

RESEARCH ARTICLE

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Screening of Finnish *RAD51C* founder mutations in prostate and colorectal cancer patients

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Abstract

Background: Rare, heterozygous germline mutations in the *RAD51C* gene have been found in breast and ovarian cancer families. In the Finnish population, we have identified two founder mutations in *RAD51C* that increase the risk of ovarian cancer but not breast cancer in the absence of ovarian cancer. Risk for other cancers has not been studied.

Methods: To study the role of *RAD51C* mutations in other common cancer types, we genotyped the Finnish *RAD51C* founder mutations c.837 + 1G > A and c.93delG in 1083 prostate cancer patients and 802 colorectal cancer patients using TaqMan Real-Time PCR.

Results: No *RAD51C* mutations c.837 + 1G > A or c.93delG were detected among the prostate or colorectal cancer patients.

Conclusions: The results suggest that the *RAD51C* mutations do not predispose to prostate or colorectal cancer.

Keywords: *RAD51C*, Prostate cancer, Colorectal cancer, Breast cancer, Ovarian cancer, Founder mutation

Background

Mutations in cancer susceptibility genes may predispose the carriers to different cancer types. The most important high penetrance breast and ovarian cancer susceptibility genes are *BRCA1* and *BRCA2* [1] but, in addition to breast and ovarian cancer, germline mutations in these genes also increase the risk of prostate cancer [2,3] and in *BRCA2* also of pancreatic cancer [4]. In addition to the hereditary breast and ovarian cancer syndrome caused by germline mutations in *BRCA1* and *BRCA2*, ovarian cancer is also present in the Lynch syndrome that is caused by germline mutations in DNA mismatch repair genes and characterized by susceptibility to colorectal cancer [5]. Increased risk of breast cancer is also present in other rare cancer predisposition syndromes, namely Li-Fraumeni, Cowden and Peutz-Jeghers syndrome and ataxia-telangiectasia, which also predispose to other cancer types as well [1].

Biallelic mutations in *BRCA2* and in moderate penetrance breast cancer susceptibility genes *PALB2* and *BRIP1* cause Fanconi anemia, a chromosomal instability disorder characterized by developmental abnormalities, bone marrow failure, and cancer susceptibility, while heterozygous germline mutations increase the risk of breast cancer [6]. In addition to breast cancer, heterozygous mutations in *PALB2* also increase the risk of pancreatic cancer [4] but not prostate cancer [7,8]. In *RAD51C*, heterozygous germline mutations have been identified in breast and ovarian cancer families [9] and a homozygous missense mutation was found in a Fanconi anemia like disorder [10]. Following the original report, we and others have found rare deleterious mutations among breast and/or ovarian cancer families [11-17] but quite a few studies have not identified any clearly pathogenic mutations [18-24]. Indeed, the *RAD51C* mutations seem to be very rare. The association with ovarian cancer is well-established but whether the mutations also confer a risk for breast cancer remains controversial. Meindl *et al.* [9,25] and Osorio *et al.* [16] state that *RAD51C* mutations predispose to breast and ovarian cancer whereas Loveday *et al.* [17] estimated the relative

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risk of ovarian cancer for *RAD51C* protein truncating mutation carriers to be 5.88 but no elevated risk for breast cancer.

We recently sequenced the *RAD51C* gene in 277 Finnish breast and/or ovarian cancer families and identified two recurrent deleterious, protein truncating mutations c.837 + 1G > A and c.93delG and subsequently genotyped the mutations in a large series of breast and ovarian cancer patients and families [12]. The mutations significantly increased the risk of ovarian cancer but not breast cancer in the absence of ovarian cancer family history, indicating *RAD51C* as the first moderate penetrance susceptibility gene for ovarian cancer. The mutation carrier families shared a common haplotype indicating a founder effect for the mutations. Moreover, many of the mutation carriers had family history of various cancer types, including for instance colon and prostate cancer. Here we have genotyped the *RAD51C* mutations c.837 + 1G > A and c.93delG in 1083 prostate and 802 colorectal cancer patients to assess the risk for these cancer types. To our knowledge, the role of *RAD51C* mutations in other cancer types than breast and ovarian cancer has not been studied so far.

Methods

Subjects

The *RAD51C* mutations c.837 + 1G > A and c.93delG were genotyped in 1083 Finnish prostate cancer cases and 802 colorectal cancer cases. The prostate cancer patients included 894 unselected cases and 189 prostate cancer families. The unselected cases were collected from the Pirkanmaa Hospital District. The patients had been diagnosed with prostate cancer at the urology outpatient clinic at the Tampere University Hospital between years 1980 and 2008. All families included two or more affected members (the youngest affected male from each family was included in the analysis) and were collected as previously described [26]. The samples were genomic DNA isolated from peripheral blood with the Puregene kit, according to the manufacturer's instructions (Gentra Systems, Inc., Minneapolis, MN, USA).

