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Oral contraceptive formulation and risk of breast cancer☆,☆☆

Polly A. Marchbanks[a,*], **Kathryn M. Curtis**[a], **Michele G. Mandel**[a], **Hoyt G. Wilson**[a], **Gary Jeng**[a], **Suzanne G. Folger**[a], **Jill A. McDonald**[a], **Janet R. Daling**[b], **Leslie Bernstein**[c], **Kathleen E. Malone**[b], **Phyllis A. Wingo**[a], **Michael S. Simon**[d], **Sandra A. Norman**[e], **Brian L. Strom**[e], **Giske Ursin**[f,g,h], **Linda K. Weiss**[i], **Ronald T. Burkman**[j], and **Robert Spirtas**[k]

[a]Division of Reproductive Health, Centers for Disease Control and Prevention, Atlanta, GA 30333, USA

[b]Fred Hutchinson Cancer Research Center, Division of Public Health Sciences, Seattle, WA, USA

[c]Department of Population Sciences, Beckman Research Institute, City of Hope, Duarte, CA, USA

[d]Division of Hematology and Oncology and Population Studies and Prevention Program, Karmanos Cancer Institute at Wayne State University, Detroit, MI, USA

[e]Center for Clinical Epidemiology and Biostatistics and Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, PA, USA

[f]Cancer Registry of Norway, Oslo, Norway

[g]Department of Nutrition, University of Oslo, Oslo, Norway

[h]University of Southern California, Los Angeles, CA, USA

[i]Office of Cancer Centers, National Cancer Institute, Bethesda, MD, USA

[j]Department of Obstetrics and Gynecology, Tufts University School of Medicine and Baystate Medical Center, Springfield, MA, USA

[k]School of Public Health and Health Services, George Washington University, Washington, DC, USA

Abstract

Background—While evidence on the association between oral contraceptive (OC) use and breast cancer generally suggests little or no increased risk, the question of whether breast cancer risk varies by OC formulation remains controversial. Few studies have examined this issue because large samples and extensive OC histories are required.

Study Design—We used data from a multicenter, population-based, case–control investigation. Women aged 35–64 years were interviewed. To explore the association between OC formulation and breast cancer risk, we used conditional logistic regression to derive adjusted odds ratios, and we used likelihood ratio tests for heterogeneity to assess whether breast cancer risk varied by OC formulation. Key OC exposure variables were ever use, current or former use, duration of use and time since last use. To strengthen inferences about specific formulations, we restricted most

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*Corresponding author. Tel.: +1 770 488 6378; fax: +1 770 488 6391. pam2@cdc.gov (P.A. Marchbanks).

analyses to the 2282 women with breast cancer and the 2424 women without breast cancer who reported no OC use or exclusive use of one OC.

Results—Thirty-eight formulations were reported by the 2674 women who used one OC; most OC formulations were used by only a few women. We conducted multivariable analyses on the 10 formulations that were each used by at least 50 women and conducted supplemental analyses on selected formulations of interest based on recent research. Breast cancer risk did not vary significantly by OC formulation, and no formulation was associated with a significantly increased breast cancer risk.

Conclusions—These results add to the small body of literature on the relationship between OC formulation and breast cancer. Our data are reassuring in that, among women 35–64 years of age, we found no evidence that specific OC formulations increase breast cancer risk.

Keywords

Oral contraceptives; Breast cancer; Hormones; Epidemiology; Case–control studies

1. Introduction

The relationship between oral contraceptives (OCs) and breast cancer is of critical public health importance due to the high prevalence of OC use and the serious consequences of breast cancer. OCs are the leading method of contraception in the United States; over 45 million US women aged 15–44 years have used OCs, and 10.7 million use them currently [1]. Breast cancer is one of the most common cancers among US women, with an estimated 230,480 new cases and 39,520 deaths annually [2].

Numerous OC formulations have been marketed over the years. The question of whether breast cancer risk might vary by OC formulation remains controversial, especially with the ongoing development of new preparations with different hormonal constituents, dosages and schedules of administration. In 2002, we published results from the National Institute of Child Health and Human Development Women's Contraceptive and Reproductive Experiences (Women's CARE) Study reporting that, among women aged 35–64 years, current or former OC use was not associated with a significantly increased risk of breast cancer [3]. We did not, however, examine breast cancer risk by individual OC formulations. In this paper, we extend our previous findings by exploring OCs and breast cancer risk by specific OC preparations. The elucidation of possible differential associations between OC formulations and breast cancer risk was one of the primary objectives of the Women's CARE Study.

