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Prevalence of Genetic Cancers Among Public in Palestine: Genetic Trends and Association with Matrix Metalloproteinase -9 as a Diagnostic Biomarker

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Abstract

Background: Cancer is the world's most troubling health problem nowadays. Research is focused on finding novel biomarker/s for early prediction of cancer. Cancer plays a crucial role in the regulation of different enzymes especially, matrix metalloproteinases (MMPs).

Objective: To study the prevalence of cancer among public in Palestine and to investigate the potential role of MMP-9 as a predictive biomarker for different cancer types. To study the public knowledge and awareness of cancer.

Materials and Methods: A validated questionnaire was distributed among Palestinians to determine the knowledge and awareness of cancer. MMP-9 in the serum of 11 cancer patients was analyzed using Human MMP-9 Quantikine ELISA Kit (Sigma-Aldrich). SPSS and graph-pad prism were used for statistical analysis and graphs.

Results: In Palestine, genetic cancers are associated with highest rate of cancer prevalence. Radiation has a moderate effect on cancer development. Highest levels of MMP-9 were found in serum samples of leukemia, colorectal, lymph nodes and breast cancer patients and presumably a quantitative relationship with different cancers stages.

Conclusion: MMP-9 was confirmed to be a useful biomarker for certain types of cancer. MMP-9 can be utilized in practice for early detection and/or prognostic studies of specific cancers.

Keywords: Biomarker, Gene expression, Breast cancer, Lymphoma, Myeloma, Colorectal cancer, Matrix Metalloproteinase -9, MMP-9.

Introduction

Cancer is the second leading cause of death worldwide (GBD 2015). Cancer is also the second leading cause of death in Palestine. Over 100 types of cancers affect humans; the majority of cancer is classified as benign cancers. There is no precise record of cancer incidence or prevalence in the Palestinian community since estimates of cancer prevalence depend on survival rates. Environmental factors, such as tobacco smoking, radiation exposure, and diet patterns are risk factors for cancer, in addition to social-health factors such as level of medical services and extended post-reproductive lifespan, are considered as major determinants of cancer prevalence [1, 2].

Early prediction and detection of cancer saves lives, guide treatment and prevention intervention trials and help prevent cancer in family members. Familial and genetic cancer studies are used in prediction of cancer, with much focus on genetic profiling and hereditary background of cancer. There is a need for new biomarker/s for early detection of cancer in the for the purpose of diagnosis, prevention, and treatment.

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MMPs are rising as an outstanding group of biomarkers for early detection of tissue and cellular immune system interactions during inflammation, infection, chronic disease and cancer.

MMPs are a large family of zinc-dependent endopeptidases, which organized into several groups, such as gelatinases, collagenases, stromelysins, matrilysins and membrane-type MMPs [3]. Interestingly, MMP-9 is an important marker in cancerous cells invasion and tumor metastasis [4]. The human MMP-9 gene is located at chromosome 20q13.12. Human MMP-9 protein contains hemopexin-like domain, catalytic domain, signal peptide, and the hinge region in addition to a propeptide region [3]. MMP-9 is as a protease plays vital role in many biological processes. It has the ability to cleave many extracellular matrix (ECM) proteins that regulate ECM remodeling [3]. MMP-9 has been widely recognized in the pathology of cancers, including- but not limited to; invasion, metastasis and angiogenesis. Furthermore, tumor cells produce MMP-9 which helps spread the tumor by degrading collagen fibers in the ECM and breaking down the basement membrane where they further released to blood and/or lymph vessels [5].

In this study, we determined the prevalence of most common cancer types in Palestine. We estimated the knowledge about and main risk factors associated with cancer. We also assayed the current hospital protocols adopted for early detection of cancer among Palestinians. We investigated MMP-9 in sera of 11 cancer patients as a potential biomarker of cancer.

Materials and Methods

The study proceeded in two parallel tracks; a cross-sectional track using questionnaire that was distributed on public, and laboratory analysis. Eight four subjects completed the questionnaire that was designed to determine the prevalence and level of awareness of different types of cancer. In addition to that an electronic version of the questionnaire was distributed through Smile of Hope foundation in Palestine to cancer patients. Results from both questionnaires were collected and analyzed using Microsoft excel program for easy access of information.

