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Cancer Aggregates Pattern among Families in Iraq

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Abstract

Breast cancer is first ranking malignancies in Iraq. Family history of cancer is an important factor for cancer occurrence and development in next generation.The study aimed to determine the validity of family history of cancer by population-based and clinic-based family registries, evaluate the concurrence of cancer affected by family history in their first-, and second-degree relatives. An observational study of total 62 relatives membered of 44 Iraqi breast cancer families were included. We conducted study at period between December 2018 and June 2019. Data collected according NCCN Genetic Testing Criteria for Hereditary Breast and Ovarian Cancer Syndrome. Risk ratio (RR) used to evaluating predilection of family cancer risk.We addressedforty-four Iraqi breast cancer families who have sixty-two members with cancer. The age mean±SD was 51.8±12.6, and median=48.5 years. Meanwhile the age mean±SD=51.6±11.9 years for relatives. M:F ratio equal to 3:1.Sister, mother and aunt/uncle were most common relative affected. Breast cancer represented the most frequent types found in 46.7% of patients. Mothers (RR=1.313), and/or sisters (RR=1.6), lead to increased risk of cancer development in other family members or next generation. The first-degree relatives recorded more than the second-degree relatives. This is the first study conducting in Iraq dealing with cancer risk at the level of families. The age of patients didn't differ from age at diagnosis, concluding there is no active screening programs run through Iraqi families. Sister, mother and aunt/uncle are the most relatives affect. The 1st-degree relatives more frequent than the 2nd-degree. Breast cancer represented the most common types found members studied. Mothers and sisters have highly risk ratio for developing family cancer among other individuals.

Keywords: Family cancer risk; Risk ratio; BRACA; 1st-degree relative; 2nd-degree relative

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Introduction

Family history information on cancer is used to deduce risk of the cancer in population-based, case-control, cohort, or family-based studies; little information is available on the accuracy of these setting. The first-degree relatives have been shown to be a risk factor associated with increased risk of developing cancer and used to distinguish individuals for genetic and molecular studies [1-3]. In many studies of validation of family history of cancer, most records focus on the first-degree relatives and most studies use case–control study designs. Inaccurate reporting can result in biased estimates of familial aggregation and represent a major source of misclassification in genetic and epidemiologic studies. In fact, in case–control studies, non-differential misclassification of the disease status of the relatives results in biased estimates of the odds ratio toward the null [4,5].

Hereditary Breast/Ovarian Cancer (*BRCA1*) is autosomal dominant. *BRCA1*, is a tumor suppressor gene at 17q21; is central to the maintenance of genome stability. It is a multifunction E3 ubiquitin ligase involved in DNA damage signaling, DNA repair, chromatin remodeling and transcription [6], and it is not homologous to *BRCA2*. Whereas, *BRCA2*, is a tumor suppressor gene at 13q12.3, is central to the maintenance of genome stability through repair of double-stranded DNA breaks by homologous recombination [1], not genetically related to *BRCA1*. There are more than 1643 distinct mutations, polymorphisms, and variants have been identified [6]. Overall, *BRCA1* and *BRCA2* account for a small proportion of all breast cancers; it is in 2% of women, that reported by the Anglican Breast Cancer Study Group [7]. Among Australian women diagnosed with breast cancer before age 40 years, 3.8% have *BRCA1* mutations [8]. In the UK, *BRCA1* or *BRCA2* mutations were found in 5.9% of women diagnosed younger than age 36 and in 4.1% of women diagnosed from ages 36-45 years [7]. In US, *BRCA1 mutations* were found in 3.3% of women aged of 20-74 years [7]. *BRCA1* and *BRCA2* mutations occur in 10-15% of all ovarian cancer [7]. *BRCA2* mutations have been identified in 25% of American families with three or more cases of female breast and/or ovarian cancer (values range from a low of 8% in Finland to a high of 64% in Iceland) [1]. In families with male and female breast cancer, *BRCA2* mutations were found in 19% of American families and in 90% of Icelandic families [3]. Globally, about two-thirds of families with three or more cases of female breast and/or ovarian cancer had either a *BRCA1* or a *BRCA2* mutation [7,8]. *BRCA1*carrier estimation frequencies have ranged from 0.056-0.24%, with a population-based Canadian study finding the highest rate yet reported, 0.32% [9]. *BRCA1*-related breast cancer tends to be of high histological grade, lymph node positive, estrogen receptor negative, progesterone receptor negative, HER2/neu negative, with expression of basal or myoepithelial markers

by immunohistochemistry ("basal phenotype") [10]. In general, the clinical differences between *BRCA1* and *BRCA2*-related breast cancers are associated with differences in prognosis, have a worse prognosis than their sporadic counterparts [11], although outcome has been reported to be similar between these two breast cancer subgroups [11].