2. Materials and methods

Detailed methods for the Women's CARE Study appear elsewhere [4]. Briefly, it was a multicenter, population-based, case–control study. Subjects were enrolled in Atlanta, Detroit, Philadelphia, Los Angeles and Seattle. The Centers for Disease Control and Prevention was the Data Coordinating Center. The study received institutional review board approval at participating centers, and participants gave written informed consent.

2.1. Cases

White women and black women aged 35–64 years who resided in study locations and had invasive breast cancer newly diagnosed during 1994–1998 were ascertained in Philadelphia by field center staff and, at other sites, through rapid reporting mechanisms of local Surveillance, Epidemiology and End Results registries. Sampling from ascertained women was conducted using selection probabilities specific to study site, race, age and month of

diagnosis. Younger women and black women were over-sampled to approximate a uniform distribution across age and race groups. Of the 5982 eligible women selected as cases, 4575 (76.5%) were interviewed.

2.2. Controls

Women without a current or past diagnosis of invasive or in situ breast cancer were identified as controls from the same geographic areas as cases using random-digit dialing with unclustered, equal-probability sampling of phone numbers. Of the residential households called, approximately 82% were screened successfully. Controls were sampled randomly throughout the study from eligible women enumerated during telephone screening at rates designed to match control interview frequencies to case interview frequencies within strata of study site, race and age. Of the 5956 eligible women selected as controls, 4682 (78.6%) were interviewed.

2.3. Interview

In-person interviews were conducted using a standardized questionnaire. Histories of hormone use were obtained until an interview reference date (cases, date of first microscopic breast cancer diagnosis; controls, date of household telephone screening during random digit dialing). Additionally, the questionnaire focused on reproductive and health histories, as well as selected other exposures. A life-events calendar [5], response showcards and photographs of hormone preparations were used to enhance recall [6]. Interviewing occurred from August 1994 through December 1998. Mean interview time was 85 min [4].

Past research suggests that any association between OCs and breast cancer is likely to be small [7,8]. Therefore, we took extensive measures to minimize exposure misclassification from (a) recording or processing errors and (b) variation in interviewing, coding and editing within or among the data collection centers. Key measures included standardized interviewer training and monitoring, standardized coding procedures and multiple quality control checks for data discrepancies, with questionnaire editing and interviewer/respondent recontact as necessary [4].

2.4. Analysis

Starting with 4575 cases and 4682 controls, we sequentially excluded from this analysis women who reported use of unknown OC formulations (1751 cases; 1624 controls), progestin-only formulations (22 cases; 30 controls) and multiple formulations (520 cases; 604 controls). These exclusions were made to strengthen the validity of our inferences regarding specific formulations containing an estrogen and progestin in each cycle. A total of 4706 women remained for analysis: 2282 cases and 2424 controls. Thirty-eight formulations were reported by the 2674 women in our analysis who reported exclusive use of one OC. However, most formulations were used by only a few women. We conducted multivariable analyses on the 10 formulations that were each used by at least 50 women. This cut point was selected with the goal of providing reasonable statistical power and precision in estimation (using multivariable models that controlled for potential confounders), while including a majority of OC users. In separate models for each OC formulation, we used conditional logistic regression to calculate odds ratios (ORs) as estimators of relative risk (incidence density ratios) [9] of breast cancer. Conditioning variables were study site, race and age. All multivariable analyses focused on the key OC exposure variables of ever use, current or former use, duration of use and time since last use. Indicator variables representing eight factors were included in all multivariable models as an a priori confounder set [3] (see footnote to Table 2). Point estimates are accompanied by 95% confidence intervals (CIs). “Significant” refers to statistical significance at the .05 level. To test whether OCs influenced breast cancer risk differently in women using

different OC formulations, we assessed OC formulation as a potential effect modifier, applying likelihood-ratio tests for heterogeneity to models that included relevant interaction terms [10].

In addition to these core analyses as described above, we conducted supplemental analyses on multiphasic formulations (regardless of sample size) due to a recent report from the Nurses' Health Study II suggesting an increased risk of breast cancer associated with current use of a triphasic formulation containing levonorgestrel as the progestin [11]. Finally, we conducted additional exploratory analyses specifically on this one triphasic preparation.

3. Results

Cases and controls had similar distributions for most characteristics (Table 1). Absolute differences in means or proportions were not large except for a family history of breast cancer that was reported more frequently among cases.

