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Cancer incidence in familial Mediterranean fever patients: a retrospective analysis from central Anatolia

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Abstract

Although chronic inflammation has been associated with increased cancer risk in various disease including hepatitis or inflammatory bowel disease, a lower incidence of cancer has been reported recently in familial Mediterranean fever (FMF) which is an auto-inflammatory disease with persistent inflammation. We have assessed cancer incidence among FMF patients with or without amyloidosis to investigate this hypothesis. We performed a retrospective review of FMF patients, diagnosed and treated in Hacettepe University hospitals between 2001 and 2018. We identified patients from the hospital medical records using the ICD-10 code for FMF. We collected data on demographic and clinical features, drug history, the presence of amyloidosis and subsequent diagnosis of cancer. The expected cancer incidence was estimated using age- and gender-specific standardized incidence rates (SIRs) in comparison with the general Turkish population according to Turkish National Cancer Registry data at 2014. Total of 3899 FMF patients (120 patients had also amyloidosis) were included. Median age was 22 and 56% were females. Thirty-eight patients were diagnosed with cancer during 100,283 person-years of follow-up. The most common cancer was breast cancer in females (7/28 patients) and leukemia (2/10 patients) in males. The overall cancer incidence among patients with FMF was significantly lower in both males {SIR 0.42 [95% confidence interval; (CI) 0.21–0.75], $p=0.019$} and females [SIR 065 (95% CI 0.44–0.93), $p=0.002$]. The overall cancer incidence among patients with FMF and amyloidosis was [SIR 1.21 (95% CI 0.49–2.52), $p=0.73$] without gender difference. Cancer incidence was significantly lower in FMF patients compared with the general Turkish population. We found no increased cancer incidence in FMF patients having amyloidosis. Possible underlying mechanisms need to be explained.

Keywords Familial Mediterranean fever · Amyloidosis · Cancer · Standardized incidence ratio

Introduction

Familial Mediterranean fever (FMF) is characterized by episodes of recurrent fever and polyserositis [1]. FMF mainly affects individuals from the eastern Mediterranean basin, including Turkey, Armenia, Israel, and North African countries and is the most common monogenic auto-inflammatory disease in these countries [2]. FMF is inherited in autosomal recessive manner. The Mediterranean fever (*MeFV*) gene is located at the short arm of the 16th chromosome and encodes the protein called *pyrin* [3]. This protein is one of the key molecules that regulate innate immunity and inflammatory response through the pyrin inflammasome. Mutations in pyrin result in excess amounts of interleukin 1-beta (IL 1-β) [4].

The association between inflammation and cancer has been known for a long time since proposed by Virchow for

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the first time [5]. Major examples include *H. pylori* infection and gastric lymphoma, chronic hepatitis and liver cancer, inflammatory bowel diseases and colorectal cancer, long-term exposure to environmental toxins and associated malignancies [6–8]. Several mechanisms are implicated in the inflammation–cancer link. The microenvironment in chronic inflammatory conditions includes inflammatory cells (lymphocytes, macrophages, etc.) and chemical mediators (cytokines, chemokines, transcription factors) which take part in tumor initiation, progression, and metastatic spread, thus supporting a malignant phenotype [9]. Inflammatory cells produce reactive oxygen species and reactive nitrogen intermediates which induce (DNA) damage, mutations in oncogenes and genomic instability [10]. Once the tumor established, tumor cells further trigger intrinsic inflammatory responses [11]. This vicious cycle results in tumor progression, increased angiogenesis, invasion, and metastases [9].

Chronic auto-inflammatory disorders such as FMF are interesting disease settings to examine the relationship between inflammation and cancer. They are characterized by episodes of unprovoked inflammation, due to dysregulation of the innate immune system, without auto-reactive T lymphocytes and autoantibodies and thus are different from classical autoimmune diseases [12]. Generalized systemic inflammation, activated inflammatory cells, and continuous cytokine exposure in these disorders are the factors which may increase the cancer risk in affected individuals [12]. On the other hand recent studies considering the risk of cancer in patients with auto-inflammatory diseases showed contradictory results; some studies showed an increased risk in particular cancers while the others showed reduced or unchanged cancer risk compared with healthy individuals [13–15]. A recent study from Israel reported lower cancer incidence in FMF patients compared with healthy controls, for the first time in literature [16].