We sought to determine the validity of family history of cancer bypopulation-based and clinic-based family registries.To evaluate the concurrence of cancer affected by family history in their first, second, and third-degree relatives. To determine the positive and negative likelihood values, and the probabilities of familial cancers among Iraqi families.

Patients and Methods

Study Design and Setting

Observational studies of total 62 relatives membered of 44 Iraqi breast cancer families were identified. Some patients' demographic data details were recorded. We conducted study at Baghdad Radiation Oncology and Nuclear Medicine Center, Baghdad Oncology Teaching Hospital, and National Cancer Center at Baghdad Medical City Complex, at period between December 2018 and June 2019.

Data collection

Data are collected according NCCN genetic testing criteria for hereditary breast and ovarian cancer syndrome to the following questionnaires sheet [12].

Ethical approval

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee from College of Medicine/Baghdad University (code:136) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Statistical analysis

After data collected in Excel sheet then transfer to analysis into a file of "IBM SPSS Statistics"statistical package for social sciences version 24 (SPSS, Chicago, USA V 24). Frequencies and relatives' frequencies were calculated for each variable. A *P* value of 0.05 or less was considered statistically significant and risk ratio (RR) used to evaluating predilection of family cancer risk.

Results

Here we presentedand addressedforty-four breast cancer Iraqi families who have sixty-two relatives or members with breast and other types of cancer.

The most frequent age group was belonging to 41-50 years 16 (36.4%), followed by 61-70 years 12 (27.3%), with mean±SD= 51.8±12.6, and median=48.5 years. When compared with age at diagnosis, approximately found the same data, shown in (Table 1), (Figure 1). Furthermore, age distribution of members of families studied illustrated in (Table 2). The frequent age group was 51-60 years as 26 (41.9%), followed by 31-40 in 12 (19.3%) of patients, with mean±SD=51.6±11.9 years. Whereas the most age group of age at diagnosis was 51-60 years as 32 (51.6%) of patients, with mean±SD= 49.8±11.9 years. A total 45 (72.5%) were females, whereas male presented as 17 (27.5%) of members, in M:F ratio equal to 3:1, as showed in (Figure 2).

Table 1: Patients age frequencies of breast cancer women of this study (n=44).

Age groups (years)	Age of patients*	Age at diagnosis**	Chi-square
	n (%)	n (%)	(P-value)
20-30	2 (4.5)	2 (4.5)	1.504
31-40	5 (11.4)	8 (18.2)	-0.08
41-50	16 (36.4)	14 (31.8)	
51-60	7 (15.9)	9 (20.5)	
61-70	12 (27.3)	9 (20.5)	
>71	2 (4.5)	2 (4.5)	
Total	44		
Mean±SD= 51.8 ± 12.6, and median=48.5* Mean ± SD= 49.8 ± 12.8, and median=46.5**			

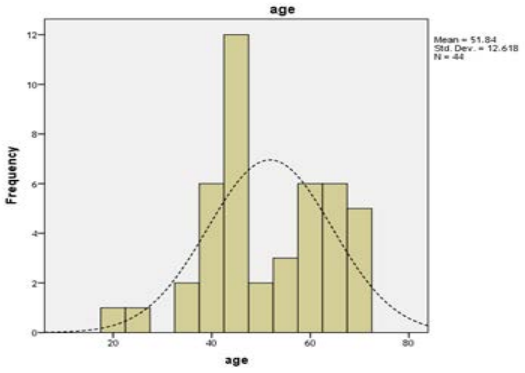

Figure 1: Histogram of age groups of the study (n=44).