The 10 formulations that were each used by at least 50 women were reported by 2158 (80.7%) of the 2674 women reporting use of one OC; the percentage of these users reporting any one of these 10 formulations ranged from 14.8% to 2.5%. Nine of the 10 formulations were monophasic. Only one of the 10 formulations was multiphasic; this was a triphasic, containing a constant estrogen dosage and three dosage levels of progestin (norethindrone). None of our models produced significantly elevated ORs, and a few ORs were significantly reduced (Table 2). Tests for effect modification by OC formulation for each of the OC exposures were not statistically significant, suggesting that OC formulation was not modifying the effect of OCs on breast cancer risk.

In total, six multiphasic formulations were reported by women who were exclusive users of one formulation; however, as mentioned above, only one of these six was used by at least 50 women, and it was a triphasic containing 35 mcg ethinyl estradiol/0.5 mg (7 days), 0.75 mg (7 days), 1.0 mg (7 days) norethindrone. The additional five multiphasic formulations contained (a) 35 mcg ethinyl estradiol/0.5 mg (7 days), 1.0 mg (9 days), 0.5 mg (5 days) norethindrone; (b) 30 mcg ethinyl estradiol/0.05 mg levonorgestrel (6 days), 40 mcg ethinyl estradiol/0.075 mg levonorgestrel (5 days), 30 mcg ethinyl estradiol/0.125 mg levonorgestrel (10 days); (c) 35 mcg ethinyl estradiol/0.18 mg (7 days), 0.215 mg (7 days), 0.25 mg (7 days) norgestimate; (d) 35 mcg ethinyl estradiol/0.5 mg (10 days), 1.0 mg (11 days) norethindrone and (e) 35 mcg ethinyl estradiol/0.5 mg (7 days), 1.0 mg (14 days) norethindrone. When we conducted supplemental analyses to examine these six multiphasic formulations in multivariable models, we did not find significantly elevated ORs (data not shown). Statistical tests for exposure–OC formulation effect modification among the six multiphasics were not significant. However, cell sizes were small, so estimation was imprecise.

Only one triphasic formulation reported in our analyses contained levonorgestrel as the progestin, which was the same formulation reported in the Nurses' Health Study II as being associated with increased breast cancer risk [11]. This was the formulation containing 30 mcg ethinyl estradiol/0.05 mg levonorgestrel (6 days), 40 mcg ethinyl estradiol/0.075 mg levonorgestrel (5 days), 30 mcg ethinyl estradiol/0.125 mg levonorgestrel (10 days). Only five cases and eight controls reported ever using this formulation exclusively (OR 0.7, 95% CI 0.2–2.4), and only two of these women were current users. Therefore, we conducted two additional exploratory analyses using multivariable models to look for suggestions in our data that this particular triphasic might be associated with increased breast cancer risk; these exploratory analyses were not restricted to exclusive use (i.e., they did not exclude users of unknown, progestin-only or multiple OC formulations). First, we examined the association between our key OC exposure variables and breast cancer risk among women who had used

this triphasic formulation. We found no significantly elevated ORs. In these analyses, 77 cases and 67 controls had ever used this triphasic (OR 1.2, 95% CI 0.8–1.8), and 37 cases and 34 controls were current users (OR 1.0, 95% CI 0.6–1.7). Second, we examined the association between our key OC exposure variables and breast cancer risk among women who had used this triphasic formulation for more total months of use than any other combination or unknown formulation. Again, we found no significantly elevated ORs. In these analyses, 31 cases and 31 controls had ever used this triphasic (OR 1.1, 95% CI 0.6–1.9), and 13 cases and 15 controls were current users (OR 0.8, 95% CI 0.3–1.7).

4. Discussion

In this analysis, we did not find evidence that breast cancer risk varies significantly by OC formulation, and no specific OC formulation was associated with a significantly increased risk of breast cancer. A few significant risk reductions were noted.

