Re: Oral Contraceptives and the Risk of Breast Cancer in BRCA1 and BRCA2 Mutation Carriers

In a recent issue of the Journal, Narod et al. (1) reported findings from a large sample of 2611 BRCA1 and BRCA2 germline mutation carriers regarding the association of oral contraceptive use with the risk of breast cancer. An interesting feature of this report—not commented on by the authors—is data regarding cigarette smoking. The proportion of breast cancer case subjects who ever smoked was 39%, and the proportion among control subjects was 41%. These data clearly suggest no material association between cigarette smoking and breast cancer risk, a finding in agreement with a recent pooled analysis of major breast cancer studies (2).

In 1998, Narod et al. published in the Journal an earlier report from the same study (3). By contrast with the current data, that analysis, based on only 372 subjects, suggested that smoking reduced the risk of breast cancer in women known to carry a germline mutation in BRCA1 or BRCA2. In that analysis, the proportion of case subjects who had ever smoked was 39% (as in the current report), whereas the proportion among control subjects was 52% (higher than in the current, larger report). With a higher smoking prevalence among the control subjects, an adjusted odds ratio of 0.54 \((P = .007)\) was found.

It is not clear what might explain the difference in findings between the two analyses. Certainly the use of clinic-based data introduces potential problems in design and interpretation (4,5). Indeed, the two different prevalences of smoking among the control samples could be the result of seemingly subtle differences in participation in genetic counseling clinics and the studies conducted there. The differences in the smoking findings may also illustrate a possible pitfall of studies with continuing enrollment. Premature or repeated analyses of evolving data may lead to a decision to publish apparently “significant” findings that have actually emerged by chance.

It is also possible that the statistics generated from the matched analyses do not appropriately reflect the association in the whole study sample. The methodology used by Narod et al. (1)—matching on mutated gene, age, and country of residence—reduces the potential for bias. However, this approach does not optimize the use of the data because a large proportion of carriers with and without breast cancer are not included. It would be interesting to see analyses that are based on less stringent matching criteria, greater control-to-case matching ratios, and/or modeling of possible confounding effects.

John L. Hopper
John A. Baron

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Narod et al. (1) reported that, among BRCA1 mutation carriers, women who used oral contraceptives might have an increased risk of early-onset breast cancer. They call for independent verification, preferably among women who are not selected through familial aggregation. We believe that it might also be of interest to assess the combined effect of the BRCA1 mutation and oral contraceptive use, and the separate effects of the mutation and of oral contraceptive use on breast cancer risk, each comparison relative to the risk in those having neither risk factor for breast cancer.

From 1984 until 1996, all primary invasive breast cancer patients who were surgically treated at the Leiden University Medical Center were asked to provide a blood sample for research purposes, regardless of age or family history. This request was approved by the Medical Ethics Committee. For patients aged younger than 50 years at diagnosis and for whom leukocyte DNA was available (n = 183) (2), data on current oral contraceptive use were obtained by a questionnaire mailed to 162 patients alive on June 1, 1997; 111 patients responded. For all other patients with breast cancer, current oral contraceptive use was verified from their medical records. For control subjects, data regarding expected oral contraceptive use were derived from a national random sample of 1971 women aged 19–49 years who had been interviewed in 1990 (i.e., the halfway point for patient accrual) regarding their current use of contraceptives (3). For our analysis, we assumed that the frequencies of oral contraceptive use among control subjects were the same, irrespective of BRCA1 mutation status, and we multiplied these frequencies with the expected population frequencies of BRCA1 germline mutations (4) to calculate the expected frequency of all combinations of oral contraceptive use and BRCA1 mutation status among the general population.