Table 2: Patients age frequencies of relatives of this study (n=44).

Age groups (years)	Age of patients*	Age at diagnosis**	Chi-square
	n (%)	n (%)	(P-value)
20-30	3 (4.8)	2 (3.2)	2.229
31-40	12 (19.3)	8 (12.9)	-0.069
41-50	10 (16.1)	13 (20.9)	
51-60	26 (41.9)	32 (51.6)	
61-70	9 (14.5)	7 (11.3)	
>71	2 (3.2)	0	
Total	62		
Mean ± SD= 51.6 ± 11.9, and median=53.5* Mean ± SD= 49.8 ± 11.9, and median=52**			

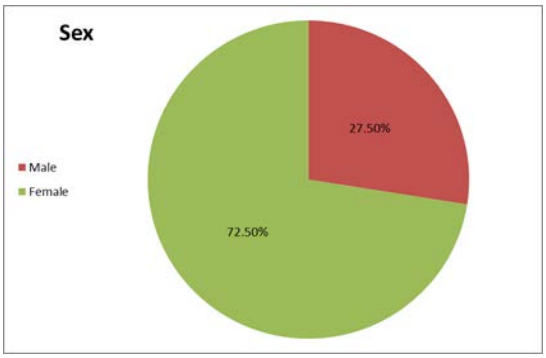

Figure 2: Pie chart of sex of the study.

Regarding the members of families studied, the most common was sister as 14 (22.6%), followed by mother and aunt/uncle as 11 (17.7%) for each. Ten members as grandmother/father. Six members presented as daughter. Four relatives recorded as father or brother, and only two as son. The 1st degree relative presented as 41(66.1%), and the 2nd degree

as 21 (33.9%), of patients, seen in (Table 3 and Figure 3, 4).

Breast cancer represented the most frequent types found in 29(46.7%) patients, followed by colorectal cancer as 12 (17.7%) patients, shown in (Table 4). Furthermore, five members have prostate cancer, and as well as for lung cancer.Lymphoma recorded in three relatives. Endometrium cancer, CNS tumor, and bone cancer reported in two relatives for each. Esophagus cancer, leukemia, and larynx cancer presented in only one member for each.

Table 3: Relative affected and degree of family history cancer.

Variables		**n (%)**
Relative affected	Mother	11 (17.7)
	Father	4 (6.4)
	Sister	14 (22.6)
	Brother	4 (6.4)
	Son	2 (3.2)
	Daughter	6 (9.6)
	Aunt/uncle*	11 (17.7)
	**Grandmother/ father	10 (16.1)
	Total	62
Degree	1st	41 (66.1)
	2nd	21 (33.9)
	Total	62
*Male =4, and female=7 ** Male=3, and female=7		

Table 4: Relative cancer types of the families.

Cancer type	**n (%)**
Breast	29 (46.7)
Colorectal	11 (17.7)
Endometrium	2 (3.2)
Esophagus	1 (1.6)
Lung	5 (8.1)
Leukemia	1 (1.6)
Larynx	1 (1.6)
Lymphoma	3 (4.8)
Bone	2 (3.2)
CNS	2 (3.2)
Prostate	5 (8.1)
Total	62

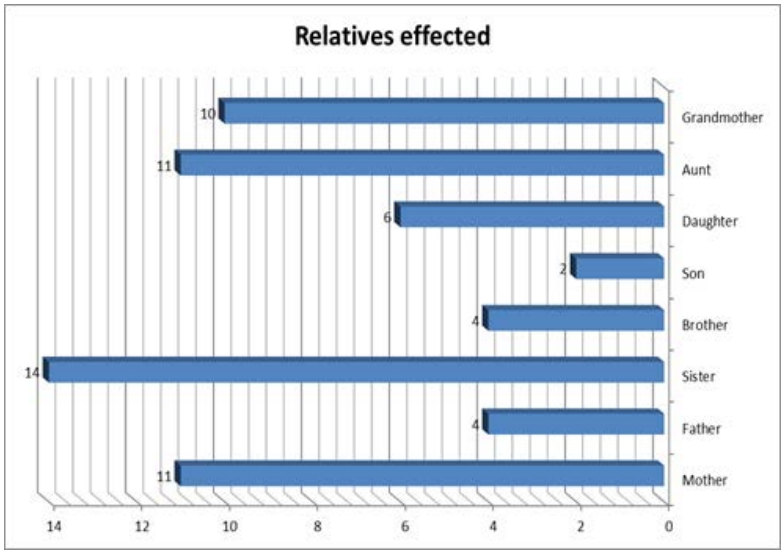

Figure 3: 3D Bar chart of members of families studied.

