Risk of Breast Cancer With Oral Contraceptive Use in Women With a Family History of Breast Cancer

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In general population samples, oral contraceptives (OCs) have been observed to be weakly associated with risk of breast cancer up to 10 years after a woman discontinues use.1 Much less is known, however, regarding this association among women with a familial predisposition to breast cancer; while some studies have shown a higher risk among women with a family history,2-6 others have found little or no such evidence.7-18 Observational studies have demonstrated a reduction in risk of ovarian cancer with OC use. As a result, women from high-risk breast-ovarian cancer families are often counseled to take OCs to reduce their ovarian cancer risk.19,20

However, a small study of Ashkenazi Jewish women with breast cancer suggests that OC use may increase the risk of breast cancer.21,22

Context Oral contraceptive (OC) use is weakly associated with breast cancer risk in the general population, but the association among women with a familial predisposition to breast cancer is less clear.

Objective To determine whether the association between OC use and risk of breast cancer is influenced by family history of the disease.

Design and Setting Historical cohort study of 426 families of breast cancer probands diagnosed between 1944 and 1952 at the Tumor Clinic of the University of Minnesota Hospital. Follow-up data on families were collected by telephone interview between 1991 and 1996.

Participants A total of 394 sisters and daughters of the probands, 3002 granddaughters and nieces, and 2754 women who married into the families.

Main Outcome Measure Relative risk (RR) of breast cancer associated with history of OC use by relationship to proband.

Results After accounting for age and birth cohort, ever having used OCs was associated with significantly increased risk of breast cancer among sisters and daughters of the probands (RR, 3.3; 95% confidence interval [CI], 1.6-6.7), but not among granddaughters and nieces of the probands (RR, 1.2; 95% CI, 0.8-2.0) or among marry-ins (RR, 1.2; 95% CI, 0.8-1.9). Results were essentially unchanged after adjustment for parity, age at first birth, age at menarche, age at menopause, oophorectomy, smoking, and education. The elevated risk among women with a first-degree family history of breast cancer was most evident for OC use during or prior to 1975, when formulations were likely to contain higher dosages of estrogen and progestins (RR, 3.3; 95% CI, 1.5-7.2). A small number of breast cancer cases (n=2) limited the statistical power to detect risk among women with a first-degree relative with breast cancer and OC use after 1975.

Conclusions These results suggest that women who have ever used earlier formulations of OCs and who also have a first-degree relative with breast cancer may be at particularly high risk for breast cancer. Further studies of women with a strong family history who have used more recent lower-dosage formulations of OCs are needed to determine how women with a familial predisposition to breast cancer should be advised regarding OC use today.

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For editorial comment see p 1837.
of breast cancer more in carriers of BRCA1 or BRCA2 mutations than in noncarriers.21

Since a family history of breast cancer may not only reflect shared genes but also shared exposures, a family study that incorporates carefully ascertained risk factor data is a robust approach for examining the potential interaction of OC use with family history. We evaluated the association between OC use and breast cancer risk according to family history of the disease in a large historical cohort of Minnesota families. We include in our analysis data on the total duration and dates of OC use and breast cancer risk according to family history of the disease in a large historical cohort of Minnesota families. We include in our analysis data on the total duration and dates of OC use and possible confounding factors. To our knowledge, this is the first study to examine this interaction in the context of a multigenerational family study.

METHODS

Study Population

Details of the study design and methods have been published elsewhere.22 Briefly, this study originated from a case-control family study initiated in 1944 at the Dight Institute for Human Genetics at the University of Minnesota, Minneapolis.23 A consecutive series of 544 women diagnosed with breast cancer was ascertained between 1944 and 1952 to examine the influence of childbearing, breastfeeding, and hereditary susceptibility on the risk of breast cancer. At that time, probands were asked to provide the names, addresses, and cancer history of their children, siblings, nieces, and nephews.