The objective of our initial publication using the Women's CARE Study data was to provide an overview of the relationship between OCs and breast cancer [3]. We performed analyses that grouped various types of OCs reported by women who had used one or more formulations. In addition to our main analyses that grouped all combination OCs, we performed analyses that grouped estrogens according to high or low dose, as well as analyses that grouped progestins according to chemical structure (i.e., estranes, gonanes or others). Unlike estrogens, progestins are difficult to group based on dose because standard equivalencies are unavailable. We also examined some groups of progestins individually, but without regard for dose or accompanying estrogen. These analyses did not reveal consistent differences in breast cancer risk according to estrogen dose or progestin type. In the current analysis reported in this paper, we did not group related OC preparations to obtain larger samples because the objective was to examine specific formulations that are distinguished by the type, dose and administration schedule of the hormonal constituents. Biologic interactions exist between hormones administered in temporal proximity [12]. The overall activity of an OC results from the biologic activities and the dosages of the individual estrogen and progestin components, as well as the potentiating and antagonistic effects of each hormone on the other [13]. Therefore, analyses that combine many different OC formulations to obtain larger numbers could mask the influence of any one specific formulation.

In 1996, a pooled analysis of 54 epidemiologic studies showed a small increased risk of breast cancer diagnosis in current users of combined OCs and in women who had stopped use in the past 10 years [7,8]. The available evidence on specific hormonal constituents did not suggest major differences in the effects of various types of estrogen or progestin on breast cancer risk.

In 2003, Althuis and colleagues [14] examined the risk of breast cancer in women 20–44 years of age according to hormonal content and potency of OCs. The authors concluded that newer pills with low-potency/low-estrogen doses may be associated with a lower risk of breast cancer than older high-potency/high-dose preparations. In our previous work [3], we did not find an increasing risk of breast cancer with higher estrogen doses, nor did the pooled analysis [7,8]. In this analysis, we did not group OCs according to estimated potencies due to the many controversies about this procedure [15–19]. These include reports of different potencies for the same hormone, concerns that some OCs have been classified incorrectly, questions about the use of animal models that may not be completely analogous to humans, uncertainties about the application of results to a particular target organ (e.g., the breast) when the potency assays have been conducted on a different target organ (e.g., the uterus), issues regarding the clinical relevance of potency differences detected in the

laboratory, ambiguities arising when multiple hormones are given simultaneously because the potency of one hormone (e.g., progestin) can change in the presence of another hormone (e.g., estrogen) and concerns that statements about the power or potency of hormones tend to be oversimplifications.

In 1986, investigators from the Cancer and Steroid Hormone (CASH) Study [20] reported breast cancer risk by ever use of 12 specific OC formulations among women who had used only one combination formulation in their lifetimes. Data for this large case–control study were collected during 1980–1982, and the study population was women aged 20–54 years. Odds ratios ranged from 0.6 to 1.6; none of the elevated ORs was statistically significant. Eight of the 10 formulations in our multivariable analyses conducted on preparations used by at least 50 women corresponded with formulations analyzed in the CASH Study; the two that did not overlap were (a) the monophasic containing 35 mcg ethinyl estradiol/1.0 mg norethindrone and (b) the triphasic containing 35 mcg ethinyl estradiol/0.5 mg (7 days), 0.75 mg (7 days), 1.0 mg (7 days) norethindrone. Among the eight overlapping formulations, the CASH Study and Women's CARE Study each found a different formulation to be associated with a significant risk reduction. While a significantly reduced OR of 0.7 was noted in the CASH Study for ever use of 100 mcg mestranol/2.5 mg norethynodrel, we noted a nonsignificant OR of 0.9. While we found a significantly reduced OR of 0.7 for ever use of 80 mcg mestranol/1.0 mg norethindrone, the CASH Study reported an OR of 1.0. Our results are consistent with the CASH Study in that no specific formulation was associated with significantly elevated breast cancer risk.

As mentioned earlier, recent results from the Nurses' Health Study II suggested a possible increased risk of breast cancer associated with current use of a triphasic formulation containing levonorgestrel (RR 3.05, 95% CI 2.00–4.66); the investigators called for replication of these findings, which were not derived from a prior hypothesis about this specific preparation [11]. Women in the Nurses' Health Study II were aged 24–43 years at enrollment in 1989, and results were based on follow-up through June 1, 2001. Questionnaires were mailed to participants every 2 years to obtain information on exposures and outcome. In our analysis, the only multiphasic preparation with exclusive use by at least 50 women was a triphasic containing norethindrone as the progestin. When we examined exclusive use of each multiphasic preparation reported in our study, regardless of sample size, we did not find significant risk elevations. Similarly, multiple exploratory analyses (that were not restricted to exclusive use) did not suggest a significantly increased risk of breast cancer with the triphasic formulation of interest, containing 30 mcg ethinyl estradiol/0.05 mg levonorgestrel (6 days), 40 mcg ethinyl estradiol/0.075 mg levonorgestrel (5 days), 30 mcg ethinyl estradiol/0.125 mg levonorgestrel (10 days). However, the sparse number of women in our study who reported use of this triphasic formulation precluded extensive analysis. In our previous work that grouped women using various types of progestins, we found no increased risk with current use of combination OCs containing levonorgestrel (OR 0.9, 95% CI 0.5–1.5) [3].

