RESEARCH COMMUNICATION

Impact of Consanguinity on Cancer in a Highly Endogamous Population

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Abstract

Background: Many epidemiological studies have indicated that inbreeding has little or no effect on the incidence of cancer. Due to the high prevalence of consanguinity in Qatar (54%), its influence may nevertheless be of special importance. Aim: The aim of this study was to examine whether parental consanguinity affects the risk of cancer in a local Arab highly inbred population. Design: Matched case-control study. Setting : The study was carried out in Al-Amal cancer hospital and primary health care centers in Qatar over a period from August 2008 to February 2009. Subjects and Methods: The study included 370 Qataris and other Arab expatriates with various types of cancers and 635 controls matched by age and ethnicity. A questionnaire that included socio-demographic information, type of consanguinity, medical history, and tumor grade was designed to collect the information of cases and controls. Results: The study revealed that the rate of parental consanguinity was similar in both cases (29.5%) and controls (29.9%) with a higher inbreeding coefficient in controls (0.017±0.03), compared to cancer patients (0.0155±0.03). Other Arab expatriates had a higher incidence of cancer (61.1%) than Qataris (38.9%). The inbreeding coefficient was higher in male cancer patients (0.0189±0.03), but lower in female cancer patients (0.014±0.03) as compared to controls. Controls were more inbred in the overall studied subjects (23.6%) and women (23.8%) than cases. The coefficient of inbreeding was lower in patients with breast (0.014), skin (0.012), thyroid (0.008) and female genital (0.014) cancers, whereas it was higher in cases for leukemia and lymphoma (0.018), colorectal (0.025) and prostate (0.017), with no significant difference between cases and controls. No significant differences were observed between cases and controls in the parental consanguinity, mean coefficient of inbreeding and proportion of more inbred subjects. Conclusions: The study findings revealed that although the consanguinity rate is high in our Arab population, it has no effect on the incidence of cancers overall. However, there was an increased risk found for leukemia and lymphoma, colorectal and prostate cancer groups, but a reduced risk in breast, skin, thyroid and female genital cancer groups.

Key Words: Consanguinity - Qatar - cancer incidence

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Introduction

Cancer is a genetic disease in which malignant cells have undergone mutations and epigenetic changes in tumor suppressor genes and oncogenes (Futreal et al., 2004). Cancers occurring among adolescents and young adults are more likely related to genetic predisposition and exposure to risk factors early in life as compared with cancers among the older population. One of the most important factors contributing to the preponderance of genetic disorders in Arab population is the deep-rooted norm of consanguineous marriages. Worldwide, some 1,000 million people live in countries where 20% to more than 50% of marriages are consanguineous, and large migrant communities from these regions are now resident in Western Europe, North America and Oceania (Bittles, 2008).

The impact of consanguinity is that it increases the inbreeding coefficient (Thornill and Nancy, 1993). Thus the frequency of homozygosity increases, while the frequency of heterozygosity decreases. Since recessive disorders phenotype are only manifested in the homozygous state, their incidence increases in inbred communities and populations with increased consanguinity rates. By creating a homozygous state for a recessive tumor gene, consanguinity may provide

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congenital setting for multistage carcinogenesis and theoretically, an increased cancer risk. In homozygotes, doubling of a cancer-susceptibility gene dose could clearly affect cancer risk and alter tumor phenotype (Bittles, 2001) Conversely, another hypothesis suggests that the long term practice of consanguinity may decrease the frequency of a deleterious gene or eliminates it from a population (Khoury et al., 1987).

The highest worldwide rates of consanguineous marriages are in the Middle East. In United Arab Emirates, this has increased to 51%. In Saudi Arabia and Kuwait, the rate of consanguineous marriage is just over 50%, whereas in other Middle Eastern countries and Egypt, it varies between 22% and 51% (Al Ghazali et al., 1997). In Qatar, the consanguineous rate is 54% (Bener and Alali, 2006). The most common type of consanguineous marriage is between first cousins who share one-eighth of their genes. Less common are marriages of double first cousins who share one quarter of genes, first cousins once removed who share one-sixteenth of genes and between more distant cousins (Harper, 1993).

