British Journal of Cancer (2000) **83**(2), 153–155

doi: 10.1054/ bjoc.2000.1248, available online at http://www.idealibrary.com on IDEAL®

Association of the I1307K APC mutation with hereditary and sporadic breast/ovarian cancer: more questions than answers

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Summary The frequency of the APC I1307K mutation and its association with disease pattern was examined in 996 Ashkenazi women consisting of individuals with either sporadic (*n* = 382) or hereditary (*n* = 143) breast and/or ovarian cancer; asymptomatic BRCA1/2 mutation carriers (185delAG, 5382insC and 6174delT) (*n* = 53) and healthy controls (*n* = 418). The I1307K allele was equally distributed among women with sporadic (17/382; 4.6%) and inherited (10/143; 7%) breast and/or ovarian cancer irrespective of their being diagnosed before or after 42 years of age and among asymptomatic (7/53; 13.2%) and cancer manifesting BRCA1/2 carriers (10/143; 7%). Taken together, the prevalence of the I1307K allele was significantly higher in BRCA1/2 carriers compared to non-BRCA1/2 carriers (17/196; 8.7% and 40/800, 5%; respectively). The high prevalence of the I1307K allele among BRCA1/2 carriers is not associated with increased cancer risk but seems to be genetically connected because of Jewish ancestry. © 2000 Cancer Research Campaign

Keywords: breast cancer; ovarian cancer; BRCA1; BRCA2; APC; I1307K polymorphism

Females with BRCA1/2 mutations have a 40% to 60% lifetime risk of developing breast cancer and a 16% to 40% risk of developing ovarian cancer (Friedman et al, 1995; Levy-Lahad et al, 1997). The incomplete penetrance of the BRCA1/2 gene mutations suggests that other factors, genetic and non-genetic, determine the phenotypic expression of mutant BRCA1/2 alleles. Candidate 'modifier genes' to consider include genes with a known relevance to breast tumorigenesis (e.g., p53), genes which physically interact with BRCA1 or BRCA2 (e.g., RAD51), or those that have an in-vitro effect on the proliferation rate of breast epithelial cells (e.g., estrogen receptor, vitamin D receptor).

In Ashkenazi Jews three predominant founder mutations were described (185delAG and 5382insC in BRCA1 and 6174delT in BRCA2) (Friedman et al, 1995; Modan et al, 1996; Neuhausen et al, 1996; Tonin et al, 1996). In this population, one could consider as putative modifier genes, genes that display a high carrier state and are known to be associated with an increased risk for cancer. The recently described I1307K missense mutation in the APC gene, seems to fit into this category. This missense mutation has been detected in 28% of Jewish Ashkenazi individuals with familial colorectal cancer, and in 6–7% of the general Jewish Ashkenazi population (Laken et al, 1997; Woodage et al, 1998). The apparent mechanism underlying cancer predisposition is the creation of a homopolymer tract (A8), resulting in tissue-specific genomic instability, prone to acquiring somatic mutation (Laken et al, 1997). Several lines of evidence suggest that the APC gene might participate in breast cancer tumorigenesis. Loss of heterozygosity involving the APC gene has been reported in sporadic breast tumours (Thompson et al, 1993; Kashiwaba et al, 1994). Woodage and coworkers (1998) reported that I1307K mutation carriers are more likely to have a first degree relative with breast cancer. Redston and coworkers (1998) have affirmed that cancer risk conferred by mutant BRCA1/2 alleles is increased by the presence of the I1307K APC polymorphism.

To better delineate an association between the I1307K mutation and breast/ovarian cancer we determined the prevalence of this mutation in Jewish patients with inherited and sporadic breast and/or ovarian cancer.

Received 2 June 1999
Revised 25 February 2000
Accepted 23 March 2000

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MATERIAL AND METHODS

Patients and controls

Patients – 366 self-referred or physician-referred patients with either breast and/or ovarian cancer visiting the Oncogenetics services at Sheba and Rambam Medical Centers and 159 unselected patients with breast cancer seen at Sheba and Rambam Oncology Clinic during 1997 and 1998. All patients were systematically screened for the three predominant BRCA1 and BRCA2 mutations and for the I1307K APC mutation.

Asymptomatic – carriers 53 family members of mutation carriers or individuals referred because of a family history of breast/ovarian cancer.

Controls – 418 healthy Ashkenazi individuals who presented for genetic testing of common recessive diseases. These were systematically screened for the I1307K APC mutation only.