After this initial study, the records on these families remained in storage, untouched for nearly 50 years, until a follow-up study was conducted between 1991 and 1996.24 Of 544 families in the cohort at the start of follow-up in 1952, we excluded 40 because the proband had prevalent breast cancer (diagnosed before 1940) and 42 because no or very few relatives were alive at start of follow-up. Of the remaining 462 families, 20 were lost to follow-up, 10 had no living members in the sampling frame, and 6 refused to participate. A total of 426 families (92.2%) after baseline exclusions) were successfully updated. Adult sisters, daughters, granddaughters, nieces, and marry-ins were eligible for the current study.

Data Collection

Data on cancer history and risk factors for breast cancer were collected through telephone interviews. The participation rate of self-respondents in the telephone interview was 93% (6194/6664). Selected data including cancer history were obtained through surrogate respondents for 2656 (96%) of 2778 women who were deceased. In addition, selected data were obtained from surrogates of 361 (96%) of 376 women who were living but incapable of responding to a telephone interview. Only 568 women in the 426 families were completely lost to follow-up.

We examined the accuracy of self-reporting of breast cancer by reviewing medical records, pathology reports, and death certificates for a sample of 138 self-reports and were able to confirm 99% of these cases of breast cancer. To increase validity of reports, we collected data on OC use only from self-respondents. We questioned them regarding ever vs never use of OCs, age use began, and age use stopped. The main analyses were thus conducted among adult sisters, daughters, granddaughters, nieces, and marry-ins in these families who participated in the telephone interview; data were also collected from surrogate respondents to help evaluate potential bias.

All subjects provided verbal informed consent, and the protocol was reviewed and approved by the University of Minnesota Institutional Review Board.

Statistical Analyses

Analyses were performed using Cox proportional hazards regression.25 Exclusions were made for cancers (other than skin) diagnosed before baseline (defined as proband’s date of breast cancer diagnosis). Follow-up began at age 18 years or age when the proband in the family was diagnosed, whichever was later. Follow-up continued until age at breast cancer diagnosis or age at interview, whichever came first.

Survival was modeled as a function of age, since age is a better predictor of breast cancer risk than is length of follow-up time in this study.25 Oral contraceptive use was modeled as a time-dependent variable. Only OC exposure occurring prior to breast cancer diagnosis was included. Analyses were stratified by birth cohort to control for potential cohort effects in OC use and breast cancer incidence. In addition, we accounted for the nonindependence of observations within families by using a robust variance estimate.26

The overall association of OC use with breast cancer risk in the entire cohort was examined first. Subsequent analyses evaluated whether the degree of relationship to the proband modified the effect of OC use on breast cancer risk. Never OC users were defined as the reference group for each category of relationship to the proband.

Since granddaughters and nieces may have a closer affected relative than the original proband in the family, analyses of OC use were also run with degree of relationship redefined as the closest affected relative. This resulted in 176 granddaughters and nieces being reclassified into the highest risk category. The results were essentially unchanged. Therefore, analyses define family history as relationship to the proband unless otherwise specified.

Potential confounding variables were evaluated for each model after allowing for the interaction of relationship to proband with OC use. A variable was considered a confounder if its addition changed the hazard ratio for any of the OC-use-by-relationship variables by more than 10%. There was no evidence for confounding by the following variables: parity and age at first birth, education, age at menarche, age at menopause, oophorectomy, lifetime alcohol intake, and body mass index. Diabetes, smoking, and fibroid tumors of the uterus, possible contraindications for OC use, were also ruled out as confounders. Polycystic ovaries and endometriosis, possible indications for OC use, were

