Progestin-Only and Combined Oral Contraceptives and Receptor-Defined Premenopausal Breast Cancer Risk: the Norwegian Women and Cancer Study

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Abbreviations: BMI = Body mass index; CI = Confidence interval; COC = Combined oral contraceptive; ER = Estrogen receptor; HR = Hazard ratio; NOWAC = The Norwegian Women and Cancer Study; OC = Oral contraceptive; POC = Progestin-only contraceptive; PR = Progesterone receptor.

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What's new: Use of combined oral contraceptives (COC) is associated with increased risk of breast cancer and, predominantly, its hormone receptor-negative subtypes. The association between progestin-only contraceptives (POC) and receptor-defined subtypes of breast cancer is unknown. This prospective, population-based cohort is the first study to assess the effect of POC use on breast cancer subtypes. Here, the authors find associations between POC use for five years or more and hormone receptor-positive subtypes.

* Disclaimer: Some of the data in this article are from the Cancer Registry of Norway. The Cancer Registry of Norway is not responsible for the analysis or interpretation of the data presented.

Abstract

Receptor-defined subtypes of breast cancer represent distinct cancer types and have differences in risk factors. Whether the two main hormonal forms of oral contraceptives (OCs); i.e. progestin-only (POC) and combined oral contraceptives (COC), are differentially associated with these subtypes are not well known. The aim of this study was to assess the effect of POC and COC use on hormone receptor-defined breast cancer risk in premenopausal women in a prospective population-based cohort – The Norwegian Women and Cancer study (NOWAC). Information on OC use was collected from 74,862 premenopausal women at baseline. Updated information was applied when follow-up information became available. Multiple imputation was performed to handle missing data, and multivariable Cox regression models were used to calculate hazard ratios (HR) for breast cancer. 1245 incident invasive breast cancer cases occurred. POC use ≥ five years was associated with ER+ (HR = 1.59, 95% CI 1.09 – 2.32, p_{trend} = 0.03) and ER+/PR+ cancer (HR = 1.63, 95% CI 1.07 – 2.48, p_{trend} = 0.05), and was not associated with ER- ($p_{heterogeneity}$ = 0.36) or ER-/PR- ($p_{heterogeneity}$ = 0.49) cancer. COC use was associated with ER- and ER-/PR- cancer, but did not increase risk of ER+ and ER+/PR+ cancer. Current COC use gave different estimates for ER/PR-defined subtypes ($p_{heterogeneity}$ = 0.04). This is the first study to show significant associations between POC use and hormone receptor-positive breast cancer. The lack of power to distinguish effects of POC use on subtype development calls for the need of larger studies to confirm our finding.

Introduction

Breast cancer is the most common cancer in women, and the leading cause of cancer death among females worldwide [1]. Reproductive factors such as early menarche, late menopause, nulliparity and high age at first birth are known risk factors for breast cancer [2-4]. The role of these reproductive factors in breast cancer etiology points towards an essential contributive effect of endogenous female sex hormones in the carcinogenesis of breast tissue. Exogenous female hormones are also associated with breast cancer. In addition to hormone therapy (HT), estrogen-progestin contraceptives (combined oral contraceptives; COCs), are classified as carcinogenic to humans with regards to cervical, breast and liver cancer by the International Agency for Research on Cancer [5].

The association between oral contraceptives (OCs) and breast cancer has been extensively studied for decades. In 1996, a comprehensive pooled analysis of 54 epidemiologic studies found a slightly increased risk of breast cancer associated with current and recent use of COC, and a cessation of risk after 10 years since last use [6]. This has later been confirmed by other studies [7-10]. Some reports suggest a stronger association between OC use and breast cancer in younger women compared to older women [11-13], reflecting the increase in risk associated with recent OC use. Due to a small proportion of women using OCs less than 10 years before onset of menopause in the NOWAC cohort (< 10%), and to the overwhelming evidence of a time-dependent relationship as a function of time since last OC use [6, 10, 14], i.e. no effect after 10 years since last use, the current article concerns premenopausal women only.

Receptor-defined subtypes of breast cancer represent distinct entities of disease and have differences in risk factors [15-17]. These subtypes are defined based on the expression of the hormone receptors estrogen receptor (ER) and progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Prior studies are inconsistent regarding associations between OC use and risk of receptor-defined subtypes of breast cancer. Some propose that OC use is associated with increased risk of hormone receptor-negative breast cancer [18-22], whereas others suggest a decreased risk of hormone receptor-positive cancers by OC use [21, 23, 24]. Conversely, positive associations with ER positive cancer

has been reported [25] as well as no association with either subtype [26-29], or similar associations across subtypes [19, 30].

The pooled analysis found no effect of progestin-only contraceptive (POC) use and breast cancer overall [31]. Previous studies on POC and breast cancer are scarce. To date, no study has addressed associations between POC use and subtypes of breast cancer. Norwegian data is suitable for studying POC use due to a substantial amount of users. Thus, the aim of this study was to assess the effect of POC and COC on hormone receptor-defined breast cancer risk in a representative sample of premenopausal Norwegian women.

Materials and methods

Study population

The Norwegian Women and Cancer study (NOWAC) is a prospective national population-based cohort of 172,000 Norwegian women. Initiated in 1991, women aged 30-70 were randomly selected by the Central Population Registry and invited to participate. Out of 327,476 invited women in total during the period 1991 to 2007, 172,478 returned a completed questionnaire, providing an overall participation rate of approximately 53%. Statistics Norway substituted identification numbers with serial numbers on the questionnaires. Questionnaire data on lifestyle and health were collected up to three times at four to six year intervals to provide updated information on exposures. NOWAC has acceptable external validity [32] and has been described in detail elsewhere [33].

For the analyses presented here, 88,258 women who were postmenopausal or 53 years of age or older at baseline were excluded [34]. Additional exclusion criteria: HT-users at baseline (n = 6,786), prevalent cancers at baseline other than non-melanoma skin cancer (ICD-10 C44) (n = 1,018), women who emigrated or died before baseline (n = 16), women who were 10 years or younger at first birth (n = 2) and women with missing OC, POC or COC status at baseline (n = 1,540). This left a total of 74,862 women for the current analyses. Follow-up information from a second questionnaire was collected from 51,850 of these women.

