prospective cohort study conducted in Norway and Sweden (n=103,027), found that regardless of duration, there was no statistically significant association between progestin-only pill use and breast cancer as compared to never users. Among women aged 30–39 and women aged 40–49 at the start of follow-up, progestin-only pill use was associated with a non-significant increased risk (RR= 1.7; 95% CI: 0.8–3.7, RR= 1.6; 95% CI: 0.9–2.6, respectively) compared to never users [21].

Other oral progestin—A prospective cohort study conducted in France by Fabre et al. in 2007, found no significant association between ever-use of progestin and breast cancer risk (RR= 1.01; 95% CI: 0.93–1.11) compared to women who had not been exposed to progestin among women ages 40–64 (n=73,664). However, this study identified a significant increase in breast cancer risk with prolonged duration of use (P= 0.01). Among current users, ≥4.5 years of continuous use was significantly associated with breast cancer risk (RR= 1.44; 95% CI: 1.03–2.00) but less than 4.5 years was not (RR= 1.09; 95% CI: 0.92–1.29) [20]. The mean duration of follow-up was 9.07 years (standard deviation: 2.4). With each additional year of progestin use, the risk of breast cancer increased (RR= 1.03; 95% CI: 1.01, 1.06) compared with never users. Adjusting for previous use or history of OC, benign breast disease, benign uterine or ovarian disease and mammographic history did not significantly alter the association between ever-use of progestin and breast cancer risk. No information was provided about the influence of temporary interruptions or changes in treatment [20].

Discussion

A limited amount of research has been published on the association between progestin-only hormonal contraceptives and breast cancer risk since the IARC Monographs' assessment of

progestin-only hormonal contraceptives. IARC analyzed eight case-control studies published between 1986 and 1996 in various countries (United Kingdom, United States, France, Kenya, Mexico, Thailand, Denmark, and New Zealand) and found no risk of breast cancer among women using progestin-only contraceptives (pill, injectable-DMPA) compared to non-users [12]. Overall findings from the current systematic review are in agreement with the IARC report. All six studies reviewed found no overall association between progestin-only formulations and breast cancer risk. One study observed an increased risk among women who had been current users for ≥4.5 years, but not among women with <4.5 years of use [20], while two other studies reported marginally significant associations in opposite directions for recent use of progestin-only formulations [18,21].

Currently, the most common type of hormonal contraception is the combined OC pill, which may increase the risk of breast cancer up to 15 years after stopping use [21,22]. Standard guidelines suggest no excess risk after 10 years of cessation, but findings are controversial [23]. The popularity of the combined OC pill has driven epidemiologic research in this area to focus on combined OCs rather than progestin-only OCs. There remains ambiguity about the risk of estrogen + progestin formulations, and more studies are needed comparing progestin-only contraceptives to the combined hormone methods [10,16,21].

The biological mechanism linking progestin and breast cancer is complex. Currently, there is substantial evidence to show that various progestins can block enzymes involved in estrogen formation and inactivation; however, more information is needed related to dose response and effects of duration of drug use [13]. Norethindrone is currently the only form of progestin used in progestin-only OCs approved for sale in the United States [24]. The structure and biologic function of certain progestin, such as norethindrone, related to women's health should be evaluated more carefully to determine the impact on breast cancer incidence.. In addition, progestin may affect breast cancer risk differently based on estrogenic environment and progestin type. However, studying individual and joint effects of progestin and estrogen can be challenging in epidemiologic studies where estrogen + progestin and progestin-only use tend to be more common among ever users of progestin [20].

The current review found only six studies examining progestin-only formulations and breast cancer risk published since 1999. Many studies of OCs lacked adequate sample size to study progestin-only use and women's health. Of the studies reviewed here, small sample sizes may have hampered abilities to observe an association. Kumle et al. found no significant increased risk of breast cancer with progestin-only pill use in a prospective cohort study. Of the 3,435 women using progestin-only pills, 29 developed breast cancer [21].

Marchbanks et al. also had a small number of cases (n=32) and controls (n=39) that used progestin-only formulations [16], and found no evidence of an increased risk of breast cancer with injectable or implantable progestin-only contraceptives in recent/current or past users, including no association with age of first exposure and duration of use.

