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The *APC* I1307K variant and male breast cancer risk: a multicenter case-control study in Italy

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Abstract

Objectives: The *APC* I1307K variant is a known moderate-risk allele for colorectal cancer (CRC), especially among Ashkenazi Jewish (AJ) individuals. However, its role in other cancers, particularly in male breast cancer (MBC), remains unclear. This study aimed to evaluate whether *APC* I1307K contributes to MBC risk in the Italian (non-AJ) population.

Methods: A multicenter case-control study was conducted involving 1028 MBC cases and 2,126 geographically matched healthy male controls. Genotyping was performed via Next Generation Sequencing or TaqMan assays. Associations between *APC* I1307K and MBC risk were analyzed using logistic regression models, including multivariate adjustments for age, enrollment center, and *BRCA1/2* status.

Results: The *APC* I1307K variant was detected in 4 MBC cases (0.4 %) and 5 controls (0.2 %). No statistically significant association with MBC risk was observed (multivariate odds ratio [OR]=3.7, 95 % CI: 0.8–17.0, p=0.09). Clinical-pathologic comparisons revealed no distinguishing features among variant carriers. None of the carriers harbored *BRCA1/2* pathogenic variants (PVs) or had personal histories of CRC or familial adenomatous polyposis.

Conclusions: These findings suggest that *APC* I1307K does not confer a significant risk for MBC in the Italian population.

Keywords: male breast cancer; *APC* I1307K; genetic susceptibility; case-control study; *BRCA*; next generation sequencing

Introduction

The adenomatous polyposis coli (*APC*) gene is a tumor suppressor located on chromosome 5q21-22 [1–3]. It encodes a key regulatory protein in the Wnt/CTNNB1 signaling

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pathway [4–7]. The APC protein also plays crucial roles in cellular proliferation, migration, DNA repair, and chromosomal segregation [1, 8, 9].

Loss-of-function pathogenic variants (PVs) in *APC* are associated with familial adenomatous polyposis (FAP), a condition that accounts for nearly 1 % of hereditary colorectal cancer (CRC) cases [8]. In contrast, the *APC* I1307K variant (rs1801155, c.3920T>A, p.Ile1307Lys) is not associated with FAP but confers a low to moderate increased risk of CRC, particularly in individuals of Ashkenazi Jewish (AJ) ancestry [8, 10]. This variant does not alter the structure of the APC protein [3, 11], which remains functionally intact. The I1307K change involves a T-to-A transition at nucleotide 3,920, converting the wild-type sequence (AAAATAAA) into an A8 homopolymer tract that is genetically unstable and prone to somatic mutation [12–16].

The I1307K variant has been identified in approximately 5–10 % of the general AJ population [10, 11, 16] and in 15–28 % of AJ individuals with a family history of CRC. It has also been detected in around 2.5 % of Sephardi Jewish (SJ) individuals [10]. In non-Jewish populations, the variant is much less common (~0.15 %) [10], and its association with cancer risk in these groups remains controversial [4, 10]. The AJ population has the highest known lifetime risk of developing CRC-up to 15%-compared to 5–6% in non-AJ populations [17, 18].

Interestingly, some studies suggested a possible link between the *APC* I1307K variant and an increased risk of other cancers beyond CRC, including breast cancer (BC), in both AJ and non-AJ populations [4, 10]. However, due to the relatively small number of *APC* I1307K carriers, only a few studies have examined its role in non-CRC cancers such as BC, and findings have been inconclusive. This variant has also been proposed as a low-penetrance BC susceptibility gene or as a genetic modifier in *BRCA1*/2 PV carriers [18–21]. Moreover, the *APC* I1307K variant has been linked to an elevated risk of multiple cancers, particularly in males [4, 16], yet its role in male breast cancer (MBC) susceptibility has not been investigated.

MBC is a rare disease, accounting for roughly 1 % of all BC and 1 % of all male cancers [22]. Its etiology appears to be primarily genetic, with *BRCA1* and *BRCA2* PVs implicated in up to 15 % of MBC cases [22]. Recent studies have also highlighted the role of other genes, including *PALB2* and *ATM*, in MBC susceptibility [23]. Interestingly, approximately 20 % of men with BC develop a second non-breast malignancy, most commonly CRC and genitourinary cancers [20, 24]. We have previously demonstrated that variants in genes primarily associated with CRC, such as *MUTYH*, may act as low- or moderate-penetrance predisposition factors for MBC [25]. Notably, our earlier data also identified the presence of the *APC* I1307K variant in MBC cases [20], although no risk estimates have yet been provided.

