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The risk for developing cancer in Israeli *ATM, BLM,* and *FANCC* heterozygous mutation carriers

Yael Laitman [a], Lital Boker-Keinan [b,c], Michal Berkenstadt [d], Irena Liphsitz [b], Daphna Weissglas-Volkov [e], Liat Ries-Levavi [d], Ifat Sarouk [f], Elon Pras [d], Eitan Friedman [a,e,*]

[a] *Susanne Levy Gertner Oncogenetics Unit, Sheba Medical Center, Tel-Hashomer, Israel;* [b] *Israel National Cancer Registry (INCR), Ministry of Health, Jerusalem, Israel;* [c] *School of Public Health, Haifa University, Haifa, Israel;* [d] *Institute of Human Genetics, Sheba Medical Center, Tel-Hashomer, Israel;* [e] *Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel;* [f] *National AT Clinic, Sheba Medical Center, Tel-Hashomer, Israel*

Cancer risks in heterozygous mutation carriers of the *ATM, BLM,* and *FANCC* genes are controversial. To shed light on this issue, cancer rates were evaluated by cross referencing asymptomatic Israeli heterozygous mutation carriers in the *ATM, BLM,* and *FANCC* genes with cancer diagnoses registered at the Israeli National Cancer Registry (INCR). Comparison of observed to expected Standardized Incidence Rates (SIR) was performed. Overall, 474 individuals participated in the study: 378 females; 25 Arab and 31 Jewish *ATM* carriers, 152 *BLM* carriers, and 170 *FANCC* carriers (all Ashkenazim). Age range at genotyping was 19–53 years (mean + SD 30.6 + 5 years). In addition, 96 males were included; 5, 34, and 57 *ATM, BLM,* and *FANCC* mutation carriers, respectively. Over 5–16 years from genotyping (4721 person/years), 15 new cancers were diagnosed in mutation carriers: 5 breast, 4 cervical, 3 melanomas, and one each bone sarcoma, pancreatic, and colorectal cancer. No single cancer diagnosis was more prevalent then expected in all groups combined or per gene analyzed. Specifically breast cancer SIR was 0.02–0.77. We conclude that Israeli *ATM, BLM,* and *FANCC* heterozygous mutation carriers are not at an increased risk for developing cancer.

Keywords Cancer risks, *BLM*, *ATM*, *FANCC*, autosomal recessive, inherited cancer syndrome, founder mutations

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Most cancer susceptibility genes of major inherited cancer syndromes harbor heterozygous inactivating mutations that follow an autosomal mode of inheritance. Heterozygous mutation carriers in these genes are at substantially increased lifetime cancer risks compared with that of the general population {reviewed in (1)}. For example, women who carry a heterozygous *BRCA1* mutation have a risk of up to 63% for developing ovarian cancer, more than a 30-fold increase over that of the general, average-risk population (2). Heterozygous mutations in other genes confer a more modest risk for developing cancer: *CHEK2* mutations are associated with a 2–3 fold increased risk for developing breast cancer (3,4). The putative contribution (if any) of heterozygous mutations in genes that are associated with autosomal recessive disorders to cancer susceptibility is still unsettled. The prime example is heterozygous mutation carriers in the *ATM* gene (OMIM# 607585), the gene that underlies Ataxia Telangiectasia (A-T) in the homozygous state. Based on initial reports published prior to the cloning of the *ATM* gene, Swift and co-workers (5) calculated that the risk for developing breast cancer in obligate carrier females is increased up to 5 times that of the general population. Subsequent studies that were based on actual genotyping of the *ATM* gene in ethnically diverse populations, yielded inconsistent results: some showing an increased risk for developing cancer, most notably breast cancer [e.g., (6–11)], while others could not demonstrate any increased cancer risk [e.g., (12,13)]. These divergent results have been attributed to the type (i.e., missense vs. inactivating) and location of the mutations along the gene, as well as to methodological differences in the study designs (8,13).

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* Corresponding author.
E-mail addresses: eitan.friedman@sheba.health.gov.il, eitan211@netvision.net.il

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Additional examples of heterozygous mutations in genes associated with autosomal recessive disorders as putative cancer susceptibility genes have been reported. Patients diagnosed with Bloom Syndrome (OMIM# 210900), an autosomal recessive disorder, are at an increased risk for developing cancer, especially hematological malignancies. Based on the report that mice engineered to carry a heterozygous *BLM* gene mutation display increased cancer risk (14), several studies were carried out to assess the possible effect of *BLM* heterozygosity on cancer risks in humans. The results of these studies are inconsistent. Some studies showed that individuals who carry *BLM* sequence variants are at an increased risk for developing rectal (15) and breast cancer (16–18). Thompson et al. (19) detected two novel truncating mutations in the *BLM* gene in 33 individuals from 15 high risk breast cancer families. Yet, *BLM* sequence variants did not seem to affect ovarian (20) or prostate (21) cancer risks. Notably, Jewish individuals carry a founder mutation the *BLM* gene (*BLM*^{ash}) detected in 1 of 111 of the general Ashkenazi population (22). Gruber and coworkers (23) reported that the rate of the *BLM*^{ash} mutation is significantly higher in colon cancer cases (1/54) compared with controls (1/118), and that it confers an Odds ratio of 2.34 for colon cancer risk. These results could not be replicated: Zauber and co-workers (24) genotyped 439 Jewish Ashkenazi colon cancer cases and detected 4 mutation carriers (0.9%), a rate similar with that of controls. Similarly, in a large case control study, Clearly et al. (25) could not show any differences in the rate of *BLM*^{ash} mutation between colon cancer cases and controls (0.80–0.85%).