After getting an approval letter to collect the samples and perform our research project from the Palestinian Ministry of Health (MOH) and the Palestinian Medical Laboratory Association, an informed consent was taken from all patients. Data collected from patients records in the period between 2013-2018; who were referred to Beit-Jallah hospital in Bethlehem, and Hebron Governmental hospital, for further cancer screening and diagnosis. Blood samples were collected from 11 cancer patients. All specimens were transported properly and kept in -20°C for storage and further use. These 5 ml samples were kept in tubes containing EDTA and were homogeneously prepared after centrifugation. The serum samples were processed and analyzed to measure the concentration of MMP-9 using Human MMP-9 Quantikine ELISA Kit (Sigma-Aldrich). All data were analyzed using Graphpad Prism version 8 and SPSS version 20S. The relationship between different types of cancer and MMP-9 concentration were determined. Other risk factors such as gender, age, and diagnostic stage of cancer were collected from the questionnaire. The knowledge and awareness of cancer of the Palestinian population were also collected and analyzed properly. The MMP-9 concentration of each cancer type was compared by Mann–Whitney test (mean ± SD). Results were considered significant at $p \leq 0.05$, our result showed that breast, colon, leukaemia, were significant at $p \leq 0.001$, $p \leq 0.0008$, $p \leq 0.0001$, respectively.

The prevalence of different cancer types among Arab countries and worldwide were also reviewed for the purpose of contrast and compare. Published studies of cancer prevalence were reviewed in five Mediterranean countries (i.e., Levantine coast). All the articles from PubMed and Medline addressing the prevalence of different cancer types among these individuals were reviewed. Search for studies conducted in these Mediterranean countries over the last couple of years for comparison were also carried out.

Results

According to prevalence rate among Public in Palestine, different cancer types were divided into three categories; most common, moderately common and less common. The most common cancer types were; breast cancer (25%), lymph nodes and leukaemia, 15.4%, and colorectal cancer, 7.1% (Table 1). Moderately common cancer types were; thyroid cancer, 4.7%, hodgkin's lymphoma, 4.7%, stomach cancer, 3.5%, sarcoma, 3.5%, benign cancer, 3.5 %, bone cancer, 2.3%, and brain cancer, 2.3 % (Table-1).

Last but not the least, was the less common cancer types; intestine cancer, lung cancer, testicular cancer, neuroblastoma, multiple myeloma, urinary bladder, optic glioma, kidney and pancreatic cancer with prevalence rate of 1.1% each (Table 1).

Data were collected from literature for different cancer types from five Mediterranean countries (Jordan, Lebanon, Cyprus, Syria and Israel) in different years [6-39] and compared with the types of cancer in Palestine as shown in Table 2.

The socio-demographic characteristics of patients were also analyzed. Females found to have higher risk of different types of cancer (59.5%) compared to males 40.4% (Table 3). Surprisingly, our data showed that patients less than 20 years old have higher risk of cancer, (30.9%), and patients at the age of 41-60 years old showed equally high percentages for development of all stages of cancer. In contrast, patients at age of 21-40 years old had a risk of cancer of 26.1% and patients at age 61 years and above showed a rate of prevalence of only (11.9%), as shown in Table 3.

Medical history of the patients and their answers about the stage at which cancer was diagnosed showed that 36.9% were diagnosed at moderate stage, 35.5% were diagnosed at an advance stage and 28.5% of the patients were at initial stage (Table 3).