To investigate this further, we conducted a large case-control study in an Italian cohort to determine the frequency of *APC* I1307K in MBC cases and assess its potential contribution to MBC susceptibility in individuals of non-AJ ancestry.

Methods

Study population

We conducted an observational, retrospective case–control study within the framework of the Italian Multicenter Study on MBC, an ongoing collaborative effort initiated in 2010 and involving 19 research centers across Italy, as previously described [20, 23, 26, 27]. A total of 3,154 men were included from 2010 to 2024 (Figure 1).

The case series comprised 1,028 MBC patients, all aged >18 years and unselected for family history of cancer, personal cancer history, or age at diagnosis. Among these, 97 patients (9.4 %) were carriers of *BRCA1/2* PVs. Detailed clinicopathologic data were collected for all cases, including tumor histology, grade, stage, nodal status, ER, PR, HER2, and Ki-67 status, as previously reported [23].

The control series consisted of 2,126 healthy men recruited from the same geographic areas as the cases (Figure 1). Eligibility criteria included age >18 years and absence of personal history of cancer. The mean age at enrollment was 50 years. Recruitment procedures have been described previously [23]. To evaluate the role of the *APC* I1307K variant as a potential genetic modifier in male *BRCA1/2* PV carriers, the control cohort was enriched with 249 unaffected *BRCA1/2* PV carriers.

DNA from peripheral blood samples was obtained for all individuals enrolled in the study and was extracted using the ReliaPrep Blood gDNA Miniprep System kit according to the manufacturer's instructions (Promega, Madison, WI, USA). The Ethical Committee of Sapienza, University of Rome approved the study (Prot. 669/17). Additionally, informed consent for the use of personal data and biological material was obtained from all participants in the study.

Peripheral blood samples or DNA from peripheral blood leucocytes were collected for all study participants. DNA from blood samples was extracted using ReliaPrep Blood gDNA Miniprep System kit, according to the manufacturer's instructions (Promega, Madison, WI, USA). The study was

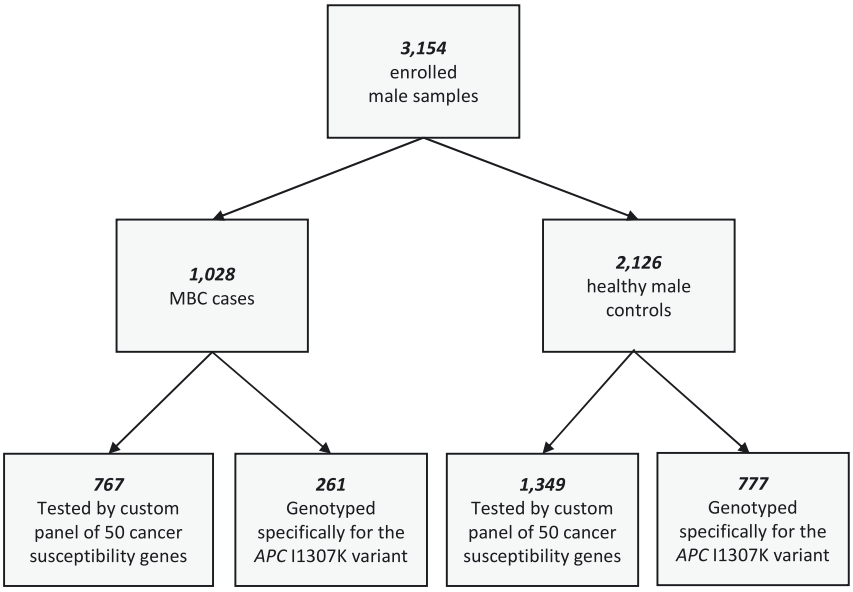

Figure 1: Diagram showing the number of male samples enrolled and tested in the present study.

approved by the Ethical Committee of Sapienza University of Rome (Prot. 669/17), and informed consent for using information and biological samples was obtained from all participants in the study.

APC gene sequencing and genotyping analysis

Of the 3,154 samples enrolled in this study, 2,116 samples (767 MBC cases and 1,349 healthy male controls) were tested by next-generation sequencing using a custom panel of 50 cancer susceptibility genes (Figure 1), including BC risk genes such as *BRCA1*, *BRCA2*, *PALB2*, as well as gastrointestinal cancer risk genes such as *APC* [20, 23]. All cases and controls analyzed were interrogated for the presence of the *APC* I1307K variant.