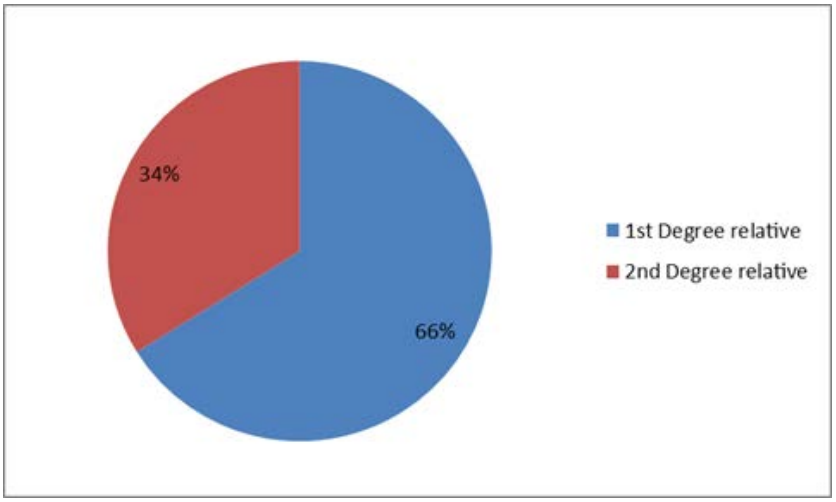

Figure 4: Pie chart of degree relatives of this study.

Family risk ratio (RR) findings showed that relatives affected as mother (RR=1.313), and/or sister (RR=1.6), lead to increased risk of cancer development in other family members or next generation for breast, colorectal and endometrium cancers, lymphoma, and CNS tumors, which were statistically significant (P=0.05), (P=0.037), respectively. Father, and son as relatives have no significant association to the family cancer risk occurrence, since RR=1. Brothers and daughters haven't influenced the family cancer risk development, (RR=0.666, P=0.3; RR= 0.6, P=0.16), respectively. In addition, next of kin like uncle/aunt (RR=0.714), and grandmother (RR=0.75), may be the family cancer risk development less than that of mother and sister, as showed in (Table 5 and Figure 5). The 1st degree relatives recorded with breast cancer in 18 members, colorectal cancer in seven, lung cancer and lymphoma in three members for each. Endometrium cancer, bone tumors, and CNS tumors in two members for each. One 1st degree relative recorded for esophagus cancer, leukemia, larynx cancer and prostate cancer. The 2nd degree relatives presented in eleven members. Four members of colorectal cancer and prostate cancer related to the 2nd degree relatives, and two members belonged to lung cancer, showed in (Table 5 and Figure 6).

Discussion

For our acknowledgment, this study is the first conducting in Iraq dealing with cancer risk at the level of Iraqi families, which not mentioned yet.

The most frequent age group of our study belong to 41-50 years 16(36.4%), with mean±SD=51.8±12.6, and median=48.5 years, this finding of 44 women have breast cancer included and their 62 of relatives who have breast cancer and other types of cancer. Furthermore, the age distribution of those members was 51-60 years as 26(41.9%), with mean±SD=49.8±11.9 years. The M:F ratio of our study was 3:1. Ziogas A, et al. [13] reported that female was the predominant gender 84.5% of population in a study of cancer family registries, and the age distribution at diagnosis with breast, ovarian, or colorectal cancer show that 28% diagnosed at an age younger than 50 years, 49.1% were diagnosed between the ages of 50-69 years, and 22.9% diagnosed at age 70 years or older with the mean age at diagnosis was 56.6 years old (SD=13.3) [13]. Prevalence rates for moderate and strong familial risk are reported for at-risk individuals lacking a personal history of breast, ovarian, endometrial, prostate, or colorectal cancer, the cause not reported for individuals with a personal history of these cancers because of small numbers of individuals within subgroups according to age, sex, or ethnicity/race. Scheuner MT, et al. [14] found the prevalence of a positive family history of cancer was greater among older individuals, and age was a significant variable associated with increased familial risk for all cancers. This is likely because more of the older individuals have family members who have lived long enough to develop these cancers [14]. The magnitude of the effect of age also

Table 5: Family risk of cancer types among relatives of the families studied.

