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The *APC* I1307K Allele and *BRCA*-Associated Ovarian Cancer Risk

To the Editor:

Most ovarian cancers attributable to autosomal dominant genetic predisposition (~10% of all cases) are associated with germ-line mutations in the *BRCA1* or *BRCA2* genes (reviewed in Boyd 1998). Estimates of the lifetime probability of developing ovarian cancer in association with a *BRCA* mutation have a range of 16%–63% (Easton et al. 1995; Struewing et al. 1997; Ford et al. 1998). This large variation in penetrance is widely presumed to reflect the effects of various hormonal, environmental, and genetic modifiers, but few such modifying factors have been identified. The use of oral contraceptives was recently shown to substantially reduce the risk of ovarian cancer in women with *BRCA* mutations (Narod et al. 1998), yet it has been suggested that bearing more offspring increases ovarian cancer risk in *BRCA1* carriers (Narod et al. 1995). The only genetic modifier of *BRCA* penetrance yet shown is the *HRAS1* locus, rare alleles of which are associated with an increased risk of ovarian cancer in *BRCA1* carriers (Phelan et al. 1996).

The *APC* I1307K allele is a plausible candidate modifier of *BRCA* penetrance. First identified as a founder mutation occurring in ~6% of the Ashkenazi Jewish population, the allele is present in a significantly higher proportion of Jewish colorectal cancer patients and in those with a family history of colorectal cancer (Laken et al. 1997). The mechanism through which this allele contributes to the development of colorectal cancer appears to involve the creation of a small hypermutable region that undergoes somatic frameshift alterations leading to *APC* inactivation and the initiation of tumorigenesis (Laken et al. 1997; Gryfe et al. 1998). Consistent with this molecular genetic scenario are the well-established roles of somatic *APC* mutations in the initiation of sporadic colorectal cancer and germ-line *APC* mutations in predisposition to familial adenomatous polyposis (Kinzler and Vogelstein 1996).

Attempts to confirm and extend the original observation of *APC* I1307K-associated cancer risk in Ashkenazi Jews have produced inconsistent findings. Results from one follow-up study implied that the *APC* I1307K mutation alone does not significantly increase the risk of colorectal cancer (Petrukhin et al. 1997). Recent data from a large community-based study of Ashkenazi Jews indicated that *APC* I1307K confers a modest but significant risk of cancer in general but that odds ratios for any particular cancer are not increased to statistically significant levels (Woodage et al. 1998). Remarkably, however, there is an apparent synergy between *APC* I1307K and a mutant *BRCA* allele in relation to breast cancer risk (Redston et al. 1998). Taken together, these data suggest that *APC* I1307K may function as a low-penetrance modifier of cancer risk in association with high-penetrance cancer-predisposition alleles such as *BRCA1* or *BRCA2*. Thus, even though *APC* I1307K alone does not appear to confer a substantial risk of

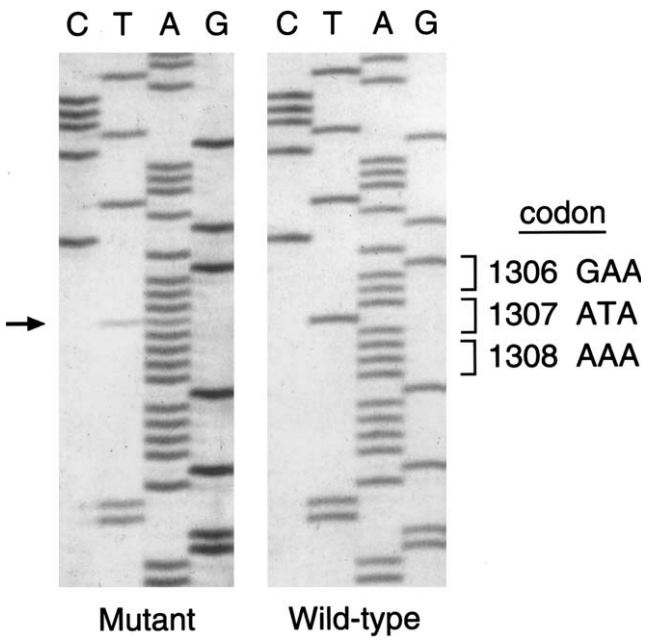

Figure 1 Sequence analysis for detection of the *APC* I1307K mutation. Shown is the sequence flanking *APC* codon 1307 from an individual with the mutant I1307K allele (*left*) and from an individual with the wild-type sequence only (*right*). The arrow indicates position of the mutation.

ovarian cancer in the Ashkenazi Jewish population generally (Abrahamson et al. 1998; Woodage et al. 1998), it remains possible that ovarian cancer risk may be increased in carriers of both *APC* I1307K and a *BRCA* mutation.