Our findings are subject to several limitations. Despite the large size of the Women's CARE Study, our samples for individual analyses were often small, and we were not able to examine all formulations. Additionally, we relied on self-reported contraceptive history. Both cases and controls may have had difficulty in remembering specific OC formulations, especially ones used in the more distant past. To minimize exposure misclassification, we used memory aids to enhance recall [6,21], including a life-events calendar and a comprehensive notebook of color photographs depicting OC preparations marketed in the United States. Finally, we are uncertain whether our results apply to women of all ages and races because the Women's CARE Study included only white women and black women 35–64 years old. Some evidence suggests that if OCs are related to an increased risk of breast

cancer, the associations might be strongest among women younger than 35 years of age [7]. The Women's CARE Study focused on older women because it was designed to address the research gap of whether OC use in the reproductive years would elevate the risk of breast cancer later in life, when the baseline incidence of breast cancer is higher.

Despite these limitations, our study has substantial strengths including a population-based design, multicenter data collection, use of community controls and oversampling of black women. Additional strengths include standardized data collection using an extensive questionnaire, substantial efforts to minimize inter- and intracenter measurement variation, special attention to reducing recording and processing errors, and control of possible confounding by a wide variety of factors. A strength of this particular analysis is that, during protocol development, we specified that examination of breast cancer risk by OC formulation was a primary study objective.

The first OC formulation was marketed in the United States in 1960 [22]. While only two estrogens (mestranol and ethinyl estradiol) have been used in OCs in the United States, numerous progestins have been used. New formulations have been marketed over the years, with the goal of identifying the lowest hormonal dosages that balance contraceptive efficacy with a favorable side effect profile [23]. Some investigators have called for a shift in our focus on possible adverse side effects of OC use to the identification of a comprehensively beneficial OC that would reduce the risk of breast, ovarian and uterine cancer without cardiovascular complications [24]. It is well documented that OC use decreases ovarian and uterine cancer [25,26]. While the significant risk reductions detected in our analyses could be chance associations, they also suggest that an OC formulation that reduces breast cancer risk might one day become a reality. The design of hormonal contraceptives enabling primary prevention of breast cancer has been discussed by the Institute of Medicine as one possible benefit of the extensive research on the controversies that continue to surround the issue of OCs and breast cancer risk [27].

This analysis highlights the dramatic decrease in sample sizes that occurs at the specific formulation level in OC studies. Although examination of breast cancer risk by specific OC formulations was a primary objective of the Women's CARE Study, we selected subjects without regard for exposure status and did not monitor during data collection the numbers of women reporting various types of OC use. Future studies would be strengthened by increasing sample sizes for specific formulations, perhaps through increasing the number of participating data collection centers and through intensifying efforts (e.g., through medical record or pharmacy review) to decrease the number of unknown formulations reported by women. Medical record or pharmacy review would also be helpful in validating use of specific formulations reported. Since it is possible that a particular OC formulation could influence the risk of breast cancer, research in this area should be ongoing. However, we urge caution in interpreting subgroup analyses, especially those not based on a prior hypothesis and strong supporting rationale. Numerous investigators have written about the challenges, opportunities and necessary cautions with subgroup analyses [28–30]. Because subgroup analyses are usually based on small samples and large numbers of significance tests, confirmation of findings by multiple independent investigations is essential to strengthen confidence in the accuracy of results. The particular challenges of epidemiologic research on OC formulations may make regular updates of large pooled analyses of individual data from multiple studies an appealing option for moving this important body of evidence forward.

In summary, these results add to the small body of literature on the relationship between OC formulation and breast cancer. Our data are reassuring in that, among women 35–64 years of age, we found no evidence that specific OC formulations increase breast cancer risk.