Assessment of OC exposure

Information on exposure to OCs was obtained by self-administered questionnaires. General questions on OC use were asked, such as ever use, age at first use, duration of use and current use. Furthermore, the women were asked to denote specific periods with OC use, which was defined as any continuous use of one specified OC brand for at least 1 month. To facilitate recall, the questionnaires contained a photo booklet with pictures and names of the different OC brands available on the Norwegian market up to the time of mailing. Up to date, no more than 42 different OC brands have been sold in Norway. We stratified OC use into POC use and COC use based on OC brands used. The internal validity with regard to OC use assessment in NOWAC has been found to be satisfying [33].

Repeated measurements

Updated information on OC exposure was obtained from follow-up questionnaires. Women who reported ever use at baseline and had missing status or reported never use at follow-up were categorized as ever users at follow-up. We applied baseline information on OC exposure until follow-up information became available. Women were censored from the study at the time they reached menopause, started using HT, were diagnosed with incident cancer (except non-melanoma skin cancer), died or emigrated, whichever occurred first. All participants were followed-up until 31. December 2015.

Identification of breast cancer cases, death and emigration

The Norwegian 11-digit national identification number, which includes information on date of birth and sex [35], allowed linkage of the participants to different national registers. Follow-up information on incident breast cancer was collected annually by linkage to the Cancer Registry of Norway, which is estimated to be virtually complete due to compulsory reporting from all pathological laboratories, hospitals and general practitioners in the country [36]. Year of diagnosis ranged from 1991 to 2015. The classification of breast cancer (ICD-10 C50) was performed according to the 10th revision of the International Statistical Classification of Diseases, Injuries and Causes of Death. Information on death and emigration was obtained through linkage to the Cause of Death Registry and the Central Population Register, respectively.

Breast cancer subtypes

ER, PR and HER2 status is ascertained by immunohistochemical and *in situ* hybridization techniques conducted at pathological departments across the country and submitted to the Cancer Registry. ER negative status was defined as <10% reactivity until January 2012, and <1% reactivity from February 2012 and onwards due to change in treatment protocols for breast cancer patients in Norway. PR negativity was defined as <10% reactivity. Contemporary epidemiological studies include HER2 in the breast cancer subtype definition. However, due to large amounts of missing values for this variable, we focused on subtypes based on hormone receptor status only. The subgroups used in the current article (i.e. ER+, ER-, ER+/PR+ and ER-/PR-) are not mutually exclusive and do not add up to the total amount of cases.

Statistical analysis

Repeated measurements of OC, POC and COC use were applied in the analysis of total, ER-defined and ER/PR-defined premenopausal breast cancer. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using Cox proportional hazards models with attained age as the time scale. Separate regression models were constructed for subtype outcomes, allowing women who experienced another subtype than the one defined as failure to be censored at the time when this subtype occurred [37].

Premenopausal breast cancer was defined as incident breast cancer diagnosed prior to or during the same year as the woman's menopause. Age at menopause was set to the given age at which the woman's menstruation stopped. If age at menopause was missing at baseline, we used reported age at menopause from follow-up questionnaires. Women with unknown menopausal status or irregular menses were considered postmenopausal at age 53 or older. This cut-off was based on the definition used in the Million Women Study[34], and later in the NOWAC study [38].

The multivariable analyses included established or potential risk factors as covariates, which were obtained from the questionnaires. If a linear trend was observed for any covariate, this covariate was treated as continuous. Covariates that changed the regression coefficient with less than 10% were removed from the model, except for age at menarche. The final multivariable model included the

following covariates: BMI (continuous), history of breast cancer in mother (yes, no), age at menarche (continuous), alcohol consumption (0, 0.1-4.9, 5-9.9, ≥ 10 g/day), and a combined variable including parity (0, 1, 2, ≥ 3 children) and age at first birth (age < 25, 25-29, ≥ 30). For the analysis addressing COC exposure, the model was adjusted for POC use (ever, never), and vice versa.

The HRs of breast cancer subtypes were tested for heterogeneity by the Wald test. For duration variables, heterogeneity between linear trends were tested. All p-values were two-sided. The proportional hazards assumption was evaluated by tests of Schoenfeld residuals and by graphical inspection of a log-log survival plot. All analyses were performed using the statistical package STATA, version 14.

Multiple imputation

Under the assumption that data was missing at random [39], multiple imputation was used to handle missing information. In order to reduce sampling variability from the imputation simulations, the missing values were replaced by imputed values from twenty duplicate datasets [39]. The imputation model included all covariates used in the multivariable analyses, age at baseline and follow-up, and the Nelson-Aalen cumulative hazard estimator as predictors.

Two types of missing values occurred due to both item and wave non-response. First, values were missing due to missing information in the questionnaires (item non-response). These included missing covariates at baseline (e.g. alcohol consumption [n = 1,651], age at menarche [n = 1,192] and BMI [n = 1,477]), missing duration of OC use at baseline (n = 1,180) or follow-up (n = 23,850), and time since last use at baseline (n = 1,293) or follow-up (n = 23,634). Second, missing values at follow-up were due to non-response of a second questionnaire (wave non-response, n = 23,012). These comprised OC status, POC status and duration, and COC status and duration. In order to avoid possible inconsistencies in status of use at the two points in time, we imputed possible changes in status of OC use and used this information to assign the status at follow-up as current, former, or never use. Similarly, we computed OC duration at follow-up from the imputation of additional use since baseline in order to avoid lower imputed values at follow-up compared to baseline [40]. The estimates from the twenty imputed datasets were combined using Rubin's rules in order to obtain HRs and

corresponding 95% CIs [41]. Sensitivity analysis was conducted to ensure that risk estimates were similar in complete case analysis and multiple imputation analysis.

Ethics

NOWAC has been approved by the Regional Committees for Medical and Health Research Ethics (REC) and the Norwegian Data Inspectorate. The participants received written information about the study and future linkages to national registers, along with invitation to receive a second questionnaire. Return of a completed questionnaire was considered consent to participate. A second questionnaire was only sent to participants who had agreed to receive one.

Results

A total of 1,245 incident premenopausal breast cancer cases occurred during 580017 person-years of follow-up. Mean follow-up time was 7.8 years. Among the 1,245 cancer cases, there were 679 ER+ cases, 191 ER- cases, 375 cases with missing ER status, 578 PR+ cases, 281 PR- cases and 386 cases with missing PR status. When combining the hormone receptor statuses, they comprised 540 ER+/PR+ cases, 130 ER+/PR- cases, 38 ER-/PR+ cases, 151 ER-/PR- cases and 386 cases with missing hormone receptor status.