To study the relationship between dietary habits and cancer patients diet was investigated where we found that the majority of cancer patients were both vegetarian and

Table 1: Major cancer types among the Palestinian Population

Different Cancer Types in Palestine Type	Frequency (n)	Percent %
Thyroid Cancer	4	4.7
Stomach Cancer	3	3.5
Intestine Cancer	1	1.1
Bone Cancer	2	2.3
Leukemia	13	15.4
Sarcoma	3	3.5
Lung Cancer	1	1.1
Hodgkin's Lymphoma	4	4.7
Testicular Cancer	1	1.1
Neuroblastoma	1	1.1
Multiple Myeloma	1	1.1
Benign tumor	3	3.5
Bladder Cancer	1	1.1
Breast Cancer	21	25
Colorectal	6	7.1
Liver cancer	1	1.1
Brain Cancer	2	2.3
Optic Glioma	1	1.1
Kidney Cancer	1	1.1
Lymph nodes cancer (Non-Hodgkin's Lymphoma)	13	15.4
Pancreatic cancer	1	1.1
Unknown	1	1.1

Table 2: Comparison between major cancer types in Palestine and other Mediterranean countries (i.e. Levantine coast) [6-39].

Different Cancer Types	Percent% in Palestine	Percent% in Jordan	Percent % in Lebanon	Percent % in Cyprus	Percent % in Syria	Percent % in Israel
Thyroid Cancer	4.7	3.6 [6]	1.6-8.2 [4,33,34]	5.52 [9]	9 [19,36]	3.98-6.93 [10,13]
Stomach Cancer	3.5	3.1 [6,32]	5.1-8.1 [4, 33,34] 2.8 [8]	4.6-7.2 [9]	7 [19,36]	8.9 [11]
Leukaemia	15.4	5 [6,40]	2.5 [8,34]	15.06 [9]	18 [19,36]	8.69-11.26 [18,27]
Hodgkin's Lymphoma	4.7	7.9 [6]	2.5 [8,34]	1.05 [9]	13 [19,36]	6.8-7.2 [27]
Bladder Cancer	1.1	4.6 [6]	9.1 [8,34]	3.1-15.9 8.80 [9]	6 [19,36]	8.07-15.21[27]
Breast Cancer	25	18.6 [6]	78.3-95.7[34]	34.19 [9]	24.5 [19,36]	15.9[27]
Colon	7.1	10.9 [6]	5.7 [8,34]	12.52 [9]	23 [36]	9.4 [27]
Pancreatic Cancer	NA	NA	2.7-4.7 [34]	2.04 [9]	NA	7.9-8.1 [27]

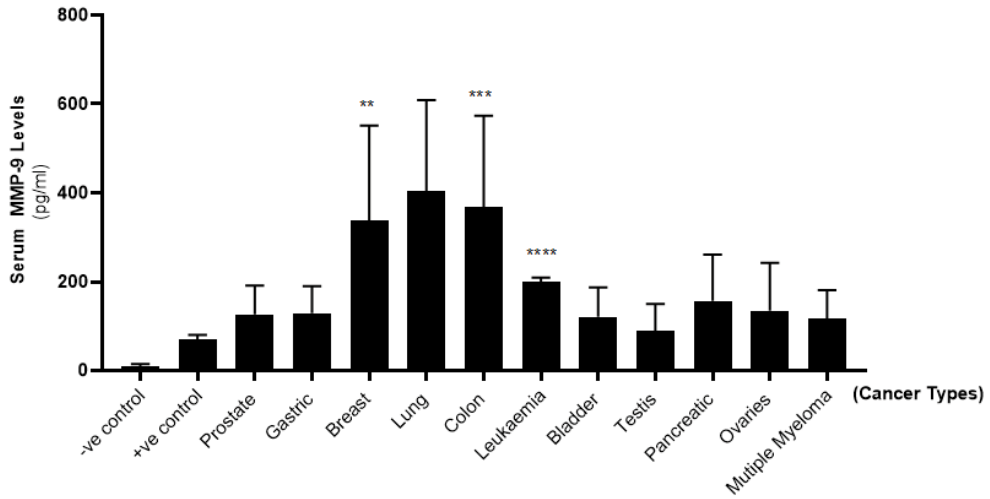

Figure 1: Significant Induction of MMP-9 expression in the serum of cancer patients in Palestine.

Table 3: Socio-demographic characteristics of cancer patients among the Palestinian Population.