The colorectal cancer patients studied included 509 consecutive patients collected between May 1994 and April 1996 and 535 consecutive patients collected between March 1996 and June 1998 at nine large regional hospitals in southeastern Finland as described previously [27,28]. DNA was isolated from normal mucosa or blood by conventional DNA extraction methods. DNA was available from 802 patients. All the samples were screened for microsatellite instability (MSI) and the MSI positive cases were screened for *MLH1* and *MSH2* mutations. Of the 802 patients, 104 had family background of colorectal cancer and *MLH1* and *MSH2* mutations were identified in 19 cases.

This study was carried out according to the Helsinki declaration with informed consents from the patients and with permissions from Institutional Review Board of the Tampere University Hospital, The Ministry of Health and Social Affairs, National Authority for Medical Affairs, National Institute for Health and Welfare and Helsinki University Hospital Ethics Committee.

Genotyping

We used TaqMan Custom Assays and TaqMan Genotyping MasterMix (Applied Biosystems, Foster City, CA, USA) to genotype the c.837 + 1G > A and c.93delG mutations. PCR was performed in 7500 Fast Real-Time PCR System or in 9800 Fast Thermal Cycler and genotype calling was performed with 7500 Fast Real-Time PCR System and ABI Prism 7500 SDS v1.4 software (Applied Biosystems, Foster City, CA, USA).

Results and discussion

Most moderate penetrance mutations identified so far, including mutations in *RAD51C*, appear to be very rare with mostly unique mutations in out-bred populations. This poses considerable challenges for investigating them in large series of patients with different cancer types to determine association also with other cancers. We took here advantage of the *RAD51C* founder mutations in Finland and genotyped the c.837 + 1G > A and c.93delG mutations in 1083 prostate and 802 colorectal cancer patients, including also familial cases. No mutations were detected among the patients.

We previously detected the *RAD51C* c.837 + 1G > A or c.93delG mutations in 1.4% of Finnish ovarian cancer patients (in 1% of unselected ovarian cancer patients and in 25% of ovarian cancer families) compared to 0.2% in controls, indicating a significantly increased risk of ovarian cancer with also clinical implications for the carriers [12]. Moreover, the mutation carrier families were found to share a common haplotype indicating a shared ancestry for the families and a founder effect for the mutations in the Finnish population. Founder mutations are typical for isolated populations, such as the Finnish population, and they may explain a major fraction of all mutations in specific genes [29,30]. In the Finnish population, strong founder mutations have been detected for instance in the breast cancer susceptibility genes *BRCA1* and *BRCA2* [31] as well as in *PALB2* [32].

Some of the *RAD51C* mutation carriers in our previous study [12] had family history of diverse cancer types (abdomen, brain, bone marrow, cervical, colon, female genital, kidney, leukemia, liver, lung, melanoma, pancreas, prostate, skin, stomach, tongue, and ventricle) but unfortunately we did not have available samples for genotyping of these relatives. Few other studies have also

identified *RAD51C* mutation carrier families with diverse cancer types [9,11,13,15-17]. This prompted us to study the effect of the mutations also on other common cancer types besides breast and ovarian cancer by screening of the founder mutations in an extensive series of prostate and colorectal cancer cases.

There is a clear genetic component in prostate cancer susceptibility and several common low-risk genomic loci for prostate cancer susceptibility have been found but no high-penetrance genes have been identified [33,34]. Linkage studies have suggested that a prostate cancer susceptibility gene may be located on chromosome 17q22 [35,36], a region including also the *RAD51C* locus, whereas genome-wide association studies (GWAS) have identified common low risk variants in 17q12 and 17q24 regions [37,38]. Finnish as well as other Northern European patients have been included both in the linkage and in the GWA studies [35,36,38]. Several low-risk loci have also been identified for colorectal cancer but 17q22 has not been implicated in colorectal cancer susceptibility [39]. It has been estimated that 15–30% of colorectal cancer may be hereditary and approximately one-quarter of the familial cases occur as part of inherited colorectal tumor syndromes, mainly the Lynch syndrome caused by mutations in DNA mismatch repair genes, such as *MSH2* and *MLH1*, and the familial adenomatous polyposis syndrome caused by mutations in the *APC* gene [40]. The absence of the *RAD51C* founder mutations among the prostate and colorectal cancer patients genotyped here suggests that *RAD51C* does not contribute to prostate or colorectal cancer predisposition. However, we cannot fully exclude a possible role of *RAD51C* as there might be mutation specific effects on cancer risk. To fully assess the role of *RAD51C* in susceptibility to other cancer types, screening of the whole coding region of the gene in large sample sets would be needed.

Conclusions

In conclusion, we did not detect the Finnish founder mutations in the *RAD51C* gene among 1083 prostate and 802 colorectal cancer patients suggesting that the *RAD51C* mutations do not predispose to prostate or colorectal cancer. These results have clinical value in assessing the cancer risks associated with *RAD51C* mutations in the mutation carrier families.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LMP and HN designed the study and wrote the manuscript. LMP and RN carried out the genotyping. JS, AG and LA contributed samples and patient information. All authors read and approved the final manuscript.

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