Distribution of characteristics at baseline among the study population and premenopausal breast cancer cases is presented in Table 1. In addition to a larger proportion with familial breast cancer, women who developed premenopausal breast cancer tended to be younger, have lower BMI, lower parity and higher age at first birth compared to the whole cohort.

Current OC use, more than 10 years duration of OC use and less than 10 years since last use were associated with premenopausal breast cancer as well as all receptor defined subtypes (Table 2), except for current OC use not being associated with ER+/PR+ cancer. More than 20 years since last use was also associated with ER-/PR- cancer. In addition, ever and former use of OCs was associated with ER- and ER-/PR- breast cancer.

The main findings of this study are presented in Tables 3 and 4, displaying stratified analysis by POC and COC use. POC use for five years or more was associated with ER+ (HR = 1.59, 95% CI

1.09 – 2.32) and ER+/PR+ (HR = 1.63, 95% CI 1.07 – 2.48) cancer. In women who were POC users and never COC users, the corresponding increase in risk was 1.87 (95% CI 1.21 – 2.91) for ER+ cancer (Table 4). However, we observed no significant difference in risk estimates between subtypes with regard to POC use ($p_{ER+vs.ER-}$=0.36 and $p_{ER+/PR+vs.ER-/PR-}$=0.49). Ever, current, former and ≥ five years use of COCs increased the risk of ER- and ER-/PR- disease. The risk of ER-/PR- cancer (HR = 2.39, 95% CI 1.14 – 5.04) was significantly different from the risk of ER+/PR+ cancer in current COC users ($p_{heterogeneity}$ = 0.04).

Appendix Table 1 displays the distribution of OC, POC and COC use and missing values among the study population at baseline and follow-up.

Results were similar in the complete case analyses. Stratified analyses on POC and COC use without using multiple imputation (Appendix Table 2) also indicated positive associations between POC use ≥ five years and ER+ cancer (HR = 1.60, 95% CI 1.09 – 2.35) and ER+/PR+ cancer (HR = 1.64, 95% CI 1.07 – 2.51).

Discussion

The main finding of our study was that POC use was associated with hormone receptor-positive premenopausal breast cancer if used for five years or more. Thus, our prospective, population-based study has unraveled more exact associations between the main hormonal constituents of OCs and receptor-defined breast cancer risk in premenopausal women. Dissimilar associations between POC and COC use on hormone receptor-defined breast cancer suggests that the exogenous hormones estrogen and progestin might have differential roles in subtype carcinogenesis.

Some of our findings confirm existing knowledge: we have observed that OC use slightly increases risk of premenopausal breast cancer. The increase in risk associated with duration of use could reflect long-term users being more likely to be current or recent users. Although the total risk elevation is modest with regard to ever use (12%), it is noteworthy due to the frequent use of OCs among premenopausal women, making OCs a contributing cause for a substantial number of cases.

Associations between OC use and ER- or ER-/PR- breast cancer is in agreement with previous studies [18, 19, 21, 22]. Dolle et al. found increased risk of ER negative breast cancer with several aspects of OC use (i.e. ever use, duration, age at first use and years since first and last use), while no significant associations were found with ER+ breast cancer [18]. Beaber et al. found significantly increased risks for both ER-positive and ER-negative breast cancer with current use and duration of use [19], as we did in our analysis.

When stratifying by hormonal content, POC and COC use were differently associated with hormone receptor-defined subtypes. However, heterogeneity tests for POC use were insignificant and unequal associations could be due to a small number of POC users in the hormone receptor-negative groups. As limited power is an issue when addressing POC use in relation to hormone receptor-negative cancer, one cannot rule out the possibility that POC use increases risk of this subtype as well. The increased risk of breast cancer provided by POC use is in line with some [9] and in contrast to other studies [31, 42]. Although used as HT, one study found increased risk of breast cancer associated with current use of oral progestins for 4.5 years or more before menopause [43]. These studies have not assessed POC associations in relation to receptor-defined breast cancer.

Our findings further imply that general OC use is also associated with hormone receptor-positive cancers, which is in contrast to most studies [18-22, 29]. Since POC use has been more common in Scandinavian countries than in the US [44], a higher portion of POCs in our data could influence OC associations towards hormone receptor-positivity. Previously mentioned studies defined OC use as equivalent to COC use only [19, 25], or they did not specify what type of OCs were encompassed as such [18, 20, 24]. Moreover, Non-Caucasians are scarce in our cohort which explains the relatively smaller portion of triple negative cases and consequently hormone receptor-negative cases in our study, as this subtype is more common among African-American women [45].

The biological mechanism linking progestin to breast cancer development is a subject of controversy. It is hypothesized that the proliferative effect of progestins on mammary epithelium increase breast cancer risk [46]. Moreover, it has been postulated that in breast cancer cells, crosstalk

between the ER and the PR enables PR activation to provide estrogen-mediated proliferative response [47], which also could influence disease development.

Several challenges arise when studying subtypes of disease. Firstly, the potential of misclassification is noteworthy. Pathologists from wide-ranging laboratories conduct hormone receptor status assays across the country. There is a certain degree of variety in laboratory techniques, scoring methods and interpretation of data. In sum, these represent a subjective influence that opens for the possibility of misclassification. Despite that, studies show satisfactory concordance of hormone receptor status across laboratories with regard to ER+, ER-, ER+/PR+ and ER-/PR- status [48], as has been the main classifications used in the current study. Moreover, a mixture of 1% and 10% cutoff for ER negativity could dilute associations, as contemporary clinical knowledge recognizes 1% cutoff as true negative ER expression.

Another major issue involves limited statistical power as we restricted our cohort to premenopausal women and only 14% were diagnosed before menopause. Further, there were a considerable amount of missing receptor status data as cases were diagnosed as of 1991, at which time receptor status testing practices was not standard procedure.

Missing information at baseline and follow-up was imputed, assuming the information was missing at random. This was done in order to keep observations in the analysis and thus improve the accuracy of associations. In analyses with smaller subgroups, this method improved the precision of the relative risk estimates substantially, without changing their values noteworthy. However, there is a possibility that some information was not missing at random, which would result in obtained estimates not being completely free from bias.

