Colorectal and Endometrial Cancer Risk and Age at Diagnosis in $BLM_{Ash}$ Mutation Carriers

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ABSTRACT: Background: Biallelic $BLM$ gene mutation carriers are at an increased risk for cancer, including colorectal cancer (CRC). Whether heterozygous $BLM$ gene mutations confer an increased cancer risk remains controversial.

Objectives: To evaluate CRC and endometrial cancer risk in $BLM$ heterozygous mutation carriers.

Methods: Ashkenazi Jews at high risk for colon or endometrial cancer, and endometrial cancer cases unselected for family history, were genotyped for the $BLM_{Ash}$ predominant mutation.

Results: Overall, 243 high-risk individuals were included: 97 men with CRC (55.12 ± 12.3 years of age at diagnosis), 109 women with CRC (56.5 ± 13.7 years), 32 women with endometrial cancer (58.25 ± 13.4 years) and 5 women with both CRC and endometrial cancer. In addition, 120 unselected Ashkenazi women with endometrial cancer (64.2 ± 11.58 years) were genotyped. The $BLM_{Ash}$ mutation was present in 4/243 (1.65%) of high-risk patients; 2/208 with CRC (0.97%) 2/35 with endometrial cancer (5.4%), and 1/120 unselected endometrial cancer patients (0.84%). Notably, in high-risk cases, $BLM_{Ash}$ mutation carriers were diagnosed at a younger age (for CRC 47.5 ± 7.8 years, $P = 0.32$; endometrial cancer 49.5 ± 7.7 years, $P = 0.36$) compared with non-carriers.

Conclusions: Ashkenazi Jews at high risk for CRC and endometrial cancer, and women with endometrial cancer have a higher rate of $BLM_{Ash}$ heterozygous mutation compared with the general population. $BLM_{Ash}$ heterozygous mutation carriers are diagnosed with CRC and endometrial cancer at a younger age compared to non-carriers. These observations should be validated and the possible clinical implications assessed.

KEY WORDS: Bloom Syndrome, Ashkenazi Jews, colon cancer, endometrial cancer, inherited cancer predisposition

Bloom syndrome (BS; MIM# 210900) is an autosomal recessive disorder characterized by chromosomal instability with an increased risk for developing various types of cancer, including colonic adenomatous polyps and colorectal cancer (CRC) [1-3]. BS is more common in individuals of Ashkenazi Jewish descent than in any other population, and approximately 1% of individuals from Ashkenazi backgrounds (1:111 in Israel) carry a single founder mutation in the $BLM$ gene (c.2207_2212delATCTGAnsTAGATTC–$BLM_{Ash}$) [4,5]. Given the increased risk for developing cancer in homozygous $BLM$ gene mutation carriers, the notion that heterozygous mutation carriers are also at an increased risk for cancer (especially CRC) has been postulated. The results of past studies that focused on the risk for developing CRC in $BLM$ gene heterozygous mutation carriers are inconsistent and conflicting, with some showing an increased CRC risk [6] while other studies failed to show such an increase [7]. A recent study by de Voer and co-authors [8] identified a pathogenic $BLM$ mutation in three of 185 (1.6%) CRC patients (≤ 50 years of age) and 1 of 532 control individuals (0.2%), suggesting that these mutations are enriched in early-onset CRC patients. Based on these observations and given the known phenotypic association between early onset CRC and endometrial cancer in the context of Lynch Syndrome [9], it seemed reasonable to explore this possible association between CRC and endometrial cancer and $BLM$ heterozygous carrier state in Ashkenazi Jews.

PATIENTS AND METHODS

STUDY PARTICIPANTS: IDENTIFICATION AND RECRUITMENT
Study participants were all Ashkenazi Jews counseled at the Oncogenetics Unit, the Institute of Human Genetics at the Sheba Medical Center, Tel Hashomer, Israel from January 1, 2008 to July 1, 2015, with a personal and family history of CRC or endometrial cancer (high-risk group). Personal and family data were collected from all participants in the course of genetic counseling. In addition, Ashkenazi Jewish women who were diagnosed with endometrial cancer during the same time period who were unselected for any family history of cancer were also recruited (unselected group). The study was approved by the ethics committee and each participant gave informed consent.