Oral contraceptive use was known for eight BRCA1 mutation carriers and for 175 non-carriers. At the time of breast cancer diagnosis, two BRCA1 mutation carriers and 30 non-carriers had used oral contraceptives. This leads to a multiplicative synergy index (5) of 1.61 (95% confidence interval [CI] = 0.31 to 8.37). The index indicates that the relative risk of oral contraceptive use is equal or, at most, slightly greater among BRCA1 mutation carriers than among non-carriers. The separate and combined effects of oral contraceptive use on the risk of breast cancer among women with and without BRCA1 mutations are shown in Table 1. The odds ratios suggest that oral contraceptive use is in itself a weak risk factor for breast cancer but increases the risk of breast cancer in BRCA1 mutation carriers from 35-fold (95% CI = 16- to 79-fold) to 58-fold (95% CI = 15- to 236-fold).

Our results support the notion that the relative risk of oral contraceptive use might be similar among BRCA1 mutation carriers and non-carriers—or at most slightly higher among carriers—but that oral contraceptive use clearly leads to a much higher total risk among women with BRCA1 mutations. We realize that our numbers are small and reflect only current use. However, most previous studies also assessed an elevated risk with current use, and the Collaborative Group on Hormonal Factors in Breast Cancer analysis of 54 studies found no difference in the relative risk associated with oral contraceptives between subgroups and, moreover, not in the subgroup of women with affected family members, where we would expect to find most BRCA1 mutation carriers (6). A small overall relative risk associated with oral contraceptive use is likely, given the known epidemiologic data, but even small relative risks will have much larger consequences among BRCA1 mutation carriers because these women already have an elevated risk resulting from the mutation.

**Table 1. Odds ratios (ORs) for the development of breast cancer associated with using oral contraceptives in carriers (n = 8) and non-carriers (n = 175) of BRCA1 mutations in an unselected population**

<table>
<thead>
<tr>
<th>Oral contraceptive use</th>
<th>–</th>
<th>+</th>
<th>–</th>
<th>+</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 mutation†</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Breast cancer patients, %</td>
<td>79.2</td>
<td>16.4</td>
<td>3.3</td>
<td>1.1</td>
</tr>
<tr>
<td>General population, %‡</td>
<td>84.3</td>
<td>15.7</td>
<td>0.1</td>
<td>0.02</td>
</tr>
<tr>
<td>OR (95% CI)§</td>
<td>1 (referent)</td>
<td>1.1 (0.7 to 1.6)</td>
<td>35 (16 to 79)</td>
<td>58 (15 to 236)</td>
</tr>
</tbody>
</table>

*Patient and population data are entered as percentage for ease of comparison. + = present; – = absent.
†In the breast cancer patients, BRCA1 mutation status was determined as described (2).
‡Expected frequencies, standardized to age distribution of case subjects (3,4).
§Confidence intervals were calculated according to Woolf (7), assuming negligible population variance.

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(5) Khoury MJ, Flanders WD. Nontraditional epidemiologic approaches in the analysis of gene-

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Afilations of authors: G. H. de Bock (Department of Medical Decision Making), R. A. E. M. Tollenaar (Department of Surgery), H. Papelard (Departments of Medical Decision Making and Surgery), T. P. M. Vlieet Vheland (Department of Rheumatology), P. Devlees (Department of Human and Clinical Genetics), C. J. Cornethse (Department of Pathology), J. P. Vandenbroucke (Department of Epidemiology), Leiden University Medical Center, Leiden, The Netherlands.
Correspondence to: G. H. de Bock, Ph.D., Department of Medical Decision Making, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands (e-mail: G.H.de_Bock@lumc.nl).

Narod et al. (1) recently presented results of a multicenter case–control study on the relationship between use of oral contraceptives and risk of breast cancer among BRCA1 and BRCA2 mutation carriers. Although the study is of high potential interest for the counseling of these women, it may have several methodologic limitations.