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Investigators in the NICHD Women's CARE Study included: *Project Officer:* Dr. Robert Spirtas; *Principal Investigators:* Dr. Leslie Bernstein, Dr. Janet R. Daling, Dr. Jonathan M. Liff, Dr. Polly A. Marchbanks, Dr. Brian L. Strom, Dr. Linda K. Weiss; *Co-Principal Investigators:* Dr. Dennis M. Deapen, Dr. Elaine W. Flagg, Dr. Jill A. McDonald, Dr. Sandra A. Norman, Dr. Michael F. Press, Dr. Hoyt G. Wilson; *Co-Investigators:* Dr. Jesse A. Berlin, Dr. Ronald T. Burkman, Dr. Ralph J. Coates, Dr. Suzanne G. Folger, Dr. Kathleen E. Malone, Dr. Michael S. Simon, Dr. Giske Ursin, Dr. Phyllis Wingo. Members of the Scientific Advisory Committee included: Dr. Barbara S. Hulka, Dr. Carrie Hunter, Dr. Dennis Lezotte, Dr. James Schlesselman.

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References

1. Mosher WD, Jones J. Use of contraception in the United States: 1982–2008. Vital Health Stat. 2010; 23:1–44.
2. American Cancer Society. Cancer facts & figures 2011. Atlanta, GA: American Cancer Society; 2011.
3. Marchbanks PA, McDonald JA, Wilson HG, et al. Oral contraceptives and the risk of breast cancer. N Engl J Med. 2002; 346:2025–32. [PubMed: 12087137]
4. Marchbanks PA, McDonald JA, Wilson HG, et al. The NICHD women's contraceptive and reproductive experiences study: methods and operational results. Ann Epidemiol. 2002; 12:213–21. [PubMed: 11988408]
5. Wingo PA, Ory HW, Layde PM, Lee NC. Cancer and Steroid Hormone Study Group. The evaluation of the data collection process for a multicenter, population-based, case–control design. Am J Epidemiol. 1988; 128:206–17. [PubMed: 3381827]
6. West, SL.; Strom, BL.; Poole, C. Validity of pharmacoepidemiologic drug and diagnosis data. In: Strom, BL., editor. Pharmacoepidemiology. 4. Sussex: John Wiley; 2005. p. 709-65.
7. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: further results. Contraception. 1996; 54(Suppl):1–106. [PubMed: 8804800]
8. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies. Lancet. 1996; 347:1713–27. [PubMed: 8656904]
9. Greenland S, Thomas DC. On the need for the rare disease assumption in case–control studies. Am J Epidemiol. 1982; 116:547–53. [PubMed: 7124721]
10. Kleinbaum, DG.; Kupper, LL.; Morgenstern, H. Epidemiologic research. Belmont, California: Lifetime Learning Publications; 1982.
11. Hunter DJ, Colditz GA, Hankinson SE, et al. Oral contraceptive use and breast cancer: a prospective study of young women. Cancer Epidemiol Biomarkers Prev. 2010; 19:2496–502. [PubMed: 20802021]
12. Nelson, AL. Combined oral contraceptives. In: Hatcher, RA.; Trussell, J.; Nelson, AL.; Cates, W.; Stewart, FH.; Kowal, D., editors. Contraceptive technology. 19. New York: Ardent Media, Inc; 2007. p. 193-270.