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Table 1. Description of a Cohort of 426 Families Ascertained Through Probandns Diagnosed With Breast Cancer at the University of Minnesota Between 1944 and 1952*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sisters (n = 72)</th>
<th>Daughters (n = 322)</th>
<th>Granddaughters (n = 1427)</th>
<th>Nieces (n = 1575)</th>
<th>Marry-ins (n = 2754)</th>
<th>Total (n = 8150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth cohort, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before 1913</td>
<td>30 (41.7)</td>
<td>30 (9.3)</td>
<td>3 (0.2)</td>
<td>133 (8.4)</td>
<td>143 (5.2)</td>
<td>339 (5.5)</td>
</tr>
<tr>
<td>1913-1925</td>
<td>38 (52.8)</td>
<td>120 (39.4)</td>
<td>65 (4.6)</td>
<td>390 (27.5)</td>
<td>639 (23.2)</td>
<td>1462 (23.8)</td>
</tr>
<tr>
<td>1926-1941</td>
<td>4 (5.6)</td>
<td>140 (43.5)</td>
<td>339 (23.8)</td>
<td>592 (37.6)</td>
<td>956 (34.7)</td>
<td>2000 (33.0)</td>
</tr>
<tr>
<td>After 1941</td>
<td>0 (0)</td>
<td>22 (6.8)</td>
<td>1020 (71.5)</td>
<td>260 (16.5)</td>
<td>1017 (36.9)</td>
<td>2319 (37.7)</td>
</tr>
<tr>
<td>Mean age (range), y†</td>
<td>79.0 (62-93)</td>
<td>67.6 (36-89)</td>
<td>45.3 (18-84)</td>
<td>65.0 (20-95)</td>
<td>57.5 (21-94)</td>
<td>57.4 (18-95)</td>
</tr>
<tr>
<td>No. of breast cancers‡</td>
<td>6</td>
<td>32</td>
<td>24</td>
<td>91</td>
<td>86</td>
<td>239</td>
</tr>
<tr>
<td>Mean age at breast cancer onset (range), y</td>
<td>60.0 (50-73)</td>
<td>56.6 (34-83)</td>
<td>50.4 (25-72)</td>
<td>57.0 (26-81)</td>
<td>57.5 (27-82)</td>
<td>56.5 (25-83)</td>
</tr>
</tbody>
</table>

*Percentages may not add to 100 due to rounding. †Diagnosed between 1952 and 1996.

Table 2. Characteristics of Oral Contraceptive (OC) Use by Relationship to Proband in a Cohort of 426 Families*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sisters and Daughters (n = 394)</th>
<th>Nieces and Granddaughters (n = 3002)</th>
<th>Marry-ins (n = 2754)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never used</td>
<td>303 (76.9)</td>
<td>1350 (45.0)</td>
<td>1341 (48.7)</td>
</tr>
<tr>
<td>Current users</td>
<td>0 (6)</td>
<td>135 (4.5)</td>
<td>71 (2.6)</td>
</tr>
<tr>
<td>Former users</td>
<td>91 (23.1)</td>
<td>1517 (50.5)</td>
<td>1342 (48.7)</td>
</tr>
<tr>
<td>Age at first OC use, mean (SD) [range], y</td>
<td>30.1 (7.1) [17-54]</td>
<td>23.8 (6.8) [11-62]</td>
<td>24.5 (6.8) [11-52]</td>
</tr>
<tr>
<td>Age at end of OC use, mean (SD) [range], y†</td>
<td>35.6 (7.4) [22-56]</td>
<td>30.5 (8.1) [14-62]</td>
<td>30.8 (8.0) [15-66]</td>
</tr>
<tr>
<td>Duration of OC use, mean (SD) [range], y†</td>
<td>6.0 (5.8) [0.5-29.5]</td>
<td>7.2 (5.9) [0.5-30]</td>
<td>6.8 (5.8) [0.5-37.5]</td>
</tr>
</tbody>
</table>

*Data are presented as number (percentage) unless otherwise indicated. †Includes current users.

Cox proportional hazards model restricted to women with nonmissing OC data was then refit using the inverse of this probability as a weighting factor. People with a high probability of missing OC use were thus weighted more heavily in the Cox model because they were underrepresented in the cohort. Data analyses were performed using the SAS (SAS Institute Inc, Cary, NC) and Splus (Mathsoft Inc, Seattle, Wash) software systems.

RESULTS

Description of the Cohort

The age at diagnosis of breast cancer among the original probands showed wide variation, ranging from 21 to 88 years. This is reflected in the birth cohorts of the relatives (Table 1). The study cohort consists of 3396 blood relatives and 2754 marry-ins (6150 total). Breast cancer occurred in 153 of the blood relatives and 86 of the marry-ins during the follow-up period, after 1952. The age at onset of breast cancer ranged from 25 to 83 years. The mean length of follow-up was 36.6 years.