Another limitation of these studies is the heterogeneity of location and administration route. The six studies come from diverse populations: France, Norway, United States, Finland, and

South Africa. Women using any type of progestin were included to examine the role of exogenous progestin on breast cancer risk and to illustrate the importance of continuing research related to progestin-only formulations. Compared to estrogen + progestin birth control options, there are less variations in the market of progestin-only contraceptives. However, different formulations are more common in different countries. For example, French doctors typically prescribe discontinuous, cyclic administration of progestin pills, which is not typical of prescription patterns (continuous, daily intake) in the United States. Furthermore, Europeans have access to additional progestin-only pills that are not sold in the United States (e.g., desogestrel). The largest study reviewed, (including 880 breast cancer cases in women using progestin-only pills before menopause) was performed in the E3N French cohort and found no overall association with ever use, but an increased risk with current use ≥4.5 years [20]. Differences in formulations used, however, may account for lack of replication of this result in other studies included in this review. In addition, due to frequent changes between OC types, it may be hard to adequately quantify the true exposure period of progestin-only use.

The majority of the contraindications to combined OC use (hypertension, migraine) do not exist with progestin-only methods [23, 25]. Many of the reviewed studies used existing information on women predating the early 2000's [16–21]. Despite our inclusion criteria (i.e., 'studies that were published after 1999'), the majority of the studies included in the review primarily took place before the year 2000. Numerous formulations of progestin have emerged since 2000 [26, 27]. Thus, findings may not demonstrate the current risk of progestin on breast cancer. Surveillance bias is often a potential bias of contraceptive studies when comparing never-users of any OCs to OC users. Some studies attempted to control for this by adjusting for breast cancer screening frequency [20].

Conclusions and Recommendations

The role of progestin-only OCs in modifying breast cancer risk is largely unknown. The majority of studies indicate no significant risk of breast cancer with progestin-only use, though number of studies and sample sizes within studies are small. The various types of progestin, modes of administration, frequency of use (continuous/discontinuous cycles), and geographic variations in types used make studying this association challenging. Further understanding of synthetic progesterone may initiate new prescription practices or guidelines for women's health.

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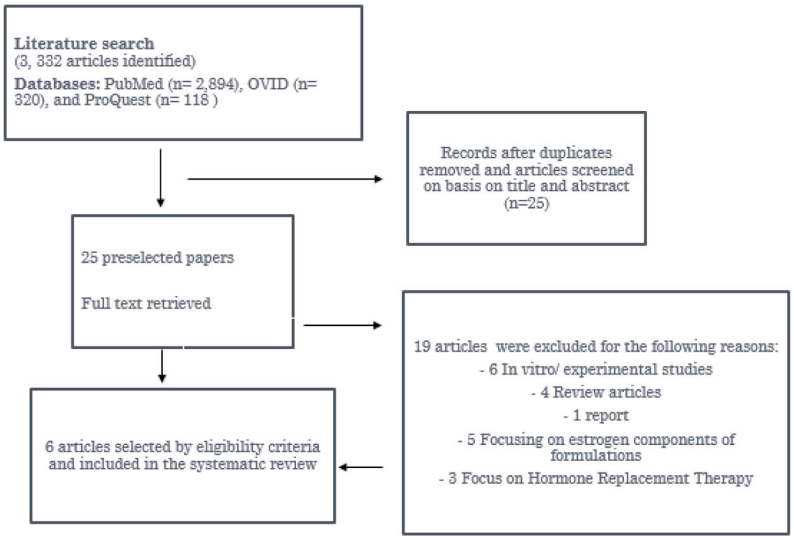

Figure I.
Flow of information through the different phases of a systematic review

Table I

Characteristics of epidemiological studies investigating progestin exposure and breast cancer risk

Reference	Location	Study design	Sample size and characteristics	Outcome and exposure assessment	Confounders included in final analysis	Results/Findings
Shapiro et al., (2000) (17)	Area surrounding Cape Town, South Africa	Case-control	• Women ages 20–54 • 2,109 women (484 cases) • Excluded white women due to low injectable progestin contraceptives (IPC)/Included Black women	Cases: • Women with first occurrences of invasive breast cancer treated between Jan. 94–Oct. 97 at two tertiary care hospitals in Cape Town • Exclusion criteria: women with carcinoma *in situ*, previous history of cancer, not resided in the study region for at least 6 of 12 previous months Controls: • Women admitted for diagnoses that were independent of contraceptive use and breast cancer risk; women admitted for conditions such as VTE, ischemic heart disease, or benign breast disease were not eligible Exposure determined through Interviews	• Age • Ethnic group • Education • Employment • Insurance coverage • Socioeconomic status	• Including women with past combined OC use, norethisterone was used by 13 cases and 64 controls (RR[a] = 0.7; 95% CI: 0.3, 1.5) • Excluding those with past combined OC use, IPCs, principally DMPA[b], did not increase the overall risk of breast cancer (RR = 0.9; 95% CI: N/A[c]) • IPCs were not associated with an increase in: – Breast cancer risk during a period lasting 4–5 years after exposure had been discontinued, – The occurrence of breast cancer at a young age – The breast cancer risk after prolonged time lapses, extending to more than two decades – Breast cancer risk among women who were exposed during adolescence or early adulthood,