To our knowledge, this is the first study to address associations between POC use and receptor-defined breast cancer. Strengths of the present study include its prospective design, avoiding concerns of selection and recall bias, which is a problem for case-control studies of OCs and breast cancer [49]. This inevitable concern was the main purpose of creating the prospective NOWAC study. Moreover, its nationally representative, population-based design allows findings to be generalizable to

the whole country or broader. Further, NOWAC is designed to study impact of hormonal constituents on cancer risk by providing reliable and detailed assessment of hormone use. Due to few available OC brands on the Norwegian market, this study has reduced potential of exposure misclassification. Potential exposure misclassification is likely to be non-differential due to the prospective design of the study, and estimates would be biased towards unity. Finally, due to including only premenopausal women in our analysis, we get valid results because risk factors and breast cancer characteristics are dissimilar in pre- and postmenopausal women [50].

Despite numerous strengths of the present study, our findings with regard to POC use require further confirmation due to our insignificant heterogeneity tests between subtypes and uncertain biological mechanisms.

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References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015;**65**: 87-108.

2. Collaborative Group on Hormonal Factors in Breast C. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. *Lancet Oncol* 2012;**13**: 1141-51.

3. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. *Am J Epidemiol* 2000;**152**: 950-64.

4. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. *Epidemiol Rev* 1993;**15**: 36-47.

5. Cogliano V, Grosse Y, Baan R, Straif K, Secretan B, El Ghissassi F, Cancer WHOIAfRo. Carcinogenicity of combined oestrogen-progestagen contraceptives and menopausal treatment. *Lancet Oncol* 2005;**6**: 552-3.

6. Collaborative Group on Hormonal Factors in Breast C. 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.

7. Hunter DJ, Colditz GA, Hankinson SE, Malspeis S, Spiegelman D, Chen W, Stampfer MJ, Willett WC. Oral contraceptive use and breast cancer: a prospective study of young women. *Cancer Epidemiol Biomarkers Prev* 2010;**19**: 2496-502.

8. Dumeaux V, Alsaker E, Lund E. Breast cancer and specific types of oral contraceptives: a large Norwegian cohort study. *Int J Cancer* 2003;**105**: 844-50.

9. Kumle M, Weiderpass E, Braaten T, Persson I, Adami HO, Lund E. Use of oral contraceptives and breast cancer risk: The Norwegian-Swedish Women's Lifestyle and Health Cohort Study. *Cancer Epidemiol Biomarkers Prev* 2002;**11**: 1375-81.

10. Gierisch JM, Coeytaux RR, Urrutia RP, Havrilesky LJ, Moorman PG, Lowery WJ, Dinan M, McBroom AJ, Hasselblad V, Sanders GD, Myers ER. Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. *Cancer Epidemiology, Biomarkers & Prevention* 2013;**22**: 1931-43.

11. Brinton LA, Daling JR, Liff JM, Schoenberg JB, Malone KE, Stanford JL, Coates RJ, Gammon MD, Hanson L, Hoover RN. Oral contraceptives and breast cancer risk among younger women. *J Natl Cancer Inst* 1995;**87**: 827-35.

12. Rookus MA, van Leeuwen FE. Oral contraceptives and risk of breast cancer in women aged 20-54 years. Netherlands Oral Contraceptives and Breast Cancer Study Group. *Lancet* 1994;**344**: 844-51.

13. Wingo PA, Lee NC, Ory HW, Beral V, Peterson HB, Rhodes P. Age-Specific Differences in the Relationship between Oral-Contraceptive Use and Breast-Cancer. *Obstetrics and Gynecology* 1991;**78**: 161-70.

14. Humans IWGotEoCRt. Combined estrogen-progestogen contraceptives and combined estrogen-progestogen menopausal therapy. *IARC Monogr Eval Carcinog Risks Hum* 2007;**91**: 1-528.

15. Anderson KN, Schwab RB, Martinez ME. Reproductive risk factors and breast cancer subtypes: a review of the literature. *Breast Cancer Res Treat* 2014;**144**: 1-10.

16. Ellingjord-Dale M, Vos L, Tretli S, Hofvind S, Dos-Santos-Silva I, Ursin G. Parity, hormones and breast cancer subtypes - results from a large nested case-control study in a national screening program. *Breast Cancer Res* 2017;**19**: 10.

17. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, Fluge O, Pergamenschikov A, et al. Molecular portraits of human breast tumours. *Nature* 2000;**406**: 747-52.

18. Dolle JM, Daling JR, White E, Brinton LA, Doody DR, Porter PL, Malone KE. Risk factors for triple-negative breast cancer in women under the age of 45 years. *Cancer Epidemiol Biomarkers Prev* 2009;**18**: 1157-66.

19. Beaber EF, Malone KE, Tang MT, Barlow WE, Porter PL, Daling JR, Li CI. Oral contraceptives and breast cancer risk overall and by molecular subtype among young women. *Cancer Epidemiol Biomarkers Prev* 2014;**23**: 755-64.

20. Ma H, Wang Y, Sullivan-Halley J, Weiss L, Marchbanks PA, Spirtas R, Ursin G, Burkman RT, Simon MS, Malone KE, Strom BL, McDonald JA, et al. Use of four biomarkers to evaluate the risk of breast cancer subtypes in the women's contraceptive and reproductive experiences study. *Cancer Res* 2010;**70**: 575-87.

21. Barnard ME, Boeke CE, Tamimi RM. Established breast cancer risk factors and risk of intrinsic tumor subtypes. *Biochim Biophys Acta* 2015;**1856**: 73-85.

22. Rosenberg L, Boggs DA, Wise LA, Adams-Campbell LL, Palmer JR. Oral contraceptive use and estrogen/progesterone receptor-negative breast cancer among African American women. *Cancer Epidemiol Biomarkers Prev* 2010;**19**: 2073-9.

23. Razzaghi H, Troester MA, Gierach GL, Olshan AF, Yankaskas BC, Millikan RC. Association between mammographic density and basal-like and luminal A breast cancer subtypes. *Breast Cancer Research* 2013;**15**: R76.

24. Phipps AI, Chlebowski RT, Prentice R, McTiernan A, Wactawski-Wende J, Kuller LH, Adams-Campbell LL, Lane D, Stefanick ML, Vitolins M, Kabat GC, Rohan TE, et al. Reproductive history and oral contraceptive use in relation to risk of triple-negative breast cancer. *J Natl Cancer Inst* 2011;**103**: 470-7.

25. Beaber EF, Buist DS, Barlow WE, Malone KE, Reed SD, Li CI. Recent oral contraceptive use by formulation and breast cancer risk among women 20 to 49 years of age. *Cancer Res* 2014;**74**: 4078-89.