In the study cohort, the lifetime prevalence of ever having used OCs was 51% overall and was similar for blood relatives and marry-ins (P = .99); 6.5% of ever users reported current use of OCs. Among women who ever took OCs, the average length of use was 7.0 years (range, 0.5-37.5 years).

Table 2 describes OC use by relationship to the proband. Sisters and daughters of the proband were less likely to have used OCs than nieces, granddaughters, and marry-ins, and were more likely to start and end OC use at later ages. The duration...
of use did not markedly differ by relationship but was slightly lower among sisters and daughters.

**Table 3.** Distribution of Breast Cancer Risk Factors by Oral Contraceptive Use in a Cohort of 426 Families, 1991-1996

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Ever Contraceptive Use</th>
<th>Never Contraceptive Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parity, age at first birth, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>358 (11.4)</td>
<td>377 (12.6)</td>
</tr>
<tr>
<td>1-2, ≤20</td>
<td>355 (11.3)</td>
<td>182 (6.1)</td>
</tr>
<tr>
<td>2, &gt;20</td>
<td>355 (11.3)</td>
<td>182 (6.1)</td>
</tr>
<tr>
<td>1-2, &gt;20</td>
<td>355 (11.3)</td>
<td>182 (6.1)</td>
</tr>
<tr>
<td>3, ≤20</td>
<td>726 (23.0)</td>
<td>589 (19.7)</td>
</tr>
<tr>
<td>3, &gt;20</td>
<td>773 (24.5)</td>
<td>1073 (35.9)</td>
</tr>
<tr>
<td>Age at menarche, mean (SD), y</td>
<td>12.9 (1.5)</td>
<td>13.1 (1.6)</td>
</tr>
</tbody>
</table>

Menopausal status

- Premenopausal: 1605 (51.5), 253 (8.6)
- Age at menopause ≤44 y: 657 (21.1), 772 (26.2)
- Age at menopause ≤45-50 y: 518 (16.6), 1045 (35.5)
- Age at menopause >50 y: 338 (10.8), 876 (29.7)

Oophorectomy: 348 (11.0), 544 (18.2)

Smoking history

- Never smoked: 1439 (45.8), 1842 (62.0)
- ≤20 pack-years: 952 (30.3), 510 (17.2)
- >20 pack-years: 754 (24.0), 620 (20.9)

Education

- <High school graduate: 369 (11.7), 888 (29.7)
- High school graduate: 1170 (37.1), 1058 (35.4)
- Some college: 1054 (33.4), 751 (25.1)
- College graduate: 562 (17.8), 294 (9.8)

Data are presented as number (percentage) unless otherwise indicated. Percentages may not add to 100 due to rounding. Distribution of each risk factor differs significantly by oral contraceptive use, P<.001.

**Table 4.** Association of Oral Contraceptive (OC) Use With Risk of Breast Cancer, by Relationship to Proband, in High-Risk Breast-Ovarian Cancer Families

<table>
<thead>
<tr>
<th>Relationship to Proband</th>
<th>Entire Cohort (426 Families)†</th>
<th>≥3 Breast or Ovarian Cancers (132 Families)‡</th>
<th>≥5 Breast or Ovarian Cancers (55 Families)§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Breast Cancers Person-Years (RR 95% CI)</td>
<td>No. of Breast Cancers Person-Years (RR 95% CI)</td>
<td>No. of Breast Cancers Person-Years (RR 95% CI)</td>
</tr>
<tr>
<td>Sisters and daughters</td>
<td>OC Use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>13</td>
<td>2533 (3.3 [1.6-6.7])</td>
<td>10</td>
</tr>
<tr>
<td>Never</td>
<td>25</td>
<td>15063 (1.0)</td>
<td>16</td>
</tr>
<tr>
<td>Nieces and granddaughters</td>
<td>OC Use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>37</td>
<td>38178 (1.2 [0.8-2.0])</td>
<td>26</td>
</tr>
<tr>
<td>Never</td>
<td>78</td>
<td>67522 (1.0)</td>
<td>61</td>
</tr>
<tr>
<td>Marry-ins</td>
<td>OC Use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>26</td>
<td>33930 (1.2 [0.8-1.9])</td>
<td>26</td>
</tr>
<tr>
<td>Never</td>
<td>60</td>
<td>67940 (1.0)</td>
<td>60</td>
</tr>
</tbody>
</table>

