Frequency of BRCA1 and BRCA2 Mutations in Unselected Ashkenazi Jewish Patients With Colorectal Cancer

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Mutations in BRCA1 and BRCA2 that predispose to breast and ovarian cancer are detected in approximately 2.5% of the Ashkenazi Jewish population. To explore whether carriers of Ashkenazi founder mutations in BRCA1 or BRCA2 have an increased risk for colorectal cancer, we screened 586 unselected Ashkenazi Jewish case patients with colorectal cancer for the three common founder mutations in BRCA1 and BRCA2. We identified six carriers (1.02%) among these case patients. After adjusting for age at diagnosis and sex by use of logistic regression analysis, we compared the incidence of carriers in this group of 586 case patients with that of 5012 healthy Ashkenazi Jewish Jewish control subjects without a known history of colorectal cancer. The presence of a founder BRCA mutation was not associated with the risk of colorectal cancer (relative risk [RR] = 0.50, 95% confidence interval = 0.22 to 1.14). We thus recommend that counseling for colorectal cancer screening and prevention in individuals with BRCA mutations be based on the personal and family history of colorectal cancer or associated syndromic malignancies. [J Natl Cancer Inst 2004;96:68–70]
in case patients with early-onset breast cancer were also comparable when the DNA was derived from lymphocytes or paraffin-embedded tissues (17,18).

Control subjects were 5012 self-identified Jewish volunteers recruited from advertisements in the Washington, DC, area. These control subjects were tested for the three Ashkenazi founder mutations, they did not have a history of colorectal cancer, and they had data available on BRCA mutation status (3). The age- and sex-specific rates were provided by the authors of this study. A logistic regression model was used to estimate the relative risk for cancer associated with BRCA mutation, after adjusting for age and sex by treating them as additional covariates in the model (19).

Ashkenazi founder mutations were identified in a total of six (1.02%) of 586 specimens. Among these case patients, two (0.34%) were carriers of BRCA1*185delAG, one (0.17%) was a carrier of BRCA1*5382insC, and three (0.51%) were carriers of BRCA2*6174delT. In the control group, 118 carriers of a BRCA1 or BRCA2 mutation were identified. Sex (odds ratio [OR] = 1.08, 95% confidence interval [CI] = 0.89 to 1.30) was not associated with risk for colorectal cancer, by logistic regression analysis. After adjusting for age (OR = 1.07, 95% CI = 1.06 to 1.08), BRCA mutation status was not statistically significantly associated with the risk of colorectal cancer (RR = 0.50, 95% CI = 0.22 to 1.14; P = .10), by logistic regression analysis.

The current study is, to our knowledge, the largest series to date that has examined the incidence of BRCA1 and BRCA2 mutations in Jewish individuals with pathologically confirmed colorectal cancer. A study of 136 consecutive Israeli Jewish patients with colorectal cancer documented a slightly elevated risk of colorectal cancer in carriers of BRCA1 and BRCA2 mutations (20), but another series of 225 unselected Jewish patients with colorectal cancer did not confirm this association (12). The lack of association in the present series of 586 case patients makes it unlikely that the presence of a BRCA founder mutation has a substantial impact on the incidence of colorectal cancer.

There are several limitations in our study design that could potentially affect our results. A bias could have been introduced if the frequency of BRCA1 and BRCA2 mutations in the Ashkenazi Jewish population in Washington, DC, was not reflective of the frequency of founder mutations in other Ashkenazi Jewish populations. The founder mutation carrier frequency from the Washington, DC, area study, however, was consistent with other large series from the United States (21) and with the observed frequency of the BRCA2 founder mutation in our study of a New York City cohort of patients undergoing prenatal genetic testing (4). The population frequencies of the three Ashkenazi founder mutations ranged from 2.3% to 2.7% among 8172 individuals (3,21); similarly, the frequency of BRCA2 6174delT was 0.9% in our series of 1255 individuals in New York City compared with 1.1% in the control series used in this study. Although these results support the appropriateness of historical control subjects from the Washington, DC, area in this study, it is important to note that, in both the case patients and the control subjects, individuals identified themselves as Jewish. Although the vast majority of Jews in the United States (approximately 90%) are of Ashkenazi Jewish ancestry, it is possible that a higher or lower proportion of Ashkenazi Jews in the case patients and control subjects could have resulted in a bias. A bias could also have been introduced by the use of a hospital-based series of patients with colorectal cancer rather than a population-based series. Such a bias would be evident if the BRCA-linked colorectal tumors had clinical features different from sporadic tumors, possibly leading to their over- or under-representation in a cancer referral center. Although such features have not been documented for BRCA-linked colorectal cancers, patients with BRCA-linked ovarian cancers have a superior prognosis (16). Such a finding might explain the under-representation of such patients in a cancer referral center and may account for the slight, statistically nonsignificant trend toward an increased prevalence in BRCA2 mutations observed in a recent population-based series of patients with colorectal cancer (22). Another plausible reason for the discrepancy between our results and the family-based analysis is misclassification of tumors in family members used for the family-based series. Because all cancers in this series were pathologically confirmed, this report does not have this limitation. Finally, families with BRCA1 and BRCA2 mutations included in prior family-based series may have been biased to include patients with sporadic colorectal cancer as well as other tumor types, leading to an apparent increased incidence of these tumors in these kindreds.

With regard to the generalizability of these findings, the three Ashkenazi founder mutations, like the vast majority of BRCA1 and/or BRCA2 mutations, cause premature protein truncation. Because there is some evidence of genotype–phenotype associations for certain BRCA2 mutations (23), it is possible that the findings of studies of these three mutations may not be generalizable and that other BRCA1 and/or BRCA2 mutations may be associated with increased susceptibility to colorectal cancer.

Although other genetic mechanisms, notably the mutations APC*11307K and possibly CHK2*1100delC, have been associated with familial breast and colorectal cancer (24–26), this study finds no evidence that carriers of founder BRCA1 or BRCA2 mutations are at a statistically significantly increased risk of colorectal cancer. Given the lack of evidence for a younger age at onset of colorectal cancer observed in prior series, the most prudent approach to colorectal cancer screening and prevention in BRCA-associated kindreds continues to include colon screening beginning at age 50 years or earlier, depending on the familial or personal history of colorectal cancer or colorectal adenomas.

References


Cancer risks in BRCA2 mutation carriers.


NOTES

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