In this study, our aim was to assess cancer incidence among FMF patients compared with the general Turkish population.

Methods

Patient selection

This study is a retrospective cohort study which included patients diagnosed with FMF and treated between 2001 and 2018 in Rheumatology, Nephrology, Gastroenterology or Pediatric Rheumatology departments of Hacettepe University Hospital, which is one of the largest and most experienced centers for the diagnosis and treatment of FMF in Turkey. Patients with FMF were identified from the hospital electronic medical records, which was established in 2001, using the International Classification of Diseases (ICD)-10 code for FMF (E85.0.). All the demographic and clinical features and follow-up data were obtained from the patient files. FMF diagnosis was confirmed with history, clinical presentation, laboratory tests during suspected FMF attack and assessing colchicine response and recruited if the diagnosis was approved by these parameters; not according to any diagnostic criteria. We excluded patients if the diagnosis could not be confirmed. Data on the use of colchicine and biologic therapies [anakinra, tocilizumab, anti-tumor necrosis factor (TNF) alpha antagonists] were also recorded. Amyloidosis was diagnosed with biopsy most of the time; however, amyloidosis was considered in a few patients after consultation with the nephrology department if they had chronic kidney disease (CKD) without another possible underlying cause. Data regarding cancer diagnosis were obtained from patient files (confirmed by biopsy results and registries of chemotherapy protocols, where available). Patients without a follow-up visit in recent 3 years considered as lost-to-follow-up. Benign tumors were excluded but skin cancers were included for calculation of the estimates. Age- and gender-specific cancer incidence of the normal population was rendered from the 2014 Turkish National Cancer Registry (TNCR) data [17].

Our study is compliant with the Helsinki Declaration and approved by Hacettepe University ethical committee (approval number: GO17/783-33).

Statistical analysis

Standardized incidence rates (SIR) were calculated after adjustment for age and gender and compared with age- and gender-specific SIR values abstracted from the 2014 Turkish National Cancer Registry (TNCR) data. As FMF is an inherited disease, person-years (PYs) of follow-up were calculated from birth to the date of last follow-up, death or April 2018, whichever occurred first. The observed number of cases is the number of all individuals diagnosed with cancer on follow-up, including those diagnosed before the clinical diagnosis of FMF. Expected cases represent the total number of patients that would have been reported to the cancer registry within the same period of follow-up as per the TNCR rates under the null hypothesis of no increased risk, given the age and gender structure. As the inflammation process is believed to be started from birth, expected case numbers were calculated cumulatively and no sensitivity analysis was performed as all cancer cases were proceeded by exposure to inflammation. The SIR was calculated by dividing the number of observed cases by the number of expected cases, a ratio greater than 1.00 indicating that there were more cases observed than expected. The 95% confidence interval for the SIR was calculated independently using OpenEpi software version 3.01.

Statistical analysis was performed using the Statistical Package for the Social Sciences software (version 23.0; IBM Corporation, Armonk, NY, USA). The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov–Smirnov, skewness and curtosis) to determine whether or not they are normally distributed. The data of descriptive analysis were expressed as the median, interquartile range. Categorical variables were compared with the Chi-square test or Fisher's exact test where appropriate. Chi-square test was used to compare proportions between two groups. p values <0.05 were considered statistically significant.

Results

Using the ICD-10 code (E85.0), we reached to records of 11,300 patients registered to our hospital system. After the assessment of patient files and considerations of the parameters previously described at methods section, we recruited a total of 3899 FMF patients and 1443 (37%) of them were under 18 years old. Median age of whole population was 22 (13–37), median age was 11 (8–15) years and 49% of the cases were females in the pediatric group, it was 32 (24–45) years and 60% of the cases were females in the adult age group (≥ 18 years old). Total follow-up duration starting from the birth was 100,283 person-years. Median follow-up duration of these patients in our institution was 81 (21–124) months and number of patients lost to follow-up was 395 (10.1%). All were on colchicine, although compliance was not assessed. Thirty-eight patients had cancer on follow-up. Table 1 provides data regarding cancer sites**.** Median age at the diagnosis of cancer was 50 years. The most common cancers were breast cancer in females (7/28 patients) and hematological cancers (leukemia/lymphoma in 3/10 patients) in males.