There has been a little epidemiological research on the effect of inbreeding on cancer risk in the Middle East countries despite the fact that the consanguinity is so high. Because of the widespread practice of consanguineous marriages in Qatar, the research team aimed this study at understanding the relationship between consanguinity and risk of cancer in this country. So far, no study has been conducted in Qatar to determine the impact of consanguinity on various types of cancers. Therefore, a case control study was performed to assess the effect of different levels of inbreeding on the risk of cancer, especially of the most common malignancies.

Materials and Methods

Subjects

From August 2008 to February 2009, 370 cases and 635 healthy controls were recruited prospectively for a case-control study of consanguinity and cancer. The study was carried out at Al-Amal cancer hospital and primary health care centers in Qatar. The Al Amal hospital is the only cancer center in the State of Qatar and it is affiliated with the Weill Cornell Medical College in the United States and Heidelberg University in Germany. The Al Amal cancer hospital provides tertiary care to its cancer patients and is a referral center for all such patients through out the country.

This study of 370 cases and 635 controls was performed to find out if it is different between the consanguineous and non-consanguineous families. For each case, two non cancer controls were selected and matched by age and ethnicity. Arab population with a histological diagnosis of various cancers were recruited from the national cancer disease registry of the cancer hospital, whereas control subjects were identified from community as healthy with no history of any malignant tumor.

Questionnaire

A questionnaire that included the socio-demographic information, type of consanguinity, medical history, tumor characteristics was designed to collect the information of cases and controls. Nurses with good communication skills in both English and Arabic were trained by investigators for the purpose of data collection. The questionnaire was translated in Arabic and back translated into English by a blinded translator to check validity of the first translation. Face to face Interview was conducted by trained nurses, whose mother tongue was Arabic, using the same standardized questionnaire for the cases and the controls. The survey instrument was then tested on 50 randomly selected cancer patients and 50 randomly selected control subjects from the community. A total number of 474 cancer patients and 846 healthy subjects were approached and 370 cases (78%) and 635 controls (75%) agreed to participate in this study.

The pathology and clinical data was extracted by the investigators and nurses from the hospital records and documented in standardized form (Bener et al., 2008). Tumor characteristics were ascertained from pathology reports. An experienced Arabic-speaking nurse, at telephone interview, asked both patients and controls whether her parents were biologically related and, if so, how. For those unable to answer, the closest family member provided the information. Controls were interviewed within the four to eight month period of the case diagnoses. The coefficient of inbreeding (F) of patients and controls was determined from their responses as per the following:

Measures of Consanguinity

Consanguinity was evaluated based upon the coefficient of inbreeding (F) which is the probability of homozygosity by descent and was determined in the offspring of six types of consanguineous union as follows (Bener and Alali, 2006; Bener and Hussain, 2006; Bener et al., 2007):

Consanguinity type/Coefficient of inbreeding (F)	
Double first cousin	0.125
First cousin	0.0625
First cousin once removed	0.03125
Second cousin	0.0015625
Second cousin once removed	0.0078125

All other types of unions were considered non consanguineous with coefficient of inbreeding set at 0. The category of first cousin was then further divided into four types (Bener et al., 2007): paternal and maternal parallel types I and II and cross-cousins types III and IV. The average level of inbreeding was assessed in terms of coefficient of kinship values for each population, which allows measuresment of the probability that a gene taken at random from one spouse is identical by descent to a gene from the same locus taken at random from their partner (Emery, 1976).

The study was approved by the Research Ethics Committee of the Hamad General Hospital, Hamad Medical Corporation. All the persons who agreed to participate in this study gave their informed consent prior to their inclusion in the study.

