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Assessing the association between hormonal contraception and breast cancer risk for *BRCA1* and *BRCA2* mutation carriers using prospective data

BACKGROUND

Hormonal Contraception and Breast Cancer Risk in the General Population

Hormonal contraceptives increase breast cancer (BC) risk in the general population. The largest study of the oral contraceptive pill (OCP) and BC risk was from the Oxford Collaborative group and pooled data from 54 epidemiological studies conducted in 25 countries. It showed that there is a small increased relative risk of BC while women are taking the OCP and for about 10 years after stopping.[1] The estimated relative risk for current users was 1.24 (95% CI 1.15-1.33), which declined to 1.16 (95% CI1.08-1.23) 1-4 years after cessation, 1.07 (95% CI 1.02-1.13) 5-9 years after cessation and 1.01 (95% CI 0.96-1.05) 10 or more years after cessation.

After recency of use was accounted for, duration of use, age at first use and dose and formulation of the OCP, parity, whether OCP use began before or after first childbirth, and breast cancer family history made little difference to the estimates.

The Nurses' Health Study reported on BC risk associated with OCP use for 116,608 women enrolled in the study in 1989 when aged 25-42. There were 1,344 invasive BCs during 1,246,967 years of follow-up. Current user of the OCP had an increased relative risk of BC of 1.33 (95% CI: 1.03-1.73) and risk decreased with increasing time since cessation.[2]

A more recent Danish Study, which used data from National registries, reported similar findings, relevant to all types of contemporary hormonal contraception, including the hormonal intrauterine device.[3] The estimated relative risk of BC was 1.20 (95% CI 1.14-1.26) for current users of hormonal contraception relative to never users. There was some evidence that commencing hormonal contraception at a younger age was associated with increased BC risk.

In women who are at average risk of BC, the relatively small increased risk associated with recent hormonal contraceptive use generally results in only a small increase in the incidence of BCs, because women generally take hormonal contraceptives at a young age when their absolute risk of BC is quite low. For example, the Danish Study[3] showed an increase in BC of 1 case per 7,690 women for each 1 year of hormonal contraception use. However, for women whose risk of early-onset BC is much higher, even this small increase in risk could translate to an important increase in the incidence of BC.

Hormonal Contraception and Breast Cancer Risk in *BRCA1* and *BRCA2* Mutation Carriers

Women with a germline *BRCA1* or *BRCA2* mutation have markedly increased risks of early-onset BC. For example, at age 20-30 years, the standardised incidence ratio for BC relative to the general population is 74 and 61 for *BRCA1* and *BRCA2* mutation carriers, respectively, and at age 31-40 years it is 46 and 20, respectively.[3]

Studies of the association between OCP use and BC risk for *BRCA1* and *BRCA2* mutation carriers have had conflicting results.[5-17] Although most studies have found a relative risk estimate >1 for *BRCA1*[5, 6, 9, 11, 12-16] and/or *BRCA2* mutation carriers[8,9,12,14,16] who ever used OCP, in few studies were the

findings statistically significant.[6, 9, 12, 13, 16] These studies are inconsistent regarding whether duration of use, age at first use, and use before first childbirth influence the risk. No data are available regarding the risk of BC associated with the use of other types of hormonal contraception, such as hormonal implants and hormonal intrauterine devices in *BRCA1* and *BRCA2* mutation carriers. Quantifying any association between use of hormonal contraceptives and BC risk is very important for these women, because it will help optimize their personal breast cancer risk management plan.

We propose to study the association between hormonal contraceptives and BC risk for *BRCA1* and *BRCA2* mutation carriers, using individual participant data from several cohort studies that have collected prospective data.

HYPOTHESES

1) Current hormonal contraception is associated with an increased risk of BC for *BRCA1* and *BRCA2* mutation carriers that decreases with time since last use.
2) The association between current hormonal contraceptive use and breast cancer risk for *BRCA1* and *BRCA2* mutation carriers does not differ from that for the general population (as estimated in the Oxford study[1]).
3) Duration of use, age at first use, and use before first birth are not associated with BC risk independently of current use and recency of use.

AIMS

1) To estimate the effect of current use, and time since last use, of hormonal contraception on BC risk for (i) *BRCA1* mutation carriers and (ii) *BRCA2* mutation carriers.
2) To test whether the effect of hormonal contraceptive use on risk of BC for BRCA1 and BRCA2 mutation carriers is consistent with that observed for the general population reported by the Oxford study[1].
3) To determine if duration of use, age at first use, and use before first birth are associated with BC risk after adjustment for current use and recency of use.

METHODS

Main Exposure

The exposure of interest is hormonal contraception i.e. any form of contraceptive pill, hormonal implant or hormone containing intrauterine device used for periods of 1 year or more. Most studies did not collect information on hormonal contraception other than OCP use, and hence there will be some contamination of the unexposed group by women who did, in fact, use other forms of hormonal contraception. This could bias the study towards the null.

Primary Outcome

Diagnosis of breast cancer - includes both invasive BC and ductal carcinoma in situ

Study Setting

The study will utilise data from 4 prospective cohort studies:

1) The kConFab Clinical Follow-Up Study[17]
2) The Breast Cancer Family Registry[18]
3) Risk Factor Analysis of Hereditary Breast and Ovarian Cancer[19]
4) Basser Center/UPenn Registry[20]

Inclusion criteria

- Pathogenic (class 4 or 5) *BRCA1* or *BRCA2* germline mutation
- Follow-up information available
- Born after 1920

Exclusion criteria

- Male
- Personal history of cancer at cohort entry (except non-melanoma skin or CIN cervix)
- History of bilateral mastectomy at cohort entry

Censoring events

- Any cancer diagnosis (except non-melanoma skin or CIN cervix)
- Bilateral mastectomy
- Death
- Last follow-up or record linkage

Confounders for Adjustment

Premenopausal bilateral oophorectomy
Parity
First-degree family history of BC
Study
Birth cohort
Menopausal status

Analysis Plan

Cox regression will be applied, with age as the timescale and entry at study enrolment (baseline questionnaire date) and exit with breast cancer, bilateral mastectomy, death, diagnosis of other cancer, or last follow-up, whichever happens first. A cluster option will be used in the regression to model the non-independent observations due to family membership. Separate analyses will be undertaken for carriers of mutations in (i) *BRCA1* (or both *BRCA1* and *BRCA2*) and (ii) *BRCA2*. We will calculate unadjusted estimates and estimates adjusting for confounders. Multiple imputation using predictive mean matching, incorporating in the imputation process the various types of interval censoring information, will be used to deal with missing data. Sensitivity analyses will be conducted to assess the influence of potential biases.

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