*RR indicates relative risk; CI, confidence interval.
† Families in which at least 3 blood relatives were diagnosed with breast or ovarian cancer. P interaction ≤.01.
‡ Families in which at least 5 blood relatives were diagnosed with breast or ovarian cancer. P interaction ≤.01.
§ Marry-ins are from all 426 families for all analyses.

**Association of OCs With Breast Cancer**

Among the entire cohort, ever use of OCs was associated with a relative risk (RR) of 1.4 (95% CI, 1.0-2.0) for breast cancer. Risk did not differ by duration of use (defined by the median split). The RR associated with 1 to 4 years of OC use vs never use was 1.5 (95% CI, 1.0-2.3), while greater than 4 years of use conferred a RR of 1.3 (95% CI, 0.9-1.9).

**Modification of the OC-Breast Cancer Association by Relationship to Breast Cancer Probands**

To determine if the apparent risk associated with OC use was modified by genetic background, analyses were performed within strata defined by relationship to the proband (Table 4). Never users served as the reference group within each stratum. In the 426 families, sisters and daughters who had ever used OCs were at significantly increased risk of breast cancer compared with sisters and daughters who had never used OCs (RR, 1.3; 95% CI, 1.6-6.7). The risk of breast cancer associated with OC use was not elevated among granddaughters, nieces, or marry-ins. The test for interaction between degree of relationship to the proband and OC use was statistically significant (P=.03). Although based on a relatively small number of cases, risk ratios did not significantly differ for any relationship category by duration of OC use (1-4 vs >4 years), by age at first use (≤25 vs >25 years old), by time since first use (≤10 vs >10 years), or by time since last use (≤10 vs >10 years; data not shown).

**Analyses in High-Risk Families**

To study families most likely to be carrying a mutation in BRCA1 or BRCA2, we conducted analyses in families defined as high risk by the number of breast and ovarian cancers among the blood relatives (Table 4). Among 132 high-risk families in which at least 3 blood relatives were diagnosed with breast or ovarian cancer, the interaction of OC use with degree of relationship reached even stronger statistical significance (P=.06) than in the entire cohort of 426 families. Among sisters and daughters in high-risk families, ever use was associated with an RR of 4.6 (95% CI, 2.0-10.7). Use of OCs...
by granddaughters, nieces, and marry-ins was not associated with significantly increased risk of breast cancer. When the analysis was limited to 35 very high-risk families in which at least 5 blood relatives were diagnosed with breast or ovarian cancer, the risk among sisters and daughters was even greater (RR, 11.4; 95% CI, 2.3-56.4).

Since defining high-risk families on the basis of the number of cancers does not take into account family size, we also calculated standardized incidence ratios. This was done by applying Iowa’s 1973-1977 age-specific incidence rates for breast and ovarian cancer in white women to the age structure of the at-risk women. A family was defined as high risk for this analysis if at least 1 more case of breast or ovarian cancer was observed than was expected based on population incidence rates. This resulted in 98 families being classified as high risk. The RRs obtained in families defined as high risk according to this classification were in the same direction as when high risk was based on a simple count of the number of cancers in the family: 3.6 (95% CI, 1.5-8.7) for sisters and daughters, 1.0 (95% CI, 0.5-2.0) for granddaughters and nieces, and 1.1 (95% CI, 0.7-1.7) for marry-ins.