Variables and its categories			Frequency (n)	Percent%
Sex	Male		34	40.4
	Female		50	59.5
Age	Less the 20 years		26	30.9
	21-40		22	26.1
	41-60		26	30.9
	61 and more		10	11.9
Education	Primary school or less		7	8.33
	Secondary		9	10.7
	Has University or high degree		64	76.1
	not educated		8	9.5
Marital Status	Single		35	41.6
	Married		49	58.3
	Divorced		0	0
	Widow		0	0
Work	Teacher		11	13
	Worker		2	2.3
	Butcher		1	1.1
	Mechanics		1	1.1
	Nurse		1	1.1
	Electronic engineering		1	1.1
	Telecommunication		1	1.1
	Bakery		1	1.1
	Press		1	1.1
	Not working		64	76.1
Medical History	Stage of cancer	Initial stage	24	28.5
		Moderate	31	36.9
		stage	29	35.5
		Advanced stage		
	Cancer spread in your body	No	64	76.1
		Yes	20	23.8
		Don't Know	0	0
	Genetic factor are major cause of cancer	No	45	53.5
		Yes	39	46.4
		Don't Know	0	0
	Is your profession related to the Cancer?	No	64	76.1
		Yes	20	23.8
		Don't Know	0	0
	Do you smoke?	No	67	79.7
		Yes	10	11.9
		Was before	7	8.3
	Are there smokers in the house?	No	39	46.4
		Yes	45	53.5
		Don't Know	0	0
	Daily Diet	Vegetarians	5	5.9
		Carnivores	2	2.3
		Both	77	91.6

carnivores. Vegetarian patients (5.9%) had a higher risk of cancer comparing to carnivores (2.3%), [Table 3]. Several studies showed that there is a link between smoking and certain types of cancer. Our data did not show any correlation between smoking and cancer, where 79.7% of our subjects were nonsmokers.

Gender as related to cancer prevalence was studied where we found that females had higher rate of different cancer types comparing to males in this study (Table 1).

Serum samples from 11 different cancer patients were collected and the concentration of MMP-9 was evaluated in each sample, in order to determine the potential application of MMP-9 as diagnostic and/or prognostic biomarker for these cancers. The relationship between cancer type and MMP-9 concentration was elucidated quantitatively. Our initial 11 serum samples were selected randomly from cancer patients. It was found that the concentration of MMP-9 in serum samples was higher than concentration in healthy volunteers (Figure 1). The increase was not significant in all cancer types. However, significant induction of MMP-9 was noticed in leukaemia, Colon and Breast cancer patients. In Colon and Breast cancer, there was a moderate but significant increase in MMP-9 levels, 590 pg/ml and 570 pg/ml, respectively. In contrast, leukaemia had a slight but markedly significant increase of titer of MMP-9, 200 pg /ml (Figure 1).

Serum samples were processed and analyzed to measure the concentration of MMP-9 using human MMP-9 Quantikine ELISA Kit (Sigma-Aldrich) following an incubation period of 2 hours at room temperature. Following multi-washing steps, 200 µL of human MMP-9 conjugate was added to each well and incubated for 1 hour at room temperature. Subsequently 200 µL of substrate solution was incubated for 30 minutes at room temperature. Finally, 50 µL of stop solution was added to each well and optical density of each well was read using a human ELISA microplate reader set to 450 nm. The MMP-9 concentration for each cancer type was compared by Mann–Whitney test (mean ± SD), n= 2 independent experiments. Results were considered significant at $p \leq 0.05$, our result showed that breast, colon, leukaemia, were significant at $p \leq 0.001$, $p \leq 0.0008$, $p \leq 0.0001$, respectively.

Discussion

Cancer is a multifactorial condition with tremendous attributing factors that are not fully understood yet. Knowledge and awareness of the public about cancer and the importance of early detection can help control or cure cancer at its early stages. Knowledge by itself can do nothing without detection of biomarkers that predict cancer in these patients. In this study surveyed the level of knowledge of the public about cancer where it is believed that knowledge about cancer can reduce the incidence of cancer. Besides, determining specific biomarker/ s can also decrease the rate of mortality of cancer.