Patients with FMF had a 43% decreased cancer incidence compared with the expected risk at the corresponding age and sex group (SIR 0.57, 95% CI 0.41–0.77, $p<0.001$). SIR values in both sexes for different age groups are given in Table 2. Because of the low number of index cases, SIR values were calculated for only three cancer subgroups; breast cancer, ovarian cancer and lymphoma in females. The women with FMF had a trend towards lower incidence of breast cancer (SIR 0.62, 95% CI 0.27–1.23), and they had a trend towards a higher incidence of ovarian cancer (SIR 2.7, 95% CI 0.86–6.52) and lymphoma (SIR 2.3, 95% CI 0.85–5.15), none being statistically significant. On the other hand, female patients lower than 20 years of age had an increased cancer incidence (SIR 3.44, 95%CI 1.26–7.64).

One-hundred and twenty patients had amyloidosis. Six of these patients (5%) had cancer on follow-up. No significant increase in cancer incidence was found in patients with FMF and amyloidosis compared with the expected counts at the corresponding age and sex group (SIR 1.21, 95% CI 0.49–2.52).

Table 1 Type of cancers in patients with familial Mediterranean fever

Type of cancer	Male (*n*)	Female (*n*)
Breast	–	7
Lung	–	1
Prostate	1	–
Colorectal	1	1
Ovarian	–	4
Endometrium	–	1
Gastric	–	1
Pancreas	1	–
Renal	1	2
Central nervous system	–	2
Leukemia	2	1
Lymphoma	1	5
Kaposi sarcoma	1	–
Connective tissue sarcoma	–	2
Yolk sac	–	1
Unclassified	2	–
Total	10	28

Median duration of biologic treatment was 42 (17–76) months. Biologic drugs (anakinra, canakinumab or any kind of anti-tumor necrosis factor alpha) were prescribed to patients with and without cancer at a similar rate (Table 3).

Discussion

In this study, we found lower cumulative cancer incidences in both sexes compared to Turkish National Cancer Registry Data. The presence of amyloidosis or the use of biological drugs were not associated with cancer incidence, although the number of patients was low in these subgroups to make a definitive conclusion. Of the particular cancer types, breast cancer incidence was lower while ovarian cancer and lymphoma risk were higher, bordering statistical significance among female FMF patients.

Inflammation affects every step of carcinogenesis including tumor initiation, promotion, escape from apoptosis, angiogenesis and metastasis [9]. Even the subclinical inflammation in obesity increases cancer risk [18]. Therefore, we hypothesized that FMF, being an auto-inflammatory disease with prominent acute inflammatory reaction during attacks and subclinical inflammatory state between attacks might increase cancer risk in affected individuals [19]. Previous studies exploring the relationship between cancer and autoimmune diseases have shown an increased cancer risk in patients with systemic lupus erythematosus (SLE),

Table 2 Standardized incidence rates for different age cut-offs in both sexes and overall cancer rate comparison for patients with and without amyloidosis among familial Mediterranean fever patients

Gender	Age	Observed/expected cancer cases	SIR	95% confidence interval	*p* value
Total	All ages	38/66.98	0.57	0.41–0.77	< 0.001
Female	< 20 years ($n = 823$)	5/1.45	3.44	1.26–7.64	0.003
	20–50 years ($n = 1095$)	6/16.8	0.35	0.15–0.74	0.003
	≥ 50 years ($n = 273$)	17/24.8	0.68	0.41–1.075	0.10
	Overall ($n = 2191$)	28/43.08	0.65	0.44–0.93	0.019
Male	< 20-years ($n = 868$)	3/1.83	1.64	0.42–4.46	0.55
	20–50 years ($n = 699$)	1/6.9	0.15	0.007–0.71	0.008
	≥ 50 years ($n = 141$)	6/15.17	0.39	0.16–0.82	0.009
	Overall ($n = 1708$)	10/23.9	0.42	0.21–0.75	0.002
Amyloidosis (+)	All ages	5/4.18	1.21	0.49–2.52	0.66

SIR standardized incidence rates

Table 3 Comparison of familial Mediterranean fever patients with and without cancer according to the use of biologic drugs