When the analysis was conducted in 38 families with 2 excess breast or ovarian cancers, the RR of breast cancer among sisters and daughters who used OCs increased to 5.2 (95% CI, 1.9-14.3) and in-creased the RR for sisters and daughters of the proband was refit for the entire cohort of 426 families using these estimated weights. People with a high probability of missing OC use were weighted more heavily in the Cox model because they were underrepresented in the cohort. Implementation of these weights had a minor influence on the results. The RR of breast cancer associated with ever use of OCs using this model compared with the unweighted model was 2.9 (95% CI, 1.3-6.5) compared with 3.3 among sisters and daughters, 1.3 (95% CI, 0.8-2.2) compared with 1.2 among granddaughters and nieces, and 1.1 (95% CI, 0.7-2.0) compared with 1.2 among marry-ins.

### Dates of OC Use

We investigated whether the elevated risk of breast cancer associated with OC use in sisters and daughters of the proband was the result of the greater likelihood that sisters and daughters were exposed to the earlier formulations of OCs that contained higher doses of estrogen and progestins. The amount of estrogen in OCs has decreased from an initial 150 µg to 50 µg or less currently, with concurrent decreases in the level of progestogens. Although we collected data on the particular years of OC use, we did not ascertain exact formulations or dosages. With the data available, we examined the relationship between breast cancer risk and estimated years of exposure to high-dose and low-dose formulations. Since all OCs initially marketed after 1975 contain 50 µg or less of ethinyl estradiol and 1 mg or less of several progestins, we used this year as the cut point. Results are presented by closest affected relative rather than by relationship to the proband to maximize statistical power (TABLE 5). Results were unchanged when analyses were conducted by relationship to the proband. No association was observed between OC use after 1975 and risk of breast cancer for any category of family history, although statistical power was limited (eg, only 2 cases among 60 exposed women with a first-degree family history of breast cancer). However, the risk of breast cancer associated with OC use before 1975 was elevated among women with a first-degree family history of breast cancer (RR, 3.3; 95% CI, 1.5-7.2), but not among women with a second-degree family history (RR, 1.3; 95% CI, 0.8-2.0) or among marry-ins (RR, 1.2; 95% CI, 0.8-1.9). Although statistical power was limited, the elevated risk among women with a first-degree family history did not appear to

### Table 5. Association of Oral Contraceptive (OC) Use Before and After 1975 With Breast Cancer Risk, by Closest Affected Relative

<table>
<thead>
<tr>
<th>Closest Affected Relative and Period</th>
<th>OC Use</th>
<th>No. of Breast Cancers</th>
<th>Person-Years</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-degree relative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1975 or earlier</td>
<td>No</td>
<td>29</td>
<td>20,264</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>16</td>
<td>3896</td>
<td>3.3 (1.5-7.2)</td>
</tr>
<tr>
<td>After 1975</td>
<td>No</td>
<td>43</td>
<td>23,231</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>2</td>
<td>929</td>
<td>0.9 (0.2-4.5)</td>
</tr>
<tr>
<td>Second-degree relative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1975 or earlier</td>
<td>No</td>
<td>75</td>
<td>67,213</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>33</td>
<td>31,923</td>
<td>1.3 (0.8-2.0)</td>
</tr>
<tr>
<td>After 1975</td>
<td>No</td>
<td>103</td>
<td>86,661</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>5</td>
<td>12,475</td>
<td>0.6 (0.2-1.3)</td>
</tr>
<tr>
<td>Marry-ins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1975 or earlier</td>
<td>No</td>
<td>60</td>
<td>71,302</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>26</td>
<td>30,568</td>
<td>1.2 (0.8-1.9)</td>
</tr>
<tr>
<td>After 1975</td>
<td>No</td>
<td>80</td>
<td>92,143</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>6</td>
<td>9727</td>
<td>1.1 (0.4-2.6)</td>
</tr>
</tbody>
</table>

*Women who used oral contraceptives both before and after 1975 contribute person-years to both groups. RR indicates relative risk; CI, confidence interval.*

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be influenced by duration of pre-1975 OC use but did appear to persist for more than 10 years after last use of such formulations (data not shown).

