In a recent issue of the Journal of the National Cancer Institute, Naoadi et al. reported findings from a large sample of 2011 BRCA1 and BRCA2 gene-mutation carriers. The study found that smoking reduces the risk of breast cancer in women with BRCA1 or BRCA2 mutations, supporting the association of oral contraceptive use with the risk of breast cancer in women who have a BRCA1 or BRCA2 mutation.

The authors noted that smoking is a well-known risk factor for several cancers, including breast cancer. Their findings provide additional evidence for the role of smoking in the development of breast cancer among individuals with BRCA1 or BRCA2 mutations.

The study suggests that smoking cessation programs should be considered an important part of breast cancer prevention strategies for women with BRCA1 or BRCA2 mutations.
collaborative group on hormonal factors in breast cancer. analysis of 54 studies found no difference in the relative risk associated with orl contraceptive use compared to non-users. the small overall relative risk was not statistically significant, and the data did not support the hypothesis that women who used orl contraceptives had a lower risk of breast cancer. the authors concluded that the data did not provide evidence for a protective or increased risk of breast cancer associated with orl contraceptive use.

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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 diagnoses (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.

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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 BRCA2 mutation carriers (1). They ask whether this 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 BRCA2 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.

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Editor’s note: The authors declined to respond to the correspondence by Rookus et al.

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