The purpose of this study was to use a case-case epidemiological design to test the hypothesis that the carrier frequency of *APC* I1307K is higher in Ashkenazi Jewish ovarian cancer patients with a deleterious germline *BRCA* mutation than in Jewish ovarian cancer patients without a *BRCA* mutation, which would imply that the mutant *APC* allele increases the penetrance of *BRCA* mutations for ovarian cancer. The study was approved by the institutional review board of the Memorial Sloan-Kettering Cancer Center. From a consecutive series of 933 ovarian cancer cases from this institution, 179 cases were identified in which the patient had indicated a religious preference of Jewish. Genomic DNA samples associated with these cases were then screened for the presence of three founder mutations, 185delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2*. Eighty-seven *BRCA*-linked cancers were identified (designated as "cases"), 66 associated with *BRCA1* (50 with 185delAG and 16 with 5382insC) and 21 associated with *BRCA2*. An additional 92 patients (designated as "controls") were found not to carry any of these *BRCA* mutations. Our procedures for the identification of these

Table 1

Frequency of *APC* I1307K in Ashkenazi Jewish Ovarian Cancer Patients

Group	No. of I1307K Carriers/Total No. of Patients (%)	Odds Ratio[a]	Confidence Interval	*P*
Controls[b]	7/92 (7.6)	1.0	...	...
Cases:[c]				
BRCA1	2/66 (3.0)	.4	.1–1.9	.24
BRCA2	1/21 (4.8)	.6	.1–5.2	.64
All *BRCA*	3/87 (3.4)	.4	.1–1.7	.24

[a] As determined by logistic regression.

[b] Ashkenazi Jewish ovarian cancer patients without one of three germ-line founder mutations in *BRCA1* or *BRCA2*.

[c] Ashkenazi Jewish ovarian cancer patients with germ-line mutations in *BRCA1* (185delAG or 5382insC) or *BRCA2* (6174delT).

BRCA founder mutations are described elsewhere in detail (Rhei et al. 1998).

The status of *APC* codon 1307 was determined in all cases and controls by PCR amplification of an 82-bp product by means of the primers specified (Laken et al. 1997), followed by SSCP and direct sequence analyses (fig. 1). Three (3.4%) of 87 *BRCA*-associated ovarian cancer cases were found to harbor the *APC* I1307K allele, as were 7 (7.6%) of 92 control subjects (table 1). The frequency of *APC* I1307K found in controls (Jewish ovarian cancer patients without germ-line *BRCA* mutations) is nearly identical to the carrier frequency of 7.2% reported in a community-based survey of >5,000 Ashkenazi Jews (Woodage et al. 1998) and to the frequency of 7.9% observed in a series of unselected Ashkenazi Jewish ovarian cancer patients (Abrahamson et al. 1998). The lowered odds ratios (.4 to .6) found in cases compared with controls were not statistically significant and do not support the hypothesis that *APC* I1307K confers an increased risk of ovarian cancer in association with a germ-line *BRCA* mutation.

To determine whether the *APC* I1307K allele contributed to ovarian tumorigenesis in those individuals found to carry this mutation, genomic DNA from the corresponding ovarian cancers was used as a template for PCR amplification of a larger, 230-bp PCR product by means of the primers specified (Laken et al. 1997). None of the 10 ovarian cancer DNA samples examined were found to harbor additional somatic mutations in the hypermutable region surrounding *APC* I1307K, nor did any of the tumors display evidence of loss of the wild-type *APC* allele. These data indicate that the variant *APC* allele does not contribute to ovarian tumorigenesis in affected carriers, consistent with the absence of elevated ovarian cancer risk in carriers with *BRCA* mutations.

These findings, together with those reported elsewhere (Redston et al. 1998), suggest that *APC* I1307K is a

significant genetic modifier of *BRCA* penetrance for breast, but not ovarian, cancer. Of interest, in this context, are observations from animal studies in which the *Min* mouse, carrying a germ-line mutation in the murine homologue of *APC*, is susceptible to mammary gland tumorigenesis, in addition to that of the gastrointestinal tract (Bilger et al. 1996). These data also support the concept that genetic modifiers of *BRCA* penetrance are likely to exert differential effects on breast and ovarian tumorigenesis, as was found for the effect of rare *HRAS1* alleles on ovarian, but not breast, cancer risk (Phelan et al. 1996). As for many other genetic disorders, penetrance of dominant cancer-susceptibility alleles is likely to depend on complex interactions between multiple genetic and environmental modifying factors; furthermore, those genetic factors that are found to affect *BRCA* penetrance are not likely to be generalizable to both breast and ovarian cancer risk.

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Germ-Line *NF2* Mutations and Disease Severity in Neurofibromatosis Type 2 Patients with Retinal Abnormalities

To the Editor:

Neurofibromatosis type 2 (NF2; MIM 101000) is a clinically variable disease caused by mutations in the *NF2* tumor-suppressor gene. Common manifestations include nervous system tumors and ocular abnormalities such as presenile lens opacities and retinal abnormalities