26. Millikan RC, Newman B, Tse CK, Moorman PG, Conway K, Dressler LG, Smith LV, Labbok MH, Geradts J, Bensen JT, Jackson S, Nyante S, et al. Epidemiology of basal-like breast cancer. *Breast Cancer Res Treat* 2008;**109**: 123-39.

27. McCredie MR, Dite GS, Southey MC, Venter DJ, Giles GG, Hopper JL. Risk factors for breast cancer in young women by oestrogen receptor and progesterone receptor status. *Br J Cancer* 2003;**89**: 1661-3.

28. Cotterchio M, Kreiger N, Theis B, Sloan M, Bahl S. Hormonal factors and the risk of breast cancer according to estrogen- and progesterone-receptor subgroup. *Cancer Epidemiol Biomarkers Prev* 2003;**12**: 1053-60.

29. Ma H, Bernstein L, Ross RK, Ursin G. Hormone-related risk factors for breast cancer in women under age 50 years by estrogen and progesterone receptor status: results from a case-control and a case-case comparison. *Breast Cancer Res* 2006;**8**: R39.

30. Bethea TN, Rosenberg L, Hong CC, Troester MA, Lunetta KL, Bandera EV, Schedin P, Kolonel LN, Olshan AF, Ambrosone CB, Palmer JR. A case-control analysis of oral contraceptive use and breast cancer subtypes in the African American Breast Cancer Epidemiology and Risk Consortium. *Breast Cancer Res* 2015;**17**: 22.

31. Collaborative Group on Hormonal Factors in Breast C. Breast cancer and hormonal contraceptives: further results. *Contraception* 1996;**54**: 1S-106S.

32. Lund E, Kumle M, Braaten T, Hjartaker A, Bakken K, Eggen E, Gram TI. External validity in a population-based national prospective study--the Norwegian Women and Cancer Study (NOWAC). *Cancer Causes Control* 2003;**14**: 1001-8.

33. Lund E, Dumeaux V, Braaten T, Hjartaker A, Engeset D, Skeie G, Kumle M. Cohort profile: The Norwegian Women and Cancer Study--NOWAC--Kvinner og kreft. *Int J Epidemiol* 2008;**37**: 36-41.

34. Beral V, Million Women Study C. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003;**362**: 419-27.

35. Lunde AS, Lundeborg S, Lettenstrom GS, Thygesen L, Huebner J. The person-number systems of Sweden, Norway, Denmark, and Israel. *Vital Health Stat 2* 1980: 1-59.

36. Larsen IK, Smastuen M, Johannesen TB, Langmark F, Parkin DM, Bray F, Moller B. Data quality at the Cancer Registry of Norway: An overview of comparability, completeness, validity and timeliness. *Eur J Cancer* 2009;**45**: 1218-31.

37. Prentice RL, Kalbfleisch JD, Peterson AV, Jr., Flournoy N, Farewell VT, Breslow NE. The analysis of failure times in the presence of competing risks. *Biometrics* 1978;**34**: 541-54.

38. Bakken K, Alsaker E, Eggen AE, Lund E. Hormone replacement therapy and incidence of hormone-dependent cancers in the Norwegian Women and Cancer study. *Int J Cancer* 2004;**112**: 130-4.

39. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, Wood AM, Carpenter JR. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;**338**: b2393.

40. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* 2011;**30**: 377-99.

41. Rubin DB. Multiple imputation after 18+ years. *J Am Stat Assoc* 1996;**91**: 473-89.

42. Samson M, Porter N, Orekoya O, Hebert JR, Adams SA, Bennett CL, Steck SE. Progestin and breast cancer risk: a systematic review. *Breast Cancer Res Treat* 2016;**155**: 3-12.

43. Fabre A, Fournier A, Mesrine S, Desreux J, Gompel A, Boutron-Ruault MC, Clavel-Chapelon F. Oral progestagens before menopause and breast cancer risk. *Br J Cancer* 2007;**96**: 841-4.

44. Cancer IAfRo. Hormonal contraceptives, progestogens only. *IARC Monogr Eval Carcinog Risks Hum* 1999;**72**: 339-97.

45. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, Karaca G, Troester MA, Tse CK, Edmiston S, Deming SL, Geradts J, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. *JAMA* 2006;**295**: 2492-502.

46. Aupperlee M, Kariagina A, Osuch J, Haslam SZ. Progestins and breast cancer. *Breast Dis* 2005;**24**: 37-57.

47. Carroll JS, Hickey TE, Tarulli GA, Williams M, Tilley WD. Deciphering the divergent roles of progestogens in breast cancer. *Nat Rev Cancer* 2017;**17**: 54-64.

48. Ma H, Wang Y, Sullivan-Halley J, Weiss L, Burkman RT, Simon MS, Malone KE, Strom BL, Ursin G, Marchbanks PA, McDonald JA, Spirtas R, et al. Breast cancer receptor status: do results from a centralized pathology laboratory agree with SEER registry reports? *Cancer Epidemiol Biomarkers Prev* 2009;**18**: 2214-20.

49. Skegg DC. Potential for bias in case-control studies of oral contraceptives and breast cancer. *Am J Epidemiol* 1988;**127**: 205-12.

50. Clavel-Chapelon F, Group ENE. Differential effects of reproductive factors on the risk of pre- and postmenopausal breast cancer. Results from a large cohort of French women. *Br J Cancer* 2002;**86**: 723-7.