Gender	Cancer present *n*, %	Cancer absent *n*, %	*p* value[b]
Female			
Receiving anakinra	0	36 (100)	0.49
Not receiving anakinra	28 (1.2)	2128 (98.8)	
Receiving canakinumab	1 (2.5)	39 (97.5)	0.48
Not receiving canakinumab	27 (1.2)	2125 (98.8)	
Receiving anti-TNF alpha drugs	1 (1.4)	68 (98.6)	0.89
Not receiving anti-TNF alpha drugs	27 (1.3)	2096 (98.7)	
Receiving biologic[a] drugs	2 (1.4)	143 (98.6)	0.91
Not receiving biologic drugs	26 (1.3)	2021 (98.7)	
Male			
Receiving anakinra	1 (3.4)	28 (96.6)	0.16
Not receiving anakinra	9 (0.5)	1669 (99.5)	
Receiving canakinumab	0	38 (100)	0.99
Not receiving canakinumab	10 (0.6)	1659 (99.4)	
Receiving anti-TNF alpha drugs	0	68 (100)	0.99
Not receiving anti-TNF alpha drugs	10 (0.7)	1629 (99.3)	
Receivingbiologic[a] drugs	1 (0.75)	134 (99.25)	0.82
Not biologic drugs	9 (0.6)	1563 (99.4)	

anti-TNF alpha anti-tumor necrosis factor alpha

[a]Anakinra, canakinumab, anti-TNF alpha drugs

[b]Chi-square

rheumatoid arthritis (RA), scleroderma and Sjögren's syndrome [14, 20–22].

We found lower overall cancer incidence in both genders of FMF patients. Our results were similar to the study of Brenner et al., which is so far the only study particularly assessing cancer risk in Jewish and Arab FMF patients [16]. The authors found that cancer incidence was lower than expected in FMF patients, with the standardized incidence ratios 0.66 (0.55–0.77) for males and 0.75 (0.64–0.86) for females of Jewish ethnicity. Breast cancer was the most prevalent cancer in females and colorectal cancer in males. The lowest SIR values for specific cancers belonged to breast cancer 0.72 (0.50–0.99) in females and non-colorectal digestive cancers 0.07 (0.00–0.40) and lymphoma 0.50 (0.18–1.0.8) in males [16]. The authors proposed that enhanced inflammasome activity secondary to pyrin mutation, potential antitumor effects of colchicine, the possible use of non-steroid anti-inflammatory drugs (NSAIDs), and the possible lower rate of risk factors such as smoking, unhealthy dietary habits and obesity in FMF patients as the potential explanations for the reduced cancer risk [16]. All these explanations are also relevant for our patient population. Colchicine inhibits

microtubule formation similar to vinca alkaloids. Several animal studies showed the inhibitory effects of the colchicine and its derivatives on different tumor cell types; such as breast, hepatocellular, ovarian, gastric, pancreas cancers and leukemia cell lines [23–27]. Also, reduction of cancer risk via colchicine treatment was shown in gout patients [28]. Although all of our patients had a history of colchicine usage, however, we could not record further information regarding cumulative colchicine dose and adherence to colchicine because of retrospective nature of the study and possible recall bias of the patients' reports. There is no clear relationship between cancer and anakinra in current literature, however; in a recent study conducted with atherosclerotic patients, authors reported that the incident lung cancer rate was lower in patients taking canakinumab [29]. Also in a recent review, it was reported that the anti-TNF (anti-tumor necrosis factor) alpha treatment has no increased effect on cancer incidence [30]. Another study from Sweden reported no increased risk for cancer recurrence in patients with RA under anti-TNF treatment [31].

Since colchicine may be suppressing inflammation we have also assessed patients who developed amyloidosis since this may reflect uncontrolled FMF inflammation. Amyloidosis, particularly serum amyloid A-related amyloidosis, is a major cause of morbidity and mortality in patients with FMF [32]. We could not find higher cancer incidence among patients with amyloidosis compared to the general population. In a study conducted in Sweden, among 1400 patients with primary amyloidosis, there was no increased cancer risk for myeloma, NHL and squamous cell skin cancer [33].

We found no difference in the cancer incidence between biological drug users and non-users, however, the numbers were too small to draw conclusions and data regarding the dose of biological drugs were missing, so these results should be interpreted cautiously. We found a trend towards a higher rate of ovarian cancer and lymphoma in females, albeit without statistical significance.