If women with a family history are more likely to undergo screening mammography than are marry-ins, then surveillance bias could account for our findings. Indeed, the mean number of mammograms was higher among unaffected women with a first-degree family history than among unaffected women with a second-degree family history or unaffected marry-ins: 6.1, 4.3, and 4.4, respectively, after adjustment for age at interview. Moreover, the mean number of mammograms was slightly higher for OC users than nonusers overall (5.6 vs 4.3). After adjustment for total number of mammograms, the RR among women with a first-degree family history and pre-1975 OC use decreased to 2.4 but remained statistically significant.

**COMMENT**

Our results suggest that the use of OCs in women with a strong family history of breast cancer may further elevate their breast cancer risk. Sisters and daughters of probands who had ever used OCs had a more than 3-fold increase in risk of breast cancer compared with similarly related women who had never used OCs. The risk was further elevated when analyses were conducted in high-risk families. The elevated risk of breast cancer was most pronounced for women with a first-degree family history of breast cancer who used OCs before 1975. However, the mean age at interview for those who used OCs after 1975 was only 43 years (range, 26-67 years).

We expected the risk of breast cancer associated with OC use among women with a second-degree family history of breast cancer to fall somewhere between that of first-degree relatives and marry-ins. Although this was not evident in the entire cohort of 426 families, there was some suggestion of an increased risk among second-degree relatives when the analyses were conducted in high-risk families and adjustment was made for other breast cancer risk factors. The lack of substantial evidence for an increased risk in the second-degree relatives may be due to the younger age of these women. The mean age of the granddaughters at the time of interview was only 45.3 years.

To our knowledge, this study is the first to examine the association of OC use with risk of breast cancer within the context of a multigenerational family study. Previously it was recommended that women with mutations in **BRCA1** or **BRCA2** consider OC use to reduce their risk of ovarian cancer. Although our findings are not directly comparable since we did not analyze DNA for these mutations in all cases, the results seen in our highest risk families suggest that women with a strong genetic predisposition may be at greatly elevated risk of breast cancer if they use OCs. Effective prevention against ovarian cancer is certainly desirable given the high mortality associated with this malignancy and the difficulty of early detection. However, breast cancer is more common than ovarian cancer in these high-risk families. Additional evidence that women at high risk should avoid OC use comes from a recent study that suggests that OCs may increase the risk of breast cancer more in carriers of **BRCA1** or **BRCA2** mutations than in noncarriers, although these results should be viewed with caution given the small sample size.

We are not aware of any studies that have examined the risk of breast cancer associated with OC use classified according to hormone dose in women with a family history of breast cancer. Considering the years of ascertainment in most published studies that examined OC use and breast cancer risk by a family history of breast cancer, women could have been exposed to either low- or high-dose formulations or both. It is possible that this heterogeneity of exposure led to some of the inconsistencies observed in previous studies. Several studies, including the Nurses’ Health Study and the Cancer and Steroid Hormone Study, did not observe significantly increased risks of breast cancer associated with OC use among women with a family history of breast cancer. Our findings may have differed because our cohort is enriched for a family history of breast cancer. Other studies that have shown an increased risk of breast cancer associated with OC use include studies focusing on early onset cases with a first-degree family history of breast cancer (eg, UK National Case-Control Study Group) and studies of known **BRCA1** or **BRCA2** mutation carriers.

In vitro experiments on breast cancer cell lines have shown that wild-type **BRCA1** inhibits the transcription activity of the estrogen receptor-α under certain conditions. Mutations in **BRCA1** may remove this inhibitory effect, thereby increasing estrogen-dependent epithelial proliferation in the breast. This proposed interaction between **BRCA1** and the estrogen receptor may contribute to the increased risk associated with OC use observed in some of our families.

The Minnesota Breast Cancer Family Study is a unique, well-defined resource for genetic epidemiologic studies that offered us several advantages in our analysis of OC use and breast cancer risk. The selection of the original breast cancer probands was essentially population-based. Participation rates by the families in this study have been very high (>93%), with an average of only 1 or 2 individuals per family lost to follow-up. The length of follow-up was extensive, on average more than 35 years, and as long as 64 years. We expect that recall of aspects of OC use that we analyzed (ever vs never use, total duration of use, and ages of use) in this population was accurate. Agreement between recalled history and records of prescribing gynecologists for these aspects of OC use has been shown to be reasonably good and nondifferential with regard to case and control status.