GENETIC STUDIES
Each participant was genotyped (on peripheral blood leukocyte derived DNA) and found not to harbor any pre-
dominant Jewish Ashkenazi mutations in BRCA1 (185delAG, 5382InsC) BRCA2 (6174delIT), MSH2 (1906G>C; A636P) and MSH6 (c.3984_3987dupGTCA; c.3959_3962delCAAG). Genotyping for 185delAG, 5382InsC and 6174delIT were carried out using NanoChip® technology (Savyon Diagnostics, Ashdod, Israel) and genotyping for the predominant MSH2 and MSH6 mutations were performed as previously described [10,11]. All participants were genotyped for the BLM c.2207_2212delATCTGAinsTAGATTC mutation (BLM<sub>Ash</sub>) using a previously published protocol based on the fact that the predominant Ashkenazi mutation introduces a novel Bst NI restriction site into exon 10 of the BLM gene [12].

**STATISTICAL ANALYSES**

The relative risk (RR) was calculated from the frequencies of BLM<sub>Ash</sub> mutation carriers among different subgroups to the frequencies of BLM<sub>Ash</sub> mutation carriers in the general Jewish Ashkenazi population (1:111). The mean age at diagnosis of BLM<sub>Ash</sub> carriers was compared with non-carriers using the t-test. The results are presented as differences between proportions, RR, 95% confidence interval (CI), and P value. A P value of 0.05 was considered statistically significant.

**RESULTS**

**STUDY POPULATION**

A total of 243 high-risk individuals were included in the study. They included 97 males affected with CRC who were 55.1 ± 12.36 years of age at diagnosis (median 56 years, range 30–78 years), 109 females with CRC who were 56.5 ± 13.72 years of age at diagnosis (median 57.5 years, range 16–85 years), 32 females with endometrial cancer 58.25 ± 13.37 years of age at diagnosis (median 61 years, range 34–82 years) and 5 females with both CRC and endometrial cancer. Overall, the study included 146 females. Of participants, 172 had a family history of cancer, with 83 (38.9%) having another first degree relative with CRC and/or endometrial cancer. Thirty-eight fulfilled the diagnosis (median 61 years, range 34–82 years) and 5 females with endometrial cancer 58.25 ± 13.37 years of age at diagnosis (median 57.5 years, range 16–85 years), 32 females with endometrial cancer 56.5 ± 13.72 years of age at diagnosis (median 57.5 years, range 16–85 years), 32 females with endometrial cancer 58.25 ± 13.37 years of age at diagnosis (median 61 years, range 34–82 years) and 5 females with both CRC and endometrial cancer. Overall, the study included 146 females. Of participants, 172 had a family history of cancer, with 83 (38.9%) having another first degree relative with CRC and/or endometrial cancer. Thirty-eight fulfilled the Amsterdam 2 criteria for Lynch Syndrome [9].

The unselected group included 120 Jewish Ashkenazi women with histopathological confirmed endometrial cancer (mean age at diagnosis 64.2 ± 11.6 years, median 65 years, range 37–89 years).

**BLM<sub>Ash</sub> CARRIER RATES**

**High-risk group**

Overall, 2 of 206 CRC high-risk CRC patients (0.97%) and 2 of 37 high-risk endometrial cancer patients (5.4%) were heterozygous carriers of the BLM<sub>Ash</sub> mutation. The difference in rates for BLM<sub>Ash</sub> carriership in the high-risk CRC cases were not statistically significant compared to those reported for the general Jewish Ashkenazi population (RR = 1.07, 95% CI, 0.98–11.7, P = 0.95). The rates among endometrial cancer cases were higher than those in the general population, but in a statistically non-significant manner (RR = 5.7, 95% CI, 0.53–61.6, P = 0.14).

All four heterozygous BLM<sub>Ash</sub> carriers were diagnosed with cancer before the age of 55. Mean age at diagnosis for CRC was 56.3 ± 12.5 years (males and females) in non-carriers compared with 47.5 ± 7.8 years in heterozygous BLM<sub>Ash</sub> mutation carriers (95% CI, -26.2–8.6, P = 0.32). The mean age at diagnosis for endometrial cancer in non-carriers was 58.2 ± 13.4 years compared with 49.5 ± 7.7 years in heterozygous BLM<sub>Ash</sub> carriers (95% CI, -28.2–10.7, P = 0.36). Analysis restricted to individuals diagnosed with CRC under age 55 years showed that the rates of BLM<sub>Ash</sub> mutation carriers was 2.32%, a twofold rate increase compared to the general population (RR = 2.54, 95% CI, 0.23–27.6, P = 0.44).