This study showed that breast cancer was the most common cancer among public in Palestine at a rate of 25%. This result matched with other studies which showed that breast cancer was among the most common cancer types in Jordanian population [40] and worldwide [41, 42]. In the second place came these cancers; lymph nodes, 15.4%, leukaemia, 15.4%, and colorectal cancer 7.1%. Breast cancer and colorectal cancer are well established as genetic and familial cancers in the Palestinian community. However, the genetic background has to be elucidated. This encourages us to investigate further the relationship between FAP (Familial Adenomatous Polyposis) syndrome and Lynch syndrome as related to MMP-9 gene(s). In the same context we can further study Hereditary Breast and Ovarian cancer. While thyroid cancer and Hodgkins lymphoma came in middle

between second and third place with rates 4.7%, for stomach cancer, 3.5% for each sarcoma and benign cancer and 2.3% for each bone and brain cancer. The third category shows the less common cancers, such as intestine cancer, lung cancer, testicular cancer, neuroblastoma, multiple myeloma, urinary bladder, optic glioma, kidney and pancreatic cancer with 1.1% for each (Table 1).

Although cancer is uncommon in young adult, interestingly, in our study we revealed that young adults with age less than 20 years constituted 30.9% of cancer cases. Adults between 41-60 years also constituted (30.9%) of cancer cases at different stages, this came in contrast to rate of cancer in age groups 21-40-year-old and ≥ 61-year-old where it was 26.1% and 11.9 %, respectively. However, some controversial in recent studies shown that ages below 20 years have high incidence rate of cancer [43]. In general, the age is a risk factor for all cancer types combined and for progression of cancer [44-47]. It was found that some cancers might be specifically related to gender. However, in our study it was difficult to establish a significant relationship to gender since other factors such as physiological differences, social, profession, habit, education, age, marital Status, diets might also play a role.

Education inequalities in cancer incidence have long been noticed. It is not clear; however, whether such inequalities persist in Palestine. In our study, the majority of the cancer patients were well educated with university degrees (76.1%). Although, education is an important indicator of socioeconomic status, in two studies it has been shown to be inversely associated with the incidence of most types of cancers [48]. In the same study, it was shown that higher level of education lowers the risk of cancer [48].

Data was further analyzed in order to check whether there is an association between dietary habits, smoking and cancer among our subjects. It was found that the majority of cancer patients were both vegetarians and carnivore. Comparing between vegetarians and carnivores in relation to cancer incidence, our data showed insignificant difference since most of the sample are both vegetarians and carnivores [vegetarians (5.9%) and carnivores (2.3%)]. However, a study in the UK showed that cancer incidence in British vegetarians was lower by 10% of all malignant cancers comparing to meat eaters patients [49]. As we know smoking is linked to certain types of cancer [50-53]. Cigarette smoking is associated with lung and breast and ovarian cancer [54].

Our data does not show any correlation between smoking habit and cancer, this might be due to the fact that most of the participants in our study were non-smokers.

Migration, invasion, metastasis, and angiogenesis of cancers are closely related but not limited to the extracellular environment [55]. Early detection of cancer saves lives and decrease mortality from the disease. Unfortunately, not all cancers have established blood or tissue biomarkers that can be detected early in sera or tissue of patients. Some cancer tissues even look same as normal tissue under the microscope at early stages of cancer. Other cancer types exhibit same patent of differentiation like adjacent normal tissue. Sometimes there is no specific method or biomarker/s for such early diagnosis. However, many researches are focusing on finding specific biomarker/s for early detection and or prognosis of cancer such as invasion, relapse and metastatic patterns. Having this said, MMP-9 plays an important role in ECM remodeling and membrane protein cleavage. It was found to be widely associated with cancer pathologies [55-65].