Relatives		Breast [n=29]	Colorectal [n=11]	Endometrium [n=2]	Esophagus [n=1]	Lung [n=5]	Leukemia [n=1]	Larynx [n=1]	Lymphoma [n=3]	Bone [n=2]	CNS [n=2]	Prostate [n=5]	Family risk ratio RR	95% CI	*P*-value
1st degree relative	Mother [n=11]	7	1	2	-	1	-	-	-	-	-	-	1.313	0.56-3.04	0.05
	Father [n=4]	-	-	-	1	1	-	1	-	-	-	1	1	0.14-7.09	0.1
	Sister [n=14]	8	2	-	-	-	-	-	2	-	2	-	1.6	0.57-4.47	0.037
	Brother [n=4]	-	2	-	-	1	-	-	-	1	-	-	0.666	0.29-1.48	0.3
	Son [n=2]	-	-	-	-	-	1	-	-	1	-	-	1	0.1-9.61	0.1
	Daughter [n=6]	3	2	-	-	-	-	-	1	-	-	-	0.6	0.29-1.23	0.16
2nd degree relative	Aunt/ Uncle [n=11]	5	2	-	-	-	-	-	-	-	-	4	0.714	0.44-1.14	0.15
	Grandmother [n=10]	6	2	-	-	2	-	-	-	-	-	-	0.75	0.5-1.12	0.16

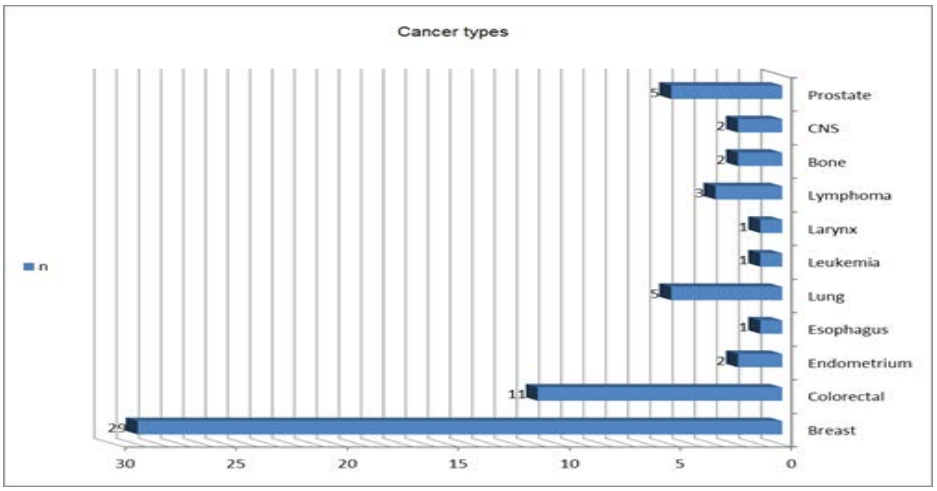

Figure 5: 3D Par chart of cancer types frequencies of the study.