The clinical data and family history of study participants in the high-risk group who were BLM<sub>Ash</sub> mutation carriers are shown in Table 1.

In addition, 1 of 120 unselected endometrial cancer patients (0.8%) was a heterozygous carrier of the BLM<sub>Ash</sub> mutation, a rate that does not show a statistically significance different from those reported for the general Jewish Ashkenazi population (RR = 0.94, 95% CI, 0.059–14.7, P = 0.96).

**DISCUSSION**

In the current study, the rate of heterozygous BLM<sub>Ash</sub> mutation carriers among Jewish Ashkenazi high-risk CRC cases (0.97%) was not statistically different from the rate in the healthy, average-risk Ashkenazi population (0.9%) (P = 0.95). These results do not support the results of a previous study from Israel [6] that reported that 1 of 54 (1.85%) Jewish individuals with CRC was a heterozygous BLM<sub>Ash</sub> mutation carrier, a rate predicted to confer a 2.3- to 2.8-fold increased risk for CRC. However, our results are in line with another study from Israel [13] and our own previously published data [14] showing that being a heterozygous BLM<sub>Ash</sub> mutation carrier is not associated with a clinically significant risk for CRC in Jewish Ashkenazi individuals. An intriguing aspect is the seemingly early age at diagnosis of the two CRC cases...
who are also BLMAsh mutation carriers (47.5 ± 7.8 years) compared to a mean age of 56.3 ± 12.5 years in males and females who are not BLMAsh mutation carriers. This difference in age at diagnosis of CRC is in line with a study by de Voer and co-authors [8] who identified pathogenic BLM mutations in 3/185 (1.6%) non-Jewish CRC patients diagnosed ≤ 50 years of age. In contrast, Gruber and colleagues [6] did not report a younger age of diagnosis of CRC in BLMAsh carriers compared with non-carriers. These differences in rates and effect on age at diagnosis in the high-risk group may be attributed to patient selection and recruitment. The study by Gruber et al. [6] was a consecutive, population-based study, whereas the current study identified participants from within a high-risk clinic population. It may also be that the current findings are a chance occurrence due to the limited number of cases, compared with that of Gruber et al [6]. Yet, the fact that both the present study and the one by de Voer et al. [8] report that early onset at CRC diagnosis may be indicative that heterozygous germline BLM mutations may act as modifiers of age at diagnosis and not as a cancer predisposition gene per se.

Due to the syndromic association between CRC and endometrial cancer in the context of Lynch Syndrome, the possible effect of being a heterozygous BLMAsh mutation carrier for endometrial cancer risk was assessed. Despite the seemingly impressive 5.6% rate and the putative effect on age at diagnosis of endometrial cancer in high-risk cases, these preliminary data that failed to reach statistical significance, should be interpreted cautiously due to the limited number of cases studied and the mode of recruitment. Moreover, it is clear that the rates in endometrial cancer cases unselected for family history or age at diagnosis, the rates are similar with that in the average risk, healthy population. Clearly more studies encompassing more cases are needed to better define the effect, if any, of heterozygous BLM mutations on endometrial cancer risk.

**CONCLUSIONS**

In conclusion, the BLMAsh mutation in the heterozygous state does not confer an overall CRC risk in Ashkenazi Jewish high-risk cases but seems to affect age at diagnosis in that population. The effect, if any, of the same mutation on endometrial cancer risk and age at diagnosis needs to be further explored.

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**References**


**Capsule**

**Targeting non-viral antigens in viral-driven cancer**

Adoptive cell transfer harnesses a patient’s own T cells to destroy cancer. The strategy can successfully treat epithelial tumors driven by human papillomavirus (HPV), but it remains unclear why only some patients respond. Stevanovic and colleagues examined the anti-tumor T cell response associated with HPV+ cervical cancers that underwent complete regression. Unexpectedly, reactive T cells were not directed against virally associated antigens, but rather against cancer-germline antigens or neoantigens not previously recognized by the immune system. These findings counter the widely held belief that T cell responses against viral antigens are responsible for therapeutic effects in HPV-driven cancers.

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