MMP-9 level as mentioned has been suggested as a biological predictor of prognosis in CRC as well as in other cancer types such as breast and cervical cancer [66]. Many studies also have explored the value of MMP-9 in many different types of cancer [67] as breast cancer [68-70], its association with chronic lymphocytic leukemia cell response [71], cervical cancer [72] thyroid carcinoma and its prediction [73, 74]. Other studies shows the prognostic significance of MMP-9 in bone cancer [75], brain cancer in which MMP-9 was as phase specific effectors molecule in experimental autoimmune encelphalomyelitis [76], lung cancer [77] and its prognostic effect in lung cancer [78], lymphnodes [79]. Recent research detected expression of MMP-9 in GCTSC in peripheral tissue and central tissue of GCTB and the correlation with survival of gastric cancer [80]. Our study finding also was consistent with these studies and confirms that MMP-9 level elevated in cancer. However, MMP-9 could be an important biomarker for detection of cancer at early stages. Besides, the level of elevation of this biomarker will indicate the type of cancer, as the elevation of MMP-9 concentration.

Therefore, we carried out this study on 11 cancer patients to determine if MMP-9 could be employed as a biomarker for cancer. MMP-9 titer was found to be higher in all 11 cancer patients comparing to healthy volunteers. This elevation of MMP-9 concentration was specifically and markedly increased in leukaemia, Colon and Breast cancer patients. In Colon and Breast cancer, we could reveal that there was a moderate but significant increase in MMP-9 levels, 590 pg/ml and 570 pg/ml respectively. In contrast, leukaemia patients had a slight but markedly significant increase in MMP-9 levels, 200 pg/ml (Figure 1). These patients had no other conditions that might lead to elevation of MMP-9 as per their profile and personal declaration, same as to volunteers.

Even not shown in our study, MMP-9 might be considered as an important biomarker for detection of cancer at early stages. However, this issue needs further investigation. Besides, the level of elevation of this biomarker will indicate the type of cancer, as the elevation of MMP-9 concentration had certain pattern in certain cancers as folds increase in usually elevated levels.

In our study, a marked significant elevation of MMP-9 came in agreement with the contribution of MMP-9 to chronic lymphocytic leukemia (CLL) by regulating cell migration and preventing spontaneous apoptosis [71,81]. Concerning colon and breast cancer, our findings showed that MMP-9 was moderately elevated but still at a higher concentration comparing to leukaemia. This result was consistent with some other MMP-9 research studied in colon cancer [82], and breast cancer [68, 70].

To precisely confirm the relationship between MMP-9 levels and type of cancer; comprehensive studies need to be carried out. Such comprehensive studies need to be carried out worldwide and in developed countries on large scale case control studies and multicenter approach.

Conclusion

This is the first study to evaluate the prevalence of different types of cancer and most common type in Palestine. The study divided the patients into three parts; early, moderate, and advanced stages of the disease progression. In conclusion, this study suggests the high need to investigate the knowledge about the percentage of different cancer types in Palestine and in addition to its association with MMP-9. Further studies with larger sample size that focuses on the prevalence of cancer in Palestine and its relationship with MMP-9 concentration levels are needed. Continuous education for population needed to prevent delays in diagnosis and to start the treatment earlier for better disease outcome. Clinicians need to develop guidelines to enhance and standardize the long-term follow-up of cancer survivors. Furthermore, these estimates are intended for patients to help recovering social activities and supporting rehabilitation demands. MMP-9 could be an important biomarker for detection of cancer at early stages and the level of elevation of this biomarker will indicate the type of cancer.

However, the lack of data among Arabs different regions; the few conducted studies; and the small number of subjects required further studies to be conducted with larger sample size and to determine the prevalence of different cancer types in Palestine using MMP-9 as indicator. More wide based population studies are needed to prevent delays in diagnosis and to start the treatment in early stages of the disease for better outcomes.

Conflict of Interest and financial Disclosure

The authors declare no competing financial interests, and no conflicts of interest with respect to the authorship and/or publication of this article.

Ethical Considerations

This research was approved from the Institutional Review Board (IRB) of Hebron University. The participation in this study was voluntary and the participants had the right to withdraw at any time. The identities of the participated patients were unknown and their identities remained confidential and only used for research aims. No intervention was made.

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