Table 1. Baseline characteristics of study population and premenopausal breast cancer cases: The NOWAC Study

	Study population (n = 74,862)	Premenopausal breast cancer cases (n = 1,245)	p^1
Age (years) at baseline, no. (%)			< 0.001
30-34	3,953 (5.3)	104 (8.4)	
35-39	20,853 (27.9)	445 (35.7)	
40-44	19,760 (26.4)	331 (26.6)	
45-49	22,410 (29.9)	297 (23.9)	
> 50	7,886 (10.5)	68 (5.5)	
Mean age (SD)	42.6 (0.0)	41.1 (0.2)	
Body mass index (kg/m^2), no. (%)			< 0.001
< 18.5	2,008 (2.7)	37 (3.0)	
18.5-24.9	52,628 (70.3)	935 (75.1)	
25-29.9	14,717 (19.7)	205 (16.5)	
≥ 30	4,032 (5.4)	46 (3.7)	
Missing	1,477 (2.0)	22 (1.8)	
Mean BMI (SD)	23.4 (0.0)	22.9 (0.1)	
Age (years) at menarche, no. (%)			0.82
≤ 11	6,624 (8.9)	112 (9.0)	
12	14,822 (19.8)	241 (19.4)	
13	21,505 (28.7)	370 (29.7)	
14	18,136 (24.2)	294 (23.6)	
≥ 15	12,583 (16.8)	196 (15.7)	
Missing	1192 (1.6)	32 (2.6)	
Mean age at menarche (SD)	13.3 (0.0)	13.2 (0.0)	
Parity, no. (%)			< 0.001
Nulliparous	7,331 (9.8)	151 (12.1)	
1	9,494 (12.7)	184 (14.8)	
2	33,028 (44.1)	557 (44.7)	
≥ 3	25,009 (33.4)	353 (28.4)	
Mean number of children (SD)	2.1 (0.0)	2.0 (0.0)	
Age (years) at first birth, no. (%)			< 0.001
< 20	9,038 (13.4)	132 (12.1)	
20-24	30,373 (45.0)	429 (39.2)	
25-29	19,820 (29.4)	359 (32.8)	
≥ 30	8,300 (12.3)	174 (15.9)	
Mean age at first birth (SD)	24.2 (0.0)	24.9 (0.1)	
Ever breastfed, no. (%)			0.07
Yes	51,613 (68.9)	899 (72.2)	
No	3,017 (4.0)	39 (3.1)	
Missing	20,232 (27.0)	307 (24.7)	
Mean duration (months) of breastfeeding (SD)	13.5 (0.1)	13.7 (0.4)	
History of breast cancer in mother, no (%)			< 0.001
Yes	3,539 (4.7)	109 (8.9)	
Alcohol consumption (g/day), no. (%)			0.08
None	18,431 (24.6)	285 (22.9)	
0.1-4.9	35,754 (47.8)	609 (48.9)	
5.0-9.9	12,704 (17.0)	209 (16.8)	
≥ 10	6,322 (8.4)	128 (10.3)	
Missing	1,651 (2.2)	14 (1.1)	
Mean alcohol consumption (SD)	3.7 (0.0)	4.0 (0.2)	
Smoking status, no. (%)			0.07
Never smoker	25,540 (34.1)	395 (31.7)	
Current smoker	24,564 (32.8)	444 (35.7)	
Former smoker	24,720 (33.0)	405 (32.5)	
Missing	38 (0.1)	1 (0.1)	

Percentages do not add up to 100% for all characteristics because of rounding. BMI = Body mass index; SD = Standard deviance.

[1]X^2 Pearson, *P* value for difference between premenopausal breast cancer cases and the whole cohort.

Table 2. Multivariable adjusted HRs (95% CI) for association between oral contraceptive use and risk of total and hormone receptor-defined premenopausal breast cancer: The NOWAC Study

	All cases		ER+ cases		ER- cases		ER+/PR+ cases		ER-/PR- cases	
	No. (n = 1,245)	**HR (95% CI)[1]**	**No. (n = 679)**	**HR (95% CI)[1]**	**No. (n = 191)**	**HR (95% CI)[1]**	**No. (n = 540)**	**HR (95% CI)[1]**	**No. (n = 151)**	**HR (95% CI)[1]**
General OC use										
Never use	379	1.00 (ref.)	216	1.00 (ref.)	49	1.00 (ref.)	167	1.00 (ref.)	37	1.00 (ref.)
Ever use	866	1.12 (0.99–1.26)	463	1.06 (0.90–1.25)	142	1.48 (1.06–2.06)	373	1.10 (0.91–1.32)	114	1.61 (1.10–2.35)
Current use	129	1.36 (1.09–1.71)	76	1.36 (1.00–1.85)	27	1.93 (1.10–3.37)	60	1.25 (0.87–1.80)	22	1.98 (1.04–3.76)
Former use	737	1.09 (0.96–1.24)	387	1.03 (0.87–1.22)	115	1.44 (1.02–2.01)	313	1.08 (0.90–1.31)	92	1.57 (1.07–2.31)
Duration (years) of use										
1-4	451	1.10 (0.96–1.26)	221	0.97 (0.81–1.18)	70	1.35 (0.93–1.95)	181	1.02 (0.83–1.27)	37	1.50 (0.99–2.28)
5-9	216	1.02 (0.86–1.21)	125	1.04 (0.82–1.30)	38	1.43 (0.92–2.22)	100	1.06 (0.82–1.37)	58	1.46 (0.88–2.41)
≥ 10	178	1.29 (1.09–1.54)	103	1.33 (1.05–1.67)	32	1.93 (1.24–2.99)	81	1.34 (1.04–1.74)	28	2.11 (1.29–3.46)
p_{trend}[2]		0.02		0.03		0.004		0.04		0.01
Time (years) since last use										
< 10	371	1.36 (1.15–1.61)	209	1.34 (1.06–1.70)	68	1.71 (1.10–2.66)	170	1.36 (1.04–1.78)	58	1.78 (1.07–2.96)
11-20	371	1.05 (0.91–1.22)	179	0.94 (0.77–1.15)	60	1.28 (0.86–1.90)	142	0.98 (0.78–1.23)	46	1.44 (0.92–2.25)
> 20	113	1.04 (0.89–1.23)	66	1.05 (0.85–1.29)	14	1.57 (1.04–2.37)	53	1.10 (0.87–1.38)	10	1.67 (1.05–2.66)
p_{trend}[2]		0.02		0.17		0.97		0.30		0.86

The subgroups (i.e. ER+, ER-, ER+/PR+ and ER-/PR-) are not mutually exclusive and do not add up to the total amount of cases. CI = Confidence interval; ER = Estrogen receptor; HR = Hazard ratio; OC = Oral contraceptives; PR = Progesterone receptor.

[1]Multivariable analysis adjusted for BMI (continuous), history of breast cancer in mother (yes, no), age at menarche (continuous), alcohol consumption (0, 0.1-4.9, 5-9.9, ≥ 10 g/day), and a combined variable including parity (0, 1, 2, ≥ 3 children) and age at first birth (age < 25, 25-29, ≥ 30).

[2]*p* value, continuous variable.