13. Dickey, RP. Managing contraceptive pill patients. 10. Dallas: EMIS, Inc; 2000.
14. Althuis MD, Brogan DR, Coates RJ, et al. Hormonal content and potency of oral contraceptives and breast cancer risk among young women. Br J Cancer. 2003; 88:50–7. [PubMed: 12556959]
15. Hatcher, RA.; Stewart, F.; Trussell, J., et al. Contraceptive technology 1990–1992. 15. New York: Irvington Publishers, Inc; 1990.
16. Hatcher, RA.; Guillebaud, J. The pill: combined oral contraceptives. In: Hatcher, RA.; Trussell, J.; Stewart, F., et al., editors. Contraceptive technology. 17. New York: Ardent Media, Inc; 1998. p. 405-66.
17. Dorflinger LJ. Relative potency of progestins used in oral contraceptives. Contraception. 1985; 31:557–70. [PubMed: 3899503]
18. American Medical Association. Drug evaluations. 6. Philadelphia: American Medical Association; 1986.
19. Speroff, L.; Darney, PD. A clinical guide for contraception. 3. Philadelphia: Lippincott Williams & Wilkins; 2001.
20. Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. Oral contraceptive use and the risk of breast cancer. N Engl J Med. 1986; 315:405–11. [PubMed: 3736618]
21. Coulter A, Vessey M, McPherson K, Crossley B. The ability of women to recall their oral contraceptive histories. Contraception. 1986; 33:127–37. [PubMed: 3698594]
22. Hatcher, RA.; Guest, F.; Stewart, F.; Stewart, GK.; Trussell, J.; Frank, E. Contraceptive technology 1984–1985. 12. New York: Irvington Publishers, Inc; 1984.
23. Kaunitz AM. Efficacy, cycle control, and safety of two triphasic oral contraceptives: Cyclessa (desogestrel/ethinyl estradiol) and Ortho-Novum 7/7/7 (norethindrone/ethinyl estradiol). Contraception. 2000; 61:295–302. [PubMed: 10906499]
24. Davidson NE, Helzlsouer KJ. Good news about oral contraceptives (editorial). N Engl J Med. 2002; 346:2078–9. [PubMed: 12087145]
25. Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. The reduction in risk of ovarian cancer associated with oral contraceptive use. N Engl J Med. 1987; 316:650–5. [PubMed: 3821795]
26. Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. . Combination oral contraceptive use and the risk of endometrial cancer. JAMA. 1987; 257:796–800. [PubMed: 3027423]
27. Committee on the Relationship Between Oral Contraceptives and Breast Cancer, Institute of Medicine, Division of Health Promotion and Disease Prevention. Oral contraceptives and breast cancer. Washington, DC: National Academy Press; 1991.
28. Stallones RA. The use and abuse of subgroup analysis in epidemiological research. Prev Med. 1987; 16:183–94. [PubMed: 3295858]
29. Klebanoff MA. Subgroup analysis in obstetrics clinical trials. Am J Obstet Gynecol. 2007; 197:119–22. [PubMed: 17689621]
30. Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ. 2010; 340:850–4.

Table 1

Selected characteristics of the women with breast cancer and controls

Characteristic	Cases (*n*=2282)	Controls (*n*=2424)
Continuous variables: mean		
Age (years)	50.9	50.4
Age at menarche (years)	12.4	12.4
Age at menopause among menopausal women (years)	47.2	45.5
Age at first term pregnancy among parous women (years)[a]	22.7	22.6
Number of term pregnancies[a]	2.1	2.3
Body mass index at reference date minus 5 years[b]	26.1	26.3
Categorical variables: percent[c]		
White race	62.3	61.3
Menopausal status		
Pre- or perimenopausal	40.7	40.2
Postmenopausal	39.2	38.0
Unable to classify	20.1	21.8
Family history of breast cancer[d]		
No	78.5	87.1
Yes	17.6	9.0
Adopted or unknown	3.9	3.9
Ever use of hormone replacement therapy	38.0	41.2

[a]For the purposes of this study, term pregnancy was defined as a gestation of at least 27 weeks; if a woman was pregnant at the time of the interview, that pregnancy was not counted.

[b]The body mass index was calculated as the weight in kilograms divided by the square of the height in meters. The reference date was the date of the diagnosis for women with breast cancer and the date of telephone screening for controls.

[c]Percentages calculated with nonmissing values.

[d]A family history of breast cancer was defined as breast cancer in the woman's mother, sister or daughter.

Table 2

Risk of breast cancer according to OC formulation in the Women's CARE Study among women who reported exclusive use of a combination OC formulation that was used by at least 50 women[a]

Variable	100 mcg mestranol/1.0 mg ethynodiol diacetate			35 mcg ethinyl estradiol/0.5 mg norethindrone			35 mcg ethinyl estradiol/1.0 mg norethindrone			50 mcg mestranol/1.0 mg norethindrone		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Total no. of subjects	1124	1085		1089	1034		1234	1172		1221	1206	
General use												
No use[b]	1032	980	1.0	1032	980	1.0	1032	980	1.0	1032	980	1.0
Ever use	81	95	0.8 (0.6–1.1)	47	44	1.2 (0.7–1.8)	192	179	1.0 (0.8–1.3)	179	213	0.8 (0.7–1.1)
Current use[c]							7	6	1.0 (0.3–3.0)			
Former use	81	95	0.8 (0.6–1.1)	46	43	1.2 (0.7–1.8)	185	173	1.0 (0.8–1.3)	177	213	0.8 (0.6–1.1)
Duration of use												
<2 years	19	23	0.8 (0.4–1.5)	28	26	1.2 (0.7–2.0)	70	68	0.9 (0.6–1.4)	50	65	0.8 (0.5–1.2)
2+ years	62	72	0.8 (0.5–1.1)	19	18	1.2 (0.6–2.3)	122	111	1.0 (0.8–1.4)	129	148	0.8 (0.6–1.1)
Time since last use												
Current use							7	6	1.0 (0.3–3.0)			
7 months–<5 years							13	11	1.1 (0.5–2.5)	8	7	1.2 (0.4–3.4)
5+ years	81	95	0.8 (0.6–1.1)	46	43	1.2 (0.7–1.8)	172	162	1.0 (0.8–1.3)	169	206	0.8 (0.6–1.0)