Data including demographics, histopathological information, treatment and outcome variables were collected and entered into a computerized database. All participants signed an informed consent form approved by the Institutional Review Board (IRB) and were genotyped for the three predominant founder mutations

Table 1 Distribution of the I1307K allele among patients and healthy participants

Groups	Subgroups	I1307K carriers	Total	%	95% CI
Total		57	996	5.7	4.40–7.40
Healthy controls		23	418	5.5	3.60–8.26
Sporadic cases					
	Late onset breast cancer[a]	15	276	5.4	3.18–8.99
	Early onset breast cancer	1	81	1.2	0.06–7.64
	Ovarian cancer	1	25	4	0.21–22.32
	All	17	382	4.6	2.70–7.17
BRCA1/2 carriers					
	Late onset breast cancer[b]	5	59	8.5	3.16–19.42
	Early onset breast cancer[c]	4	55	7.3	2.36–18.43
	OC	1	29	2.8	0.18–19.63
	Asymptomatic	7	53	13.2	5.91–25.95
	All	17	196	8.7	5.29–13.75

[a]Includes 2 patients with both breast and ovarian cancer. [b]Includes 10 patients with both breast and ovarian cancer. [c]Includes 4 patients with both breast and ovarian cancer.

Table 2 Prevalence of the I1307K allele among breast and/or ovarian cancer patients and healthy controls with/without BRCA1/2 mutations.

Groups	Total	BRCA1/2 carriers					Non-BRCA1/2 carriers								
		Total	I1307K carriers		I1307K non-carriers		Total	I1307K carriers		I1307K non-carriers					
			No.	%	No.	%		No.	%	No.	%	χ^2	p	OR	95% CI
All patients	525	143	10	7	133	93	382	17	4.4	365	95.6	1.07	0.2	1.5	0.7–3.4
Breast cancer patients	471	114	9	7.9	105	92.1	357	16	4.5	341	95.5	2	0.122	1.8	0.8–4.2
Early onset breast cancer	136	55	4	7.3	51	92.7	81	1	1.2	80	98.8	3.4	0.086	6.275	0.7–57.7
Late onset breast cancer	335	59	5	8.5	54	92.5	276	15	5.4	261	94.6	0.8	0.265	1.6	0.6–4.6
Ovarian cancer patients	54	29	1	2.8	28	98.2	25	1	4	24	96	0.01	0.72	0.86	0.02–33.5
Healthy participants	471	53	7	13.2	46	76.8	418	23	5.5	395	94.5	4.68	0.04	2.6	1.1–6.4
Total	996	196	17	8.7	179	91.3	800	40	5	760	95	3.615	0.046	1.7	1–3.1

in BRCA1 (185delAG and 5382insC) and BRCA2 (6174delT) and for I1307K APC mutation.

Genotyping

All genotyping was performed on DNA extracted from lymphocytes.

The 185delAG, 5382insC (BRCA1) and 6174delT (BRCA2) were detected by PCR amplification with specific primers that produce a modified restriction enzyme digest made to distinguish the wild-type allele from the mutant allele, as previously described (Abeliovich et al, 1997; Rohlfs et al, 1997). The I1307K mutations (APC) was detected using specific primers that produce a modified restriction enzyme digest made to distinguish the wild-type allele from the mutant allele (unpublished data). Alternatively, the APC I1307K mutation was detected by DGGE and direct sequencing as previously described (Patael et al, 1999).

Statistical analysis

The χ^2 (Pearson and Fisher exact) tests were used for comparisons between groups. Proportions and 95% confidence intervals were calculated. Odd ratios and 95% confidence intervals were used to evaluate the prevalence of the APC I1307K mutation in BRCA1/2 carriers and non-carriers whether patients or controls.

RESULTS

Characteristics (tables 1.2)

Patients – 525 patients (mean age 50.9 ± 12.27; range 26–86): 471 with breast cancer (including 16 with both breast and ovarian cancer); of whom 136 were diagnosed prior to age 42 years and 335 diagnosed after that age; and 54 with ovarian cancer only. Of these 143 were BRCA1/2 mutation carriers (mean age of onset 44 ± 9.97; range 28–79); 114 with breast cancer (including 14 with both breast and ovarian cancer); of whom 55 were diagnosed prior to age 42 years and 59 diagnosed after that age; and 29 with ovarian cancer only.