Table 3. Multivariable adjusted HRs (95% CI) for association between combined and progestin-only oral contraceptive use and risk of hormone receptor-defined premenopausal breast cancer: The NOWAC Study

	All cases		ER+ cases		ER- cases			ER+/PR+ cases		ER-/PR- cases		
	No. (n = 1245)	**HR (95% CI)[1]**	**No. (n = 679)**	**HR (95% CI)[1]**	**No. (n = 191)**	**HR (95% CI)[1]**	***p*[2]**	**No. (n = 540)**	**HR (95% CI)[1]**	**No. (n = 151)**	**HR (95% CI)[1]**	***p*[3]**
COC use[4]												
Never OC use	379	1.00 (ref.)	216	1.00 (ref.)	49	1.00 (ref.)	0.07	167	1.00 (ref.)	37	1.00 (ref.)	
Ever COC use	652	1.10 (0.97 - 1.26)	353	1.04 (0.87–1.24)	111	1.50 (1.06–2.13)	0.07	288	1.08 (0.88–1.32)	87	1.60 (1.07–2.38)	0.08
Current use	77	1.32 (0.99 - 1.77)	43	1.17 (0.77–1.78)	19	2.38 (1.25–4.54)	0.10	33	0.91 (0.53–1.55)	16	2.39 (1.14–5.04)	0.04
Former use	575	1.09 (0.95 - 1.24)	310	1.03 (0.86–1.23)	92	1.44 (1.01–2.05)		255	1.09 (0.89–1.33)	71	1.54 (1.03–2.31)	0.13
Duration (years) of use												
< 5	346	1.09 (0.94 - 1.27)	180	0.99 (0.81–1.22)	52	1.31 (0.88–1.96)		152	1.06 (0.84–1.33)	42	1.44 (0.92–2.27)	
≥ 5	306	1.11 (0.95 - 1.30)	173	1.09 (0.89–1.34)	59	1.73 (1.17–2.56)	0.36	136	1.10 (0.87–1.39)	45	1.79 (1.14–2.80)	
p_{trend}[5]		0.755		0.35		0.12			0.73		0.28	0.43
POC use[6]												
Never OC use	379		216	1.00 (ref.)	49	1.00 (ref.)	0.49	167	1.00 (ref.)	37	1.00 (ref.)	
Ever POC use	171	1.16 (0.95 - 1.42)	97	1.16 (0.89–1.52)	29	1.42 (0.85–2.39)	0.96	79	1.18 (0.87–1.60)	23	1.64 (0.92–2.92)	0.32
Current use	28	1.42 (0.90 - 2.26)	18	1.52 (0.84–2.77)	6	1.58 (0.48–5.20)	0.47	16	1.75 (0.93–3.28)	5	2.30 (0.69–7.68)	0.69
Former use	143	1.13 (0.92 - 1.39)	79	1.12 (0.85–1.48)	23	1.41 (0.83–2.40)		63	1.13 (0.82–1.54)	18	1.58 (0.87–2.87)	0.33
Duration (years) of use												
< 5	120	1.06 (0.85 - 1.33)	64	1.01 (0.74–1.37)	23	1.41 (0.80–2.47)		52	1.02 (0.72–1.44)	18	1.59 (0.85–2.99)	
≥ 5	51	1.45 (1.08 - 1.95)	33	1.59 (1.09–2.32)	6	1.46 (0.64–3.31)	0.36	27	1.63 (1.07–2.48)	5	1.79 (0.74–4.36)	
p_{trend}[5]		0.067		0.03		0.97			0.05		0.86	0.49

CI = Confidence interval; COC = Combined oral contraceptives; ER = Estrogen receptor; HR = Hazard ratio; OC = Oral contraceptives; POC = Progestin-only contraceptives; PR = Progesterone receptor.

[1]Multivariable analysis adjusted for BMI (continuous), history of breast cancer in mother (yes, no), age at menarche (continuous), alcohol consumption (0, 0.1-4.9, 5-9.9, ≥ 10 g/day), and a combined variable including parity (0, 1, 2, ≥ 3 children) and age at first birth (age < 25, 25-29, ≥ 30).

[2]X^2 Wald, *p* heterogeneity between estimate for ER+ and ER- cancer.

[3]X^2 Wald, *p* heterogeneity between estimate for ER+/PR+ and ER-/PR- cancer.

[4]Analyses on COC use are adjusted for POC use in addition to the above-mentioned covariates.

[5]*p* value, continuous variable.

[6]Analyses on POC use are adjusted for COC use in addition to the above-mentioned covariates.

Table 4. Multivariable adjusted HRs (95% CI) for association between combined oral contraceptive users among never progestin-only users and progestin-only users among never combined oral contraceptive users and risk of ER-defined premenopausal breast cancer: The NOWAC Study

	ER+ cases		ER- cases		
	No. (n = 679)	**HR (95% CI)**[1]	**No. (n = 191)**	**HR (95% CI)**[1]	***p***[2]
COC use					
Never OC use	216	1.00 (ref.)	49	1.00 (ref.)	
Ever COC use, never POC use	301	1.03 (0.86–1.23)	95	1.50 (1.06–2.14)	0.06
Current COC use only	38	1.26 (0.81–1.96)	17	2.64 (1.36–5.14)	0.07
Former COC use only	263	1.02 (0.85–1.22)	78	1.42 (0.99–2.04)	0.10
Duration (years) of use					
< 5 yrs	150	0.99 (0.80–1.22)	44	1.31 (0.87–1.98)	
≥ 5 yrs	151	1.08 (0.87–1.33)	51	1.73 (1.16–2.58)	
p_{trend}[3]		0.462		0.004	0.03
POC use					
Never OC use	216	1.00 (ref.)	49	1.00 (ref.)	
Ever POC use, never COC use	45	1.11 (0.80–1.53)	13	1.44 (0.78–2.66)	0.46
Current POC use only	9	1.50 (0.62–3.64)	3	2.59 (0.63–10.68)	0.52
Former POC use only	36	1.07 (0.76–1.51)	10	1.33 (0.69–2.57)	0.56
Duration (years) of use					
< 5 yrs	24	0.79 (0.51–1.22)	10	1.40 (0.68–2.85)	
≥ 5 yrs	21	1.87 (1.21–2.91)	3	1.54 (0.56–4.29)	
p_{trend}[3]		0.08		0.18	0.69

CI = Confidence interval; COC = Combined oral contraceptives; ER = Estrogen receptor; HR = Hazard ratio; OC = Oral contraceptives; POC = Progestin-only contraceptives; PR = Progesterone receptor.