Reference	Location	Study design	Sample size and characteristics	Outcome and exposure assessment	Confounders included in final analysis	Results/Findings
						when the breast was growing when the breast was growing when the breast was growing • <35years of age: (RR = 1.1; 95% CI: 0.5, 2.4); 35–44 years: (RR = 1.1; 95% CI: 0.7, 1.6); 45–54 years: (RR = 0.8; 95% CI: 0.6, 1.1) total years of all ages: (RR= 0.9; 95% CI: 0.7,1.2) • Total relative risk for duration was insignificant (protective or null risk)
Marchbanks et al., (2002) (16)	Atlanta, Detroit, Philadelphia, Los Angeles, and Seattle	Matched Case-control	• Women ages 35–64 • 11,938 women (4,575 cases) • Race/ Ethnicity: Black (35%) and White (65%) • Progestin-only type of OC accounted for 0.5 percent of the population (32 cases/39 controls)	Cases: • Women in age group who had invasive breast cancer initially diagnosed between 1994–98 through field center staff in PA and SEER cancer registries in other locations Controls: • Women without a diagnosis of invasive/*in situ* breast cancer in the same geographic location as cases, using random-digit dialing to contact residential households by telephone	Not included because additional factors did not alter point estimates	• The risk of breast cancer among women who currently or had previously used a progestin-only contraceptive (POC) formulation compared to those who had never used an OC (OR= 0.9; 95% CI: N/A) • Aspects of oral-contraceptive use (any, current, or former use; duration of use; age at first use; interval since last use; and estrogen dose) revealed no association with breast cancer • Results did not differ by race

Reference	Location	Study design	Sample size and characteristics	Outcome and exposure assessment	Confounders included in final analysis	Results/Findings
Strom et al. (2004)(18)	Metropolitan areas of Atlanta, GA, Detroit, MI, Los Angeles, CA, Philadelphia, PA, and Seattle, WA	Case-control	• Women ages 35–64 • 9,257 women (4,575 cases) • 4575 cases were a random sample of white and black women aged 35 to 64 with histologically confirmed primary invasive breast cancer diagnosed from July 94 through April 98 • Younger women/blacks were oversampled	Pennsylvania: Cases and controls through area hospitals SEER: cases through National Cancer Institute-funded SEER registries Exposure through interviews: exposure to contraceptive implants-required exposure to Norplant use exposure to contraceptive injections-required DMPA, by brand name or generic name; known other (but not listed) contraceptive injection; or unknown contraceptive injections	• Age – At menarche – At menopause – At first full-term pregnancy among parous women • BMI 5 years before the reference date • First-degree family history of breast cancer • Menopausal status • Parity • Among menopausal women: – Combined OC – Hormone replacement therapy (HRT) – Patch replacement therapy – Unopposed estrogen pill or patch replacement therapy	• No significant association for women who had ever been exposed to injections or implants • Results did not change between pre or post-menopausal women or after adjustment • Risk was not significantly decreased/ increased among: – Current users (women who used injectable contraceptives within 1 year of reference date) (OR[d]= 0.7; 95% CI: 0.4, 1.3) – Women who initiated use in the 5 years immediately preceding the reference date (OR= 0.9; 95% CI: 0.5, 1.4) – Women whose first use was before age 25 (OR= 1.3; 95% CI: 0.7, 2.3) – Among those whose use began before age 35 (OR= 0.9; 95% CI: 0.6, 1.3) • Risk was significantly reduced among women whose first use was within 1 year of the reference date (OR= 0.3; 95% CI: 0.1, 0.9) [e]