Asymptomatic BRCA1/2 carriers – 53 women (mean age 45.8 ± 11.24; range 27–79).

Control – 418 Ashkenazi individuals.

No statistically significant mean age differences were found between symptomatic and asymptomatic BRCA1/2 carriers and between these and non-BRCA1/2 carrier patients.

Distribution of the I1307K APC mutation

Overall 57 (6%) I1307K APC mutation carriers were identified. The I1307K mutation was equally prevalent among patients with either sporadic (17/382; 4.6%) or inherited (10/143; 7%) breast and/or ovarian cancer (OR = 6.27, 95% CI = 0.7–57.7) and among

patients with breast cancer only (25/471; 5.3%) whether inherited (9/114; 7.9%) or sporadic (16/357; 4.9%) (OR = 1.6, 95% CI = 0.6–4.6).

The I1307K APC mutation was equally distributed among asymptomatic (7/53; 13.2%) and cancer manifesting BRCA1/2 carriers (10/143; 7%) (P = 0.14; OR = 2, 95% CI = 0.7–5.6). The I1307K APC mutation was equally distributed among BRCA1/2 carriers diagnosed with breast cancer prior to (4/55; 7.3%) and after (5/59; 8.5%) age 42 years (P = 0.545; OR = 0.8, 95% CI = 0.2–3.33). Among women with sporadic breast cancer the prevalence of the I1307K APC mutation was higher, although not statistically different, among those diagnosed after 42 years (15/276; 5.4%) than before (1/81; 1.2%) (P = 0.09; OR = 0.22, 95% CI = 0.03–1.7).

The overall distribution of I1307K APC mutation among BRCA1/2 carriers (17/196; 8.7%) was found to be significantly elevated compared to that observed among non-BRCA1/2 carriers (40/800; 5%) (P = 0.046; OR = 1.7, 95% CI = 1–3.1). The frequency of the I1307K allele was significantly higher among asymptomatic BRCA1/2 carriers (7/53; 13.2%) than among healthy controls (23/418; 5%) (P = 0.04; OR = 2.6, 95% CI = 1.1–6.4).

DISCUSSION

Previous studies suggest that the APC I1307K missense mutation may act as a low penetrance gene/modifier both for sporadic breast cancer and breast cancer in BRCA1/2 mutation carriers (Redston et al, 1998; Woodage et al, 1998). In this study, we show that the I1307K polymorphism occurs at similar rates in the general Ashkenazi population and in women with sporadic breast (and/or ovarian) cancer. Yet among BRCA1/2 mutation carriers a higher frequency of I1307K mutation carriers was observed. The majority of patients with sporadic breast cancer patients who carried the I1307K APC mutation (15/16) had their breast cancer diagnosed after 42 years of age. No trend for 'early onset breast cancer' (< 42 years of age) was observed among double heterozygotes for both the APC I1307K polymorphism and a BRCA1/2 mutation. Taken together, these results do not support previously reported data indicating that this specific mutation, or rather polymorphism, confers a modest increased risk to developing breast cancer in Ashkenazi women (Redston et al, 1998; Woodage et al, 1998). Intriguingly, the rate of I1307K mutation in BRCA1/2 germline mutation carriers, was significantly higher than that observed in non-BRCA1/2 carriers with the asymptomatic BRCA1/2 mutation carriers having the highest rate of APC polymorphism. This observation seems to counteract the prediction (Redston et al, 1998; Woodage et al, 1998) that the effect of these two germline mutations would be additive, as anticipated from cancer susceptibility genes. A significantly higher rate of APC mutation carriers with sporadic breast cancer were indeed diagnosed after rather than before the age of 42 years, showing again that the APC polymorphism does not predispose to breast cancer.

Altogether, our results seem to weaken the notion that the I1307K APC gene polymorphism may act as a low penetrance gene/modifier in either sporadic or hereditary breast cancer. The high prevalence of APC mutation carriers among BRCA1/2 carriers does not seem to impinge upon morbidity even though some possibility of survivor bias should be taken into consideration. A plausible explanation is that the I1307K and BRCA1/2 mutated alleles are genetically connected because of Jewish ancestry and are not related with cancer risk.

ACKNOWLEDGEMENTS

This work was performed in partial fulfillment of the requirements for the Ph.D. degree from the Sackler School of Medicine at the Tel-Aviv University for Yael Patael. This study was partially supported by the ICRF fund and the MECC to Dr Eitan Friedman.

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