Several complicating factors must be considered when interpreting the results of this study. Trends in OC use in the United States have been pronounced. Prevalence of OC use has increased markedly over time, especially among younger women. Total
duration of use has also increased. In addition, substantial changes in the type and concentration of the estrogen and progestin components of OCs have occurred since their introduction in 1960, from 150 µg of mestranol to 50 µg or less of ethinyl estradiol, and 9.85 µg of norethynodrel to 1 mg or less of several progestins.30 The rising incidence of breast cancer over the years of follow-up further complicates the analysis. Although we adjusted for quartiles of birth cohort, we were unable to completely control for all temporal trends. Our estimation of low-dose vs high-dose formulations of OCs was based on use before or after 1975 since all formulations of OCs initially marketed after 1975 contain 50 µg or less of ethinyl estradiol and 1 mg or less of several progestins.30 Therefore, some misclassification of high-dose vs low-dose exposure likely occurred. Since most instances of misclassification would result in individuals with low-dose exposure being classified as having high-dose exposure, we consider this to be a conservative approach.

Surrogate data on OC use were not collected due to their potentially low reliability. Therefore, data on OCs are limited to women who were alive and able to complete the telephone interview between 1991 and 1996. If OCs are associated with improved survival after breast cancer, one would expect to see an increased risk of breast cancer associated with OC use in this cohort. While some evidence exists for breast cancers in OC users being at an earlier stage, it is unknown whether this stems from earlier detection of breast cancer in these women, from the biological effects of the OCs, or from a combination of factors.1 To help assess whether survivor bias was a concern in our study, we compared the length of time from breast cancer to interview among OC users and nonusers. After adjustment for birth cohort, the mean survival time was not significantly different between OC users (12.0 years) and OC nonusers (11.9 years), P=.92. In addition, the RR of breast cancer associated with OC use among the marry-ins in our cohort is comparable with published estimates in general population samples.1

The possibility of surveillance bias, specifically whether OC users and women with a family history of breast cancer had more frequent mammograms and therefore were more likely to have a breast cancer detected, was addressed by adjusting the model of pre-and post-1975 use for total number of mammograms. In this model, the risk among women with a first-degree family history who used OCs before 1975 was attenuated (RR, 2.4 vs 3.3) but still significantly increased. Therefore, surveillance bias does not appear to strongly affect our observations.

An important advantage of this study population is the complete knowledge of the sampling frame. Even when family members had died, we had knowledge of their existence and obtained selected data on these women as well as on living women who were unable to complete a telephone interview. This information was used to try to control for potential bias due to missing data on OC use. Implementation of weights based on the probability of non-missing data on OC use had a negligible impact on the results; thus, the absence of data on OC use among selected women was an unlikely explanation for our findings.

In summary, women with a first-degree family history of breast cancer who used OCs prior to 1975 were at significantly increased risk of breast cancer. We saw no evidence for an increased risk of breast cancer associated with use of OCs after 1975 in first-degree relatives, second-degree relatives, or marry-ins. However, only 60 women with a first-degree family history of breast cancer used OCs after 1975 and only 2 of these were diagnosed with breast cancer, so our estimated RR is somewhat unstable for this group of younger women. Also, because of the potential for misclassification of exposure, we are hesitant to draw conclusions about the influence of more recent OC formulations on breast cancer risk in women with a first-degree family history of breast cancer. Further follow-up is needed to investigate any association between current formulations of OCs and breast cancer incidence in these high-risk women. In addition, we will be completing BRCA1 and BRCA2 mutation screening in the high-risk families to determine whether these or other genes are responsible for the modifying effect of family history on the association between OC use and breast cancer. Women who have a first-degree family history of breast cancer and OC exposure may want to be particularly vigilant regarding appropriate breast cancer screening practices.

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**REFERENCES**


As no two persons are exactly alike in health so neither are any two in disease; and no diagnosis is complete or exact which does not include an estimate of the personal character, or the constitution of the patient.
—Sir James Paget (1814-1899)