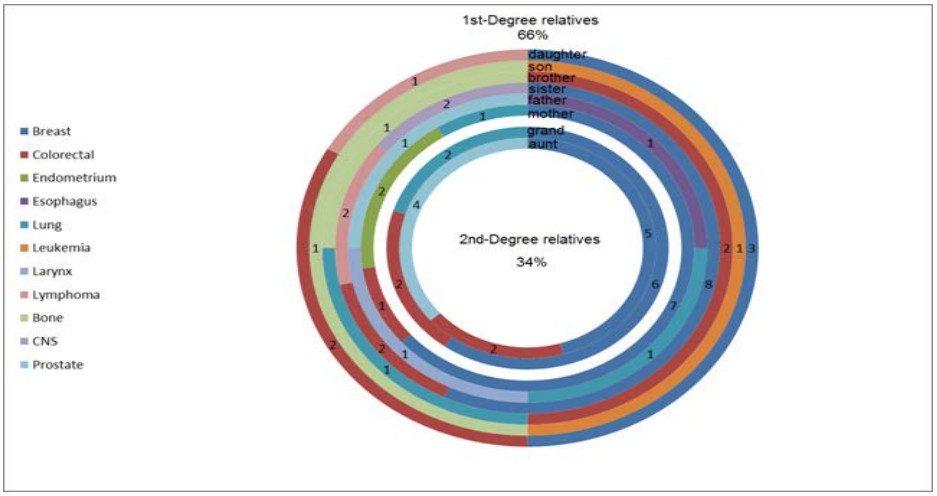

Figure 6: 1st-degree and 2nd-degree relatives' distribution among cancer types.

seemed to be dependent on the cancer types. Older individuals were about twice as likely to report a moderate or strong familial risk for colorectal cancer, but for ovarian cancer the proportion of older and younger individuals with moderate and strong family histories was relatively similar [13,14]. Regarding sex, he demonstrated a significant variable associated with increased familial risk for all cancers except prostate cancer and found that women were more likely than men to report a family history of cancer, particularly a family history of endometrial cancer [15]. Because specificity of self-reports of cancer family history is high with lower rates of sensitivity, it seems more likely that men are underreporting their family histories than women over reporting [15]. Moreover, because reports of family history of prostate cancer were similar among men and women, it seems that underreporting by men may be attributable to a perceived lack of relevance of the family history of these cancers for men [14]. Recent estimates indicate that clinically significant mutations in either of the *BRCA* genes increase a woman's risk of breast cancer by age 70 years to 45-65% [16,17].

Regarding the family's members studied, sister was prevalently recorded as 22.6%, followed by mother and aunt/uncle as 17.7% for each. The 1st-degree relative presented as 66.1%, and the 2nd-degree as 33.9% of the relatives recorded. There was a system estimated population the prevalence for persons with a family history of cancer known as the National Health Interview Survey (NHIS) [15]. The NHIS assessed prevalence of individuals with one or more 1st relatives with breast, colorectal, lung, prostate, and ovarian cancer. However, the limitations presented like this system did not ascertain data about cancer in 2nd relatives, and the data analysis did not consider age at diagnosis or combinations of cancer diagnoses; all of which are necessary for familial risk stratification and recognition of hereditary cancer syndromes. Furthermore, the NHIS analysis did not consider prevalence rates according to the personal history of cancer [15].

Family history of BRCA-related cancer is a vital in estimating individual risk for a *BRCA1*or *BRCA2* mutation in women without cancer. Among women with first-degree relatives with cancer, the relative risk for cancer has rated in meta-analyses as 2.1 for breast cancer, and 3.1 for ovarian cancer [18].

Breast cancer represented the most common types found in 46.7% of members studied, followed by colorectal cancer as 17.7%. Furthermore, five members have prostate cancer, and as well as for lung cancer. Lymphoma recorded in three relatives. Endometrium cancer, CNS tumor, and bone cancer reported in two relatives for each. Esophagus cancer, leukemia, and larynx cancer presented in only one member for each.

Mothers (RR=1.313), and/or sisters (RR=1.6), mostly affect individual for increasing risk of cancer development in family or next generation for, and this ratios ranked in descending order of the highest frequency and percentage of breast cancer, followed by colorectal and endometrium cancers, lymphoma, and to the least number and proportion of CNS tumors, which were statistically significant (P=0.05), (P=0.037), respectively. Father and son as relatives haven't statistically significant association to the family cancer risk occurrence, since RR=1. Brothers and daughters haven't influenced the family risk of cancer, (RR=0.666, P=0.3; RR=0.6, P=0.16), respectively. Besides, next of kin like uncle/aunt (RR=0.714), and grandmother (RR=0.75), may be the family cancer risk development less than that of mother and sister influences.