[1]Multivariable analysis adjusted for BMI (continuous), history of breast cancer in mother (yes, no), age at menarche (continuous), alcohol consumption (0, 0.1-4.9, 5-9.9, ≥ 10 g/day), and a combined variable including parity (0, 1, 2, ≥ 3 children) and age at first birth (age < 25, 25-29, ≥ 30).

[2]X^2 Wald, *p* heterogeneity between estimate for ER+ and ER- cancer.

[3]*p* value, continuous variable.

Appendix Table 1. Distribution of general, combined, and progestin-only oral contraceptive use and missing values according to study population at baseline and follow-up – The NOWAC Study

	Study population at baseline (n = 74,862)	Study population at follow-up (n = 51,850)
General OC use, no. (%)		
Never use	26,251 (35.1)	18,073 (24.1)
Ever use	48,611 (64.9)	33,777 (45.1)
Current use	5,361 (7.2)	1,956 (2.6)
Former use	43,250 (57.8)	31,821 (42.5)
Missing	0 (0)	23,012 (30.7)
Duration (years) of OC use[1]		
1-4	26,656 (35.6)	18,598 (24.8)
5-9	12,246 (16.4)	8,490 (11.3)
≥ 10	8,529 (11.4)	5,851 (7.8)
Missing	1,180 (1.6)	23,850 (31.9)
Time (years) since last OC use[1]		
< 10	16,430 (22.0)	5,569 (7.4)
11-20	22,077 (29.5)	12,949 (17.3)
> 20	8,811 (11.8)	14,637 (19.6)
Missing	1,293 (1.7)	23,634 (31.6)
COC use, no. (%)		
Never use	38,896 (52.0)	26,738 (35.7)
Ever use	35,966 (48.0)	25,112 (33.5)
Current use	3,239 (4.3)	950 (1.3)
Former use	32,727 (43.7)	24,162 (32.3)
Missing	0 (0)	23,012 (30.7)
Duration (years) of COC use[1]		
< 5	19,765 (26.4)	13,992 (18.7)
≥ 5	16,201 (21.6)	11,120 (14.9)
Missing	0 (0)	23,012 (30.7)
POC use, no. (%)		
Never use	65,771 (87.9)	44,737 (59.8)
Ever use	9,091 (12.1)	7,113 (9.5)
Current use	968 (1.3)	379 (0.5)
Former use	8,123 (10.9)	6,734 (9.0)
Missing	0 (0)	23,012 (30.7)
Duration (years) of POC use[1]		
< 5	6,862 (9.2)	5,423 (7.2)
≥ 5	2,229 (3.0)	1,690 (2.3)
Missing	0 (0)	23,012 (30.7)

COC = Combined oral contraceptives; OC = Oral contraceptives; POC = Progestin-only contraceptives.

[1]Among ever-users.

Appendix Table 2. Multivariable adjusted HRs (95% CI) for association between COC use and POC use and risk of hormone receptor-defined premenopausal breast cancer: The NOWAC Study – complete case analyses

	ER+ cases		ER- cases		ER+/PR+ cases		ER-/PR- cases	
	No. (n = 643)	**HR (95% CI)**[1]	**No. (n = 184)**	**HR (95% CI)**[1]	**No. (n = 513)**	**HR (95% CI)**[1]	**No. (n = 145)**	**HR (95% CI)**[1]
COC use[2]								
Never OC use	203	1.00 (ref.)	45	1.00 (ref.)	157	1.00 (ref.)	34	1.00 (ref.)
Ever COC use	338	1.00 (0.89–1.14)	108	1.23 (0.98–1.56)	276	1.01 (0.88–1.16)	84	1.33 (1.03–1.72)
Current use	41	1.12 (0.72–1.73)	19	2.53 (1.32–4.86)	31	0.82 (0.47–1.46)	16	2.52 (1.19–5.34)
Former use	297	1.03 (0.86–1.24)	89	1.48 (1.02–2.13)	245	1.10 (0.90–1.35)	68	1.56 (1.03–2.37)
Duration (years) of use								
< 5	176	1.01 (0.82–1.24)	50	1.33 (0.88–2.01)	149	1.09 (0.86–1.37)	40	1.44 (0.90–2.30)
≥ 5	162	1.07 (0.87–1.32)	58	1.80 (1.20–2.70)	127	1.08 (0.85–1.38)	44	1.84 (1.16–2.92)
p_{trend}[3]		0.80		0.002		0.43		0.01
POC use[4]								
Never OC use	203	1.00 (ref.)	45	1.00 (ref.)	157	1.00 (ref.)	34	1.00 (ref.)
Ever POC use	93	0.99 (0.87–1.13)	29	1.17 (0.92–1.49)	76	0.98 (0.85–1.13)	23	1.26 (0.97–1.65)
Current use	16	1.31 (0.68–2.51)	6	1.68 (0.51–5.55)	14	1.49 (0.75–2.96)	5	2.44 (0.73–8.19)
Former use	77	1.12 (0.85–1.49)	23	1.48 (0.87–2.54)	62	1.14 (0.83–1.57)	18	1.66 (0.91–3.05)
Duration (years) of use								
< 5	61	0.98 (0.71–1.34)	23	1.48 (0.84–2.62)	50	1.01 (0.71–1.43)	18	1.67 (0.88–3.17)
≥ 5	32	1.60 (1.09–2.35)	6	1.55 (0.68–3.54)	26	1.64 (1.07–2.51)	5	1.91 (0.78–4.67)
p_{trend}[3]	203	0.07	45	0.19	157	0.07	34	0.05

CI = Confidence interval; COC = Combined oral contraceptives; ER = Estrogen receptor; HR = Hazard ratio; OC = Oral contraceptives; POC = Progestin-only contraceptives; PR = Progesterone receptor.

[1]Multivariable analysis adjusted for BMI (continuous), history of breast cancer in mother (yes, no), age at menarche (continuous), alcohol consumption (0, 0.1-4.9, 5-9.9, ≥ 10 g/day), and a combined variable including parity (0, 1, 2, ≥ 3 children) and age at first birth (age < 25, 25-29, ≥ 30).

[2]Analyses on COC use are adjusted for POC use (ever, never) in addition to the above-mentioned covariates.

[3]*p* value, continuous variable.

[4]Analyses on POC use are adjusted for COC use (ever, never) in addition to the above-mentioned covariates.