Survival bias is a major concern for this study of prevalent cases of breast cancer with a mean survival of 8.2 years, especially because, in the general population, use of oral contraceptives has been associated with lower stage disease at diagnosis (2). The authors disregard survival bias by indicating that no difference was found between women who completed the questionnaire within 5 years of their breast cancer diagnosis (odds ratio [OR] = 1.26, 95% confidence interval [CI] = 0.98 to 1.64) and those who completed the questionnaire after 5 or more years (OR = 1.13, 95% CI = 0.93 to 1.37). At first sight, this is indeed suggestive of lack of survival bias. However, during the study period (1970 through 2000), 20%–30% of breast cancer patients in the general population died within 5 years, and prognosis for mutation carriers may have been worse (3). Thus, the difference in risk between women who completed the questionnaire within 2 years and those who completed the questionnaire after 2 or more years would have been more informative. Moreover, the higher risks associated with earlier years at diagnosis (1970–1979: OR = 1.98, 95% CI = 1.16 to 3.40; 1980–1989: OR = 1.26, 95% CI = 0.94 to 1.70; 1990–2001: OR = 1.11, 95% CI = 0.90 to 1.36) in combination with a rather small range of calendar years for data collection (cases: mean = 1999, standard deviation = 2.0) suggest that the study is not free of survival bias. Therefore, it would be helpful to see the main analyses restricted to recent cases.

A study among known BRCA mutation carriers may contain selection bias because women with cancer may seek genetic testing more frequently and for other reasons than women without cancer. For example, among women without cancer, parous women may seek genetic testing more often than nulliparous women (4). Thus, use of oral contraceptives may also differ between unaffected carriers who know their mutation status and unaffected carriers who do not.

Information on oral contraceptive use was collected by questionnaire. It is not clear whether the procedure for administering the questionnaire was similar for case patients and control subjects, especially in the centers that did not use the standard questionnaire (mainly in Europe). Part of the heterogeneity across countries (United States/Canada/Israel: OR = 1.33 to 1.38 and Europe: OR = 0.46 to 1.27) and part of the possibly country-related differences between Jewish and non-Jewish women (ORs are 1.37 and 1.11, respectively) may be associated with differences in data collection. Furthermore, it is not clear how the collected information on oral contraceptives (starting and stopping dates, duration and current use at date of interview) enabled the authors to define recent use and duration at “pseudo”-diagnosis in control subjects, when the control subjects were as old as their matched case patients at diagnosis.

MATTI A. ROOKUS
RICHARD BROHET
FLORA E. VAN LEEUWEN

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NOTES
Affliation of authors: Department of Epidemiology, The Netherlands Cancer Institute, Amsterdam, The Netherlands. Correspondence to: M. A. Rookus, Ph.D., Department of Epidemiology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands (e-mail: m.rookus@nki.nl).

RESPONSE

Hopper and Baron point out that there was no apparent difference in the smoking histories of the breast cancer case patients and matched control subjects in our recent case–control study of breast cancer among BRCA mutations carriers (1). They ask whether our observation is consistent with our data from an earlier report of the same study population, in which we proposed that cigarette smoking protected against breast cancer in BRCA mutation carriers (2). Hopper and Baron are correct. We have re-addressed the question of smoking and breast cancer in a much larger sample of BRCA mutation carriers and now find no support for the presence of a reduced risk (3). In our analysis, smoking was reported by 41.2% of 1097 case patients and by 40.4% of matched control subjects (3). The methods of this study and our earlier study (2) are almost identical, and the different results are likely due to a difference in sample size. In the rush to publish in a competitive area, it is often the case that epidemiologic studies with marginal sample sizes, but that show interesting preliminary re-
results, are the first to reach print. The report from Leiden by de Bock et al. might be another example of this phenomenon.

STEVEN NAROD
PARVIZ GHADIRIAN

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Editor’s note: The authors declined to respond to the correspondence by Rookus et al.
Affiliation of authors: Centre for Research on Women’s Health, University of Toronto and Epidemiology Research Unit, Centre hospitalier de l’Université de Montréal.
Correspondence to: Steven Narod, M.D., F.R.C.P.C., University of Toronto, Centre for Research on Women’s Health, 790 Bay St., Toronto, Ontario M5G 1N8, Canada (e-mail: steven.narod@swchsc.on.ca).