In addition, a total of 1,038 samples (261 MBC cases and 777 controls), whose amount of DNA available was not sufficient for NGS analysis, were genotyped specifically for the *APC* I1307K variant (Figure 1). Genotyping analysis was performed by allelic discrimination Real-Time PCR, on the Quant Studio 12K flex (Life Technologies, Carlsbad, CA, USA), using a commercially available TaqMan SNP genotyping assay (assay IDc_170962692_10 rs1801155, Life Technologies, Carlsbad, CA, USA) and according to the manufacturer's instructions. In each experiment, positive (cases for which genotype was confirmed by Sanger Sequencing) and negative (distilled water) controls were always included. All samples identified as positive were validated for the presence of *APC* I1307K variant using Sanger Sequencing (primers available upon request).

Statistical analysis

The genotype frequency of the *APC* I1307K variant was evaluated in both case and control groups. Chi-square test was used in a case-case analysis to explore possible associations between the *APC* I1307K variant and specific clinical-pathologic characteristics. The association between the variant and overall MBC risk was estimated using odds ratio (OR) and its corresponding 95 % confidence interval (CI) by univariate logistic regression, and also by two different multivariate analyses, including adjustment for (1) age and center of enrollment; (2) age, center of enrollment, and *BRCA1*/2 PV status. A p-value <0.05 was considered statistically significant. All the analyses were performed using the STATA version 18 statistical program (StataCorp, College Station, TX, USA).

The genotype frequency of the *APC* I1307K variant was evaluated in both series of cases and controls. Chi-square test was performed in a case-case analysis in order to evaluate potential associations between the *APC* I1307K variant and specific clinical-pathologic characteristics. The association between the variant and overall MBC risk was measured by the odds ratio (OR) and its corresponding 95 % confidence interval (CI) by univariate logistic regression, and also by two different multivariate analyses, including adjustment for (1) age and center of enrollment; (2) age, center of

enrollment, and *BRCA1*/2 PV status. A p-value <0.05 was considered statistically significant. All the analyses were performed using the STATA version 18 statistical program (StataCorp, College Station, TX, USA).

Results

In this study we enrolled a total of 3,154 males comprising 1,028 MBCs and 2,126 healthy male controls (Figure 1).

The clinical and pathological characteristics of the 1,028 MBC cases, both overall and stratified by *APC* I1307K variant status, are summarized in Supplementary Table S1.

Overall, 63.0 years (range: 22–91) was the mean age at first MBC diagnosis. A first-degree family history of breast and/or ovarian cancer (BC/OC) was reported in a total of 332 MBC patients (32.3 %). Additionally, a first-degree family history of other types of cancer was reported in a total of 442 MBC patients (43.1 %). In addition, 191 patients (18.6 %) had previously been diagnosed with cancer other than BC, most frequently colorectal and prostate cancer. A high percentage of tumors were invasive ductal carcinomas (82.9 %), positive for estrogen receptor (ER+, 95.4 %), progesterone receptor (PR+, 89.7 %), and human epidermal growth factor receptor 2 (HER2-, 79.2 %).

Overall, the mean age at first MBC diagnosis was 63.0 years (range: 22–91). A total of 332 patients (32.3 %) reported a first-degree family history of breast and/or ovarian cancer (BC/OC), while 442 (43.1 %) had a first-degree family history of other types of cancer. Additionally, 191 patients (18.6 %) had a personal history of cancer other than BC, most commonly colorectal and prostate cancer. The majority of tumors were invasive ductal carcinomas (82.9 %), estrogen receptor-positive (ER+, 95.4 %), progesterone receptor-positive (PR+, 89.7 %), and human epidermal growth factor receptor 2 (HER2-, 79.2 %).

The *APC* I1307K variant was found in heterozygosity in 4 out of 1,028 MBC cases (0.4 %). Among these carriers, the mean age at BC diagnosis was 60 years. None of the four carriers had a personal or family history of FAP or CRC (Table 1).

Three of the four *APC* I1307K carriers (75.0 %) reported a family history of cancers other than BC, including leukemia, lymphoma, and head and neck cancers. All four MBC cases were negative for *BRCA1/2* PVs and had hormone receptor-positive tumors (ER+, PR+) with negative HER2 status.

Overall, the comparison of clinical-pathologic features between APC I1307K carriers and non-carriers revealed no statistically significant differences (Supplementary Table S1).

In the control group, the *APC* I1307K variant was identified in heterozygosity in 5 out of 2,126 individuals (0.2 %). The mean age at enrollment for male controls carrying the variant was 35 years, and all were negative for *BRCA1/2* PVs.

A case-control association analysis was conducted using the full cohort of 1028 MBC cases and 2,126 healthy male controls. Genotype distribution and risk estimate for the *APC* I1307K variant are shown in Table 2. No statistically significant differences were observed in the univariate analysis (p=0.75), nor in the two multivariate analyses adjusted for (1) age at diagnosis, enrollment, and for center of origin (p=0.09), and (2) age at diagnosis, enrollment, center of origin, and for *BRCA* PV status (p=0.10).