Reference	Location	Study design	Sample size and characteristics	Outcome and exposure assessment	Confounders included in final analysis	Results/Findings
						• Short-term users were at a decreased risk relative to never users (OR= 0.6; 95% CI: 0.4, 1.0) • Among women with at least 24 months of use, there was a non-significant increased risk relative to never users (OR= 1.4; 95% CI: 0.8, 2.5). No increased risk was observed when comparing long-term users with nonusers. • After excluding short-term users, there was a non-significant decreased risk with increasing duration of exposure The non-significantly increased risk seen with longer duration of use when short–term users were included, may have been due to the decreased risk in short-term users as explained by the author • No increased risk of breast cancer associated with the use of injectable or implantable progestin-only contraceptives
Backman et al., (2005) (19)	Finland	Retrospective Cohort	• Women ages 30–54 • 141, 892 women (17, 360 women used levonorgestrel-releasing intrauterine systems and 165 cases)	• Questionnaire/ Exposure determined through interviews • Levonorgestrel-intrauterine system inserted between 1990–93 Cases:	Not included	• No difference between the levonorgestrel system users and the average Finnish female population in any of the 5-year age groups: Age 30–34 (P= 0.84) Age 35–39 (P= 0.06) Age 40–44 (P= 0.99)

Reference	Location	Study design	Sample size and characteristics	Outcome and exposure assessment	Confounders included in final analysis	Results/Findings
				• Identified through the national Finish Cancer Registry (FCR) • Diagnosed with breast cancer from 1990–2000 <u>Comparison Group</u>: • Average Finnish female population identified through the national FCR		Age 45–49 (P= 0.41) Age 50–54 (P= 0.85) • No association between length of time elapsed from intrauterine system insertion up to 10 years and the yearly incidence of breast cancer in any 5-year age category or in the pooled data Follow-up time: 10 years
Fabre et al., (2007)(20)	France	Prospective Cohort	• Women ages 40–64 • 73,664 women (880 cases)	• Restricted to women who had never used a progestin before the age of 40 • Women reached menopause after age 40 <u>Cases</u>: • Identified from self-reports of participants: all questionnaires asked whether any cancer had been diagnosed, requesting the address of their physicians and permission to contact them to obtain the pathology reports • Identified through the E3N	• Age – At menarche – Late age at first birth – Late age at menopause • HRT • OC use • Parity	• There was no significant association between ever-use of progestin and breast cancer risk (RR= 1.01; 95% CI: 0.9, 1.1) • Mean duration of follow-up: 9.1 years (SD: 2.4) • The relationship between ever-use of progestin and breast cancer risk did not vary significantly by previous use of OC, by personal history of benign breast disease, by personal history of benign uterine or ovarian disease or mammographic history. • Increasing risk of breast cancer per additional year of progestin use: (RR= 1.03; 95% CI: 1.01, 1.06)[e] Interval since first use (RR= 0.99; 95% CI: 0.98, 1.01)

Reference	Location	Study design	Sample size and characteristics	Outcome and exposure assessment	Confounders included in final analysis	Results/Findings
				prospective study prospective study <u>Comparison Group</u>: • Identified through the E3N prospective study		Interval since last use (RR=0.99; 95% CI: 0.98, 1.01) • Among current users, use longer than 4.5 years was significantly associated with breast cancer risk (RR= 1.44; P= 0.03) [e], but not use shorter than 4.5 years (RR= 1.09; 95% CI: 0.92, 1.29) • No significant association between breast cancer risk and ever-use of a progestin before menopause
Kumle et al., (2002) (21)	Norway and Sweden	Prospective Cohort	• Women ages 30–49 • 103,027 women (54 cases)	<u>Cases:</u> • Identified from questionnaire administered at cohort enrollment • Sweden: Identified through the Swedish Central Population Registry (SCPR) • Norway: Identified through the Central Population Register (CPR) <u>Comparison Group:</u> • Norway: Random sample from CPR • Sweden: randomly	• Age – At menarche – At first birth – At cohort enrollment • BMI • History of breastfeeding • History of breast cancer • HRT • Menopausal status • Parity	• Risk of breast cancer according to exclusive use of progestin-only oral pills compared to never users among: • Ever-users: (RR= 1.1; 95% CI: 0.8, 1.7) • Current/Recent progestin-only contraceptive users: (RR= 1.6; 95% CI: 1.0, 2.4) • Current/Recent progestin-only contraceptive users by age at cohort enrollment-Ages 30–39: (RR= 1.7; 95% CI: 0.8, 3.7) Ages 40–49: (RR= 1.6; 95% CI: 0.9, 2.6) The start of follow-up was defined by the return of the Questionnaire and ended December 31, 1999 or at emigration, death, or primary breast cancer diagnosis, whichever occurred first.

Reference	Location	Study design	Sample size and characteristics	Outcome and exposure assessment	Confounders included in final analysis	Results/Findings
				sampled from SCPR sampled from SCPR		

[a] RR: Relative Risk;

[b] N/A: Not Applicable;

[c] DMPA: depot medroxyprogesterone acetate;

[d] OR: Odds Ratio;

[e] Statistically Significant; SD: Standard deviation