The first-degree relatives recorded with breast cancer in 18 members, colorectal cancer in seven, lung cancer and lymphoma in three members for each. Endometrium cancer, bone tumors, and CNS tumors in two members for each. One 1st-degree relative recorded for esophagus cancer, leukemia, larynx cancer and prostate cancer. The second-degree relatives presented in eleven members. Four members of colorectal cancer and prostate cancer related to the 2nd-degree relatives and two members belonged to lung cancer. In the study by Nelson HD, et al. [18] a report of breast cancer in a first-degree relative of a healthy individual had a sensitivity of 82%, specificity of 91%, the positive likelihood ratio of 8.9, and negative likelihood ratio of 0.20. A more recent population-based study by Mia et al., in the US indicated the accuracy of self-reported breast cancer history in a first-degree relative as 64.9% sensitivity and 99.0% specificity [19].In this study, the accuracy of the first-degree relatives was higher than for second-degree relatives. Another report of ovarian cancer in a first-degree relative was less reliable than for breast cancer, and had a sensitivity of 50%, a specificity of 99%, the positive likelihood ratio of 34.0, and negative likelihood ratio of 0.51 [15].

Positive family history can increase an individual's risk of cancer from 2 to 5 times, and this risk generally increases with an increasing number of affected relatives and earlier ages of cancer onset [20]. In Addition, other features of high-risk family histories include the

occurrence of bilateral cancers, cancer in the less often affected sex (e.g., male breast cancer), and related cancer diagnoses in a pattern suggestive of a hereditary syndrome [20].

AlwanNAS, et al. [20,21], discussed breast cancer and its relation to family history in Iraq, either to breast itself or other types of cancer, in 2019 reported 25.6% of women in her study to have family history of breast cancer and 38% have a family history of different types of cancer; in 2018 the percent were 51.1% and 49.3%; in 2017 the percent was 20.2% and 14.6%, respectively, with no significant differences. These discrepancies between those studies findings may be due to there was no comprehensive cancer registry program or inadequate screening strategies. Globally, between 20-25% of women with breast cancer have a positive family history, and approximately 10% of women with breast cancer are from families who display an autosomal dominant pattern of breast cancer inheritance [21,22].

There is a 5-10% of women with breast cancer have a mother or sister with breast cancer, and up to 20% have either a first- or second-degree relative with breast cancer [18]. Several factors are associated with an increased likelihood of family risk. Those including breast cancer diagnosed at an early age (before age 40 or 50 years), bilateral breast cancer, triple-negative breast cancer diagnosed before age 50 years, history of both breast and ovarian cancer, breast cancer in male relatives, multiple cases of breast cancer in the family, both breast and ovarian cancer in the family, and family members with two primary breast cancers [18].

Family history of cancer is an important non-modifiable risk factor for cancer, but we may be preventing by guiding screening and prevention strategies for many common cancers, including genetic testing. Also, by intensive preventive interventions which include recommendations for lifestyle changes; more aggressive screening for early cancer detection beginning at younger ages, occurring at more frequent intervals and with more intensive methods than used for average or low-risk individuals and those at highest risk, if possible prophylactic surgeries. The multidisciplinary team decisions about a referral, testing, and risk-reducing interventions are often base on self-reports of family histories that include type of cancer, relationship within the family, and age of onset is the necessary point of management.

Conclusion

This is the first study conducting in Iraq dealing with cancer risk at the level of Iraqi families. The age of patients didn't differ from age at diagnosis, from that we conclude there is no active screening programs run through Iraqi families. Sister, mother and aunt/uncle are the most relatives affect. The 1st degree relatives more frequent than the 2nddegree. Breast cancer represented the most common types found in members studied. Mothers and sisters have highly risk ratio for developing family cancer among other individuals. The requirement for more studies with larger patients' sample and longer periods of follow-up are still required to assess the family risk cancer run in Iraqi families. Active screening program for those people of family cancer history. The counseling of individuals with hereditary cancer risk. The increased public awareness of the genetic aspects of cancer susceptibility has resulted in more enquiries from clinical and surgical oncologists about which would be the best approach for their patients so that appropriate management could be provided. Suggestion of a high-quality approach of delivering hereditary cancer risk assessment within a multidisciplinary context.

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