Discussion

To date, the risk of extracolonic cancers in carriers of the *APC* I1307K variant remains poorly understood, particularly in non-AJ populations. While some associations with specific cancer types, especially in males, have been proposed, available data are limited. Further large-scale case-control studies, involving diverse ethnic backgrounds and multiple cancer types, are necessary to clarify these associations.

To address this gap, we investigated the impact of the *APC* I1307K variant on MBC risk. To the best of our

Table 1: Clinical-pathologic characteristics of four out of 1,028 MBCs *APC* I1307K carriers.

Case id	Age of BC onset	BRCA1/2 PV status	First-degree FH of cancer (age)	PH of other cancer (age)	Stage	Tumor histotype	ER	PR	HER2	Ki67/ MIB1
#1	56	Negative	Lymphoma NH (55)	Negative	NA	Invasive ductal	+	+	+	−
#2	75	Negative	Negative	Negative	2	Invasive micropapillary	+	+	−	+
#3	67	Negative	Leukemia (67)	Negative	2	Invasive ductal	+	+	−	+
#4	53	Negative	Head and neck cancer (60)	Negative	3	Invasive ductal	+	+	−	−

Cut-offs used: ER/PR positive if >1 % of positive nuclei; HER2 positive if 3+ by immunohistochemistry or 2+ if amplified by fluorescence *in situ* hybridization; Ki67/MIB1 high if >20 % of positive nuclei. BC, breast cancer; FH, family history; PH, personal history; NH, non-Hodgkin; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2. +, positive and −, negative.

Table 2: Distribution of 1,028 MBCs and 2,126 healthy male controls, according to genotype frequencies and MBC risk estimates for *APC* I1307K variant.

Genotype	Cases, n, %	Controls, n, %	Univariate analysis		Multivariate analysis[a]		Multivariate analysis[b]	
			OR (95 % CI)	p-Value	OR (95 % CI)	p-Value	OR (95 % CI)	p-Value
TT	1,024 (99.6)	2,121 (99.8)	1.6 (0.4–6.1)	0.75	3.7 (0.8–17.0)	0.09	3.6 (0.8–16.8)	0.10
TA	4 (0.4)	5 (0.2)						
AA	0 (0.0)	0 (0.0)						

[a]Odds ratios (OR) with 95 % confidence interval (CI) and p-values from multivariate logistic regression analysis, adjusted for age at diagnosis, enrollment and for center of origin. [b]Odds ratios (OR) with 95 % confidence interval (CI) and p-values from multivariate logistic regression analysis, adjusted for age at diagnosis, enrollment, center of origin and for *BRCA* PV status.

knowledge, no data are currently available on this topic. Given the limited sample sizes in previous studies, which hindered reliable conclusions, we analyzed the largest MBC series to date, collected within a single country, including geographically matched controls. This cohort comprised 3,154 Italian males enrolled through the Italian Multicenter Study on MBC [20, 23, 25–27].

This study enabled us to provide the estimates of *APC* I1307K variant frequency in the male Italian population. Previous MBC cohort studies using multigene panels that included the *APC* gene did not report the frequency of the *APC* I1307K variant, likely because it is not classified as a PV [23, 28–33].

In our cohort, the variant was found in 0.4 % of MBC cases and 0.2 % of controls. This is higher than frequencies previously reported in non-AJ populations, which range from 0.2 % in cancer patients to 0.1 % in controls [1, 4]. This discrepancy may reflect the large size and unique composition of our sample, or genetic variation among non-AJ European populations. However, we cannot exclude potential misclassification due to inaccurately self-reported ancestry. Future studies could benefit from using ancestry-informative markers to confirm non-AJ origin and reduce this bias.

To assess whether MBC carriers of the *APC* I1307K variant exhibit distinct clinical-pathologic features, we compared carriers and non-carriers. No statistically significant differences emerged, possibly due to the small number of variant carriers identified. Interestingly, none of the MBC patients carrying the *APC* I1307K variant reported a personal or family history of FAP, CRC, or other cancers. However, three out of the four carriers had a first-degree family history of non-CRC cancers. It is noteworthy that these MBC patients were diagnosed at a mean age of 60, which is younger than the average CRC diagnosis age of 70 [34]. Therefore, the possibility remains that these individuals could still develop CRC later in life. Based on this, *APC* I1307K carriers should be advised to participate in CRC screening programs.