Another example pertains to Fanconi Anemia (FA) complementation group C [*FANCC* (OMIM # 602241)]. Patients who carry bi-allelic *FANCC* mutations, have been reported to have an increased risk for developing leukemias. Based on this observation and the functional similarities between established cancer susceptibility genes (e.g., *FANCD/BRCA2/FANCJ/BRIP1* and *FANCN/PALB2*) and the Fanconi anemia genes it was hypothesized that *FANCC* heterozygous mutations confer increased cancer risk. Indeed, some studies showed a marginally increased risk for developing breast cancer (19) and early onset pancreatic cancer (26) in *FANCC* mutation carriers. Yet, other studies have failed to show such an increased risk in acute leukemia (27) or breast cancer (28).

These inconsistent results prompted us to perform the present study in order to assess the possible contribution of heterozygous mutations in the *ATM, BLM*, and *FANCC* genes to cancer risks in Jewish individuals, taking advantage of having several founder mutations for the relevant genes in that population.

Material and methods

Patient identification and recruitment

All individuals who were referred for prenatal testing at the Genetics institute, Sheba Medical Center, Tel-Hashomer from January 1, 1998 to December 31, 2009, who were found to harbor a known pathogenic, heterozygous mutation in the *ATM, BLM*, or *FANCC* genes were eligible for participation (~60,000 genotyped individuals throughout the study period). The reasons for referral were either a family history of an affected member with one of these diseases or in the context of prenatal screening. Prenatal screening is not mandatory in Israel, and except for cystic fibrosis, spinal muscular atrophy, fragile X, Tay Sachs, familial dysautonomia and Canavan disease in Jewish Ashkenazim (29), is not covered by the Healthcare Basket (i.e., the basic healthcare services provided by National Health Insurance Law that are financially covered by the national health care system for every Israeli citizen). Approximately 5000 individuals undergo prenatal testing for a panel of autosomal recessive diseases and fragile X syndrome at the genetics institute each year (30). The mutations genotyped were *ATM* [c.103C > T (p.Arg35Ter), c.1339C > T (p.Arg447Ter) c.7240del CAAG (p.Gln2414fs*2), c.6672delGG/6677delTACG (p.Met2224fs*20), 2787delGT (p.Met929fs*3), ISAT-del (i.e., a large genomic deletion spanning approximately 85 Kb within the ATM gene- p.(Glu166fs)] *BLM*^{ash} c.2281delATCTGAinsTAGATTC (p.Tyr735fs), and *FANCC* c.456 + 4A > T (IVS4+4A > T) genes. All genotyped individuals fill a short questionnaire that includes demographic and personal medical history data, as well as lifestyle and exposure data and details about the family history.

Mothers of children with clinically and genetically confirmed A-T who attend the national A-T clinic at the Sheba Medical Center, who are obligate and confirmed carriers of heterozygote mutations in the *ATM* gene, were also recruited. The national A-T clinic has been active since 2004 and serves as a national referral center in Israel (www.a-t.org.il).

The study was approved by the local IRB and each participant gave an informed consent.

Genotyping

Genotyping of the predominant mutations in the *ATM, BLM*, and *FANCC* genes was carried out using either a PCR enzymatic digestion based assay, as previously described (22,31) or a multiplexed assay by the NanoCHIP® electronic microarray. The latter assay detects all recurring mutations in the Jewish and non Jewish populations in the tested genes in Israel in a single PCR reaction. The NanoCHIP® microarray technology is based on hybridization of DNA strands to probes on a chip array and the use of fluorescently labeled reporter for detecting the presence or absence of a particular mutation. Each mutation was validated by an independent DNA genotyping using Sanger sequencing. Of note, all mutations genotyped by the NanoChip are confirmed pathogenic mutations.

Cross referencing with the database of the Israeli National Cancer Registry

Cancer diagnoses and dates of these diagnoses were obtained from the Israeli National Cancer Registry (INCR) by cross referencing the ID numbers of all participants with the list of cancer diagnoses reported to the INCR. The INCR, a passive, national, population-based cancer registry, was established in 1960. Since 1982 reporting on all cancer cases to the INCR is compulsory by law. The INCR completeness with respect to solid tumors is over 93% (32). The expected rates of developing each cancer type for the study participants were taken from the published database of the Israeli Health Ministry and the INCR database by age standardized rates (ASR). These data are updated to December 31, 2012.

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