Variable	80 mcg mestranol/1.0 mg norethindrone			100 mcg mestranol/2.0 mg norethindrone			100 mcg mestranol/2.5 mg norethynodrel			30 mcg ethinyl estradiol/0.3 mg norgestrel		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Total no. of subjects	1177	1168		1171	1137		1097	1047		1138	1081	
General use												
No use[b]	1032	980	1.0	1032	980	1.0	1032	980	1.0	1032	980	1.0
Ever use	132	178	0.7 (0.6–0.9)*	129	146	0.8 (0.6–1.1)	55	57	0.9 (0.6–1.3)	95	90	1.0 (0.7–1.4)
Current use[c]												
Former use	131	178	0.7 (0.6–0.9)*	129	146	0.8 (0.6–1.1)	55	57	0.9 (0.6–1.3)	85	86	1.0 (0.7–1.3)
Duration of use												
<2 years	40	60	0.6 (0.4–0.99)*	55	52	1.1 (0.7–1.6)	21	27	0.8 (0.4–1.4)	41	28	1.5 (0.9–2.6)

Variable	80 mcg mestranol/1.0 mg norethindrone			100 mcg mestranol/2.0 mg norethindrone			100 mcg mestranol/2.5 mg norethynodrel			30 mcg ethinyl estradiol/0.3 mg norgestrel		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
2+ years	92	118	0.8 (0.6–1.0)	74	94	0.7 (0.5–0.9) *	34	30	1.0 (0.6–1.7)	53	62	0.8 (0.5–1.1)
Time since last use												
Current use												
7 months–<5 years												
5+ years	131	175	0.7 (0.6–0.96) *	129	145	0.8 (0.6–1.1)	55	57	0.9 (0.6–1.3)	83	82	1.0 (0.7–1.4)

Variable	50 mcg ethinyl estradiol/0.5 mg norgestrel			35 mcg ethinyl estradiol/0.5 mg (7 days), 0.75 mg (7 days), 1.0 mg (7 days) norethindrone		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Total no. of subjects	1112	1085		1062	1038	
General use						
No use[b]	1032	980	1.0	1032	980	1.0
Ever use	68	94	0.8 (0.5–1.1)	20	48	0.5 (0.3–0.8) *
Current use[c]						
Former use	68	92	0.8 (0.5–1.1)	18	44	0.5 (0.3–0.8) *
Duration of use						
<2 years	24	25	1.1 (0.6–2.0)	7	17	0.5 (0.2–1.4)
2+ years	44	69	0.6 (0.4–0.98) *	13	31	0.4 (0.2–0.8) *
Time since last use						
Current use						
7 months–<5 years						
5+ years	67	91	0.8 (0.5–1.1)	18	38	0.5 (0.3–0.97) *

* Denotes statistical significance at the .05 level; mcg denotes micrograms; mg denotes milligrams.

[a] Odds ratios were derived by conditional logistic regression with the study site, race and age (in 5-year categories) as conditioning variables and were adjusted using categorical variables for menopausal status (pre- or perimenopausal, postmenopausal, unable to classify); age at menarche (<12 years, 12 years, >12 years); age at menopause among menopausal women (<45 years, 45–49 years, ≥50 years, unknown); number of term pregnancies (0, 1, 2, ≥3); age at first term pregnancy among parous women (<20 years, 20–24 years, ≥25 years); body mass index 5 years before reference date (<25, ≥25); family history of breast cancer in the woman's mother, sister or daughter (no, yes, adopted or unknown); and ever use of hormone replacement therapy (no, yes). Women with missing values not included in one of the specified categories were excluded. Cell sizes, ORs and CIs were left blank when an OC exposure measure for a specific OC formulation had any cell size <5 due to imprecision or incalculability; no calculable OR that was omitted due to a cell size <5 was statistically significant.

[b] The reference group was the group of women who had never used OCs.

[c] Current use was defined as use within 6 months before the reference date.