A recent position statement recommended considering non-AJ *APC* I1307K carriers as having average CRC risk [10]. However, the NCCN guidelines advise colonoscopy every 5 years, rather than the standard 10 years for average-risk individuals, or all *APC* I1307K heterozygotes. Screening should begin at age 40 or 10 years earlier than the youngest CRC diagnosis in a first-degree relative, based on data showing similar CRC incidence in AJ and non-AJ *APC* I1307K carriers [35].

To evaluate whether APC I1307K increases MBC risk, we conducted a case-control study. No significant association was found in either univariate or multivariate analyses adjusted for age and center of enrollment. We also explored whether APC I1307K could modify MBC risk in *BRCA1*/2 PV carriers, as previous evidence suggested higher variant frequency in AJ BC cases with *BRCA1*/*2* PVs [18]. However, none of the MBC or control carriers of *APC* I1307K harbored *BRCA1*/2 PVs, and multivariate logistic regression analysis (adjusted for age, center, and *BRCA* status) yielded no significant associations. These contrasting results may again point to genetic differences between males and females, and between AJ and non-AJ populations.

One previous study reported associations between *APC* I1307K and melanoma, female BC, and prostate cancer in non-AJ white individuals, suggesting a generally elevated cancer risk in this population, while AJ carriers appeared to have a more limited spectrum of cancer risk centered on CRC [4]. Although an increased BC risk was observed in females, we did not replicate this finding in men, suggesting a possible sex-specific effect. Sex-related differences in cancer risk linked to *APC* I1307K were also suggested by a study in AJ individuals, where male carriers showed elevated risk for pancreatic, lung, kidney, urinary tract, skin, and stomach cancers, whereas female carriers showed increased prevalence only for breast and skin cancers [16]. These observations may reflect both ethnic and sex-based differences in cancer susceptibility. In support of this, our data suggest no association between the *APC* I1307K variant and breast cancer risk in non-AJ men, thereby excluding MBC from the

range of cancers potentially influenced by this variant in males.

Overall, this work shows some limitations. Firstly, we were not able to collect other samples from family members of APC I1307K carriers to perform cosegregation analyses. In addition, we were not able to collect other data from the population controls, including family history of cancer, thus not allowing additional sensitivity analyses. Although our analysis was based on a large, well-characterized cohort of MBC cases and controls, a key limitation is the small number of *APC* I1307K carriers, which limits statistical power. While this study had sufficient power to detect moderate risk effects, smaller effects, which may still be clinically relevant, could go undetected. Thus, the lack of a significant association should be interpreted cautiously, and a minor role for *APC* I1307K in MBC risk cannot be fully excluded. In addition, we cannot exclude that the *APC* I1307K variant may have a possible role in AJ men with BC.

Conclusions

In conclusion, this study provides important new data regarding the role of *APC* I1307K in extracolonic cancers among non-AJ individuals. Our findings do not support a significant contribution of this variant to MBC susceptibility in the Italian male population. Additionally, exploring the interaction between *APC* I1307K and other genetic factors, such as *BRCA1*/2 mutations, could provide more clarity on its role in cancer risk across different ethnic groups.

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Research ethics: The study was approved by the Ethical Committee of Sapienza University of Rome (Prot. 669/17).

Informed consent: Informed consent for using information and biological samples for research purposes was obtained from all participants in the study.

Author contributions: Conceptualization: Laura Ottini. Methodology: Valentina Silvestri. Validation: Agostino Bucalo, Virginia Valentini, Virginia Porzio, Formal Analysis: Agostino Bucalo, Valentina Silvestri. Investigation: Agostino Bucalo, Virginia Valentini, Virginia Porzio, Valentina Silvestri. Resources: Valentina Arcangeli, Bernardo Bonanni, Daniele Calistri, Ileana Carnevali, Laura Cortesi, Giuseppe Giannini, Viviana Gismondi, Siranoush Manoukian, Livia Manzella, Marco Montagna, Paolo Peterlongo, Paolo Radice, Antonio Russo, Maria Grazia Tibiletti, Daniela Turchetti, Alessandra Viel, Valentina Zampiga, Ines Zanna, Giovanna Masala. Data curation: Agostino Bucalo, Valentina Silvestri. Writing – original draft preparation: Agostino Bucalo, Virginia Valentini, Virginia Porzio, Valentina Silvestri, Laura Ottini. Writing – Review and Editing: all authors. Visualization: Agostino Bucalo, Valentina Silvestri. Supervision: Laura Ottini. Project Administration: Laura Ottini. Funding acquisition: Laura Ottini. All authors approved the study for publication.

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Data availability: Data are available from the corresponding author upon reasonable request.

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