Female patients lower than 20 years of age had an increased cancer incidence in our study, which seems contradictory to overall results of the study. Five patients were diagnosed with glial tumor, Wilms' tumor, ovarian yolk sac tumor, synovial sarcoma and marginal zone lymphoma, each with one diagnosis. Although some information about the relationship of these cancer types and inflammation is available, we cannot make a definite judgment because of the small number of cancer cases [34–37]. Increased cancer risk in pediatric FMF patients may have a biological rationale; children may be more vulnerable to potential carcinogenic effect of ongoing inflammation. On the other hand, this may simply reflect referral bias, as our pediatric oncology department is a reference center in Turkey with a high patient referral rate from other sites, resulting in an enriched number of pediatric cancer cases.

Our findings might have implications on our understanding of cancer. Innate immunity is the main pathway for the inflammation seen in FMF patients [12]. Pyrin mutations enhance inflammasomes, which function to induce maturation and secretion of major inflammatory cytokines such as interleukin 1β (IL-1β) and interleukin 18 (IL-18) against intrinsic or extrinsic pathogenic insults [38–40]. Structure of inflammasome comprises NOD-like protein (NLR), the adaptor apoptosis-associated speck-like protein (ASC) and a caspase-1 [11]. Binding of ligands to NLR and activation of caspase-1-dependent conversion process leads to turning off pro-IL-1 and 18 to their active forms activating the inflammatory cascade [11]. Pyroptosis is defined as inflammasome-dependent cell death and it is critical for regulation of microbial infections [11]. Pyroptotic cell death of premalignant cells is the main anti-tumor mechanism induced by inflammasomes [11]. The actions of different components of inflammasome may act differently in tissues. For example, mice deficient for several components of inflammasome were found highly susceptible to chemically induced colitis-associated colon cancer [41, 42]. The inflammasome is also involved in chemotherapy-induced anticancer immune responses by sensing antigenic signals released from dying cells [11]. IL1R and caspase-1-deficient mice were protected against chemically induced skin cancer [43]. In studies with melanoma cell lines, authors found that tumorigenesis was dependent for IL-1β secretion, either stimulated endogenously or exogenously [44]. Another study showed elevated levels of IL-1β in the mouse and human breast cancer tissues and revealed the critical role of IL-1β in promotion and metastasis of breast cancer [45]. There are several other genomic studies showing inflammasome-cancer interaction for pancreatic and hepatocellular cancers [46, 47]. Therefore, the inflammasome seems to have a reciprocal action depending on the context, stimuli, microenvironment and cancer stage. Innate immunity seems to function as a "double-edged sword" throughout cancer development; prevention by eradicating premalignant cells in early phases but it may favor cancer progression, once immunoediting, evasion, and escape occur in tumor cells [9]. Understanding the molecular mechanism and regulatory factors of inflammasomes in carcinogenesis may have implications in the prevention of various cancers [9].

Our study has several limitations. First, *MeFV* mutations of many patients were unknown. This can be important for studies investigating the biology of the disease and association with other diseases. Second, patients diagnosed with cancer out of our institution might have been overlooked, so our findings might be biased towards the alternative hypothesis. However, over 90% of the patients were on regular follow-up in our hospital, rendering a major deviation of SIR rates unlikely. Our patient population was young (median age was 22) compared to study by Brenner et al. (mean age

was 43.7) and the number of expected and observed cancer cases was low, attenuating the reliability of our SIR results. However, age-specific incidences were used for comparison, and the results were both statistically and clinically meaningful and consistent with the previous research. Another limitation of our study was the lack of duration and dosage of colchicine and other drugs, limiting further analysis on treatment-cancer risk association, because possible anti-neoplastic effects of colchicine may complicate the understanding of association of the inflammation and cancer. Effects of colchicine should be addressed with prospective studies in this patient group. Finally, we did not have any data regarding the distribution of other factors that affect the cancer risk among FMF patients and the control group. As we considered all of these limitations, results of this study should be treated cautiously.

In conclusion, our findings confirm the previous large study from Israel showing a reduced cancer risk in FMF patients. Whether this protective effect is secondary to the drugs used in FMF treatment, lifestyle issues, and other confounding factors or whether there is a real risk reduction associated with the pyrin inflammasome and the underlying mechanism(s) remains unknown. Further studies in this patient population may open up new avenues regarding cancer risk assessment, immunoprevention, and even treatment of cancer, particularly in patients with a high risk.

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Compliance with ethical standards

Conflict of interest None of the authors have any potential conflict of interest.

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