Statistical Analysis

The data were analyzed using the Statistical Package for Social Sciences. Student t-test was used to ascertain differences between the mean values of two continuous variables and confirmed by non-parametric Mann-Whitney test. $\chi 2$ was utilized to establish the association between categorical variables. Where the sample size was small, the Fisher exact test was used instead of $\chi 2$. The level of inbreeding was assessed in terms of coefficient of kinship values for each population where a measures the probability that a gene taken at random from one spouse is identical by descent to a gene from the same locus taken at random from their partner. All P values are two-tailed and those less than 0.05 were considered statistically significant

Results

Table 1 shows the socio-demographic characteristics of the studied cancer patients and controls. The mean age of cancer patients was 47.3±16.7 years and controls 45.7±15.9 years. Cancer incidence was higher in subjects above 40 years of age (72.4% and 27.6% below 40 years). The proportion of cancer cases was higher in other Arab expatriate subjects (61.1%) than in Qatari nationals (38.9%). There was a significant difference observed between cases and controls in terms of occupation and household income ($p<0.001$).

Table 2 compares the inbreeding characteristics of cancer patients and controls. The rate of parental consanguinity was similar in studied cancer patients (29.5%) and controls (29.9%) with a higher inbreeding coefficient in healthy Arab population (0.017±0.03) compared to cancer patients (0.0155±0.03). Among men, the parental consanguinity and inbreeding coefficient were higher in younger (38.2% & 0.0191±0.03) and older cancer patients (34.2% & 0.0189) than in controls. But in females, the parental consanguinity and inbreeding coefficient were lower in younger (27.3% & 0.013±0.03) and older (26.8% & 0.0141±0.03) cancer patients than in controls.

Table 3 shows the inbreeding category of cancer patients and controls by more vs less inbred. Controls were more inbred in overall studied subjects (23.6%) and women (23.8%) than cases, but similar in men for both cases (23.9%) and controls (23.2%). In younger subjects below 30 years old, more inbred controls than patients were found among females (31.3%) and overall (26.6%), but for men more inbred was among cancer patients (23.5%). As for the older age group above 30 years old, more inbred controls was higher in females (22.4%) and overall (22.9%) than patients.

Table 4 examines the inbreeding characteristics of patients with the most common types of neoplasms and controls. The coefficient of inbreeding (F) was lower in patients with cancers of breast (0.014), skin (0.012), thyroid (0.008) and female genital (0.014), whereas it was higher in cases for leukemia and lymphoma (0.018), colorectal (0.025) and prostate (0.017) with no significant difference between cases and controls. Parental consanguinity was more frequent in patients with prostate cancer (50%) and colorectal cancer (39.1%), female genital (36%), thyroid (30.8%), and leukemia and lymphoma (31.8%), but the differences were not statistically significant between cases and controls. The

Table 1. Socio-demographic Characteristics of the Studied Cases (N= 370) and Controls (N= 635)

Variables		Cases	Controls	P Value
Mean age		47.3±16.7	45.7±15.9	0.123
Age groups	<30	65 (17.6)	116 (18.3)	
	30-39	37 (10.0)	71 (11.2)	
	40-49	88 (23.8)	174 (27.4)	0.536
	50-59	92 (24.9)	138 (21.7)	
	≥ 60	88 (23.8)	136 (21.4)	
Gender	Males	113 (30.5)	207 (32.6)	0.499
	Females	257 (69.5)	428 (67.4)	
Nationality	Qatari	144 (38.9)	286 (45.0)	0.059
	Other Arabs	226 (61.1)	349 (55.0)	
Education	Illiterate	48 (13.0)	96 (15.1)	
	Primary	51 (13.8)	111 (17.5)	
	Intermediate	83 (22.4)	125 (19.7)	0.273
	Secondary	112 (30.3)	166 (26.1)	
	≥University	76 (20.5)	137 (21.6)	
Household	<5,000	16 (4.3)	92 (14.5)	
income	5,000-9,999	122 (33.0)	139 (21.9)	
	10,000-15,000	126 (34.1)	178 (28.0)	<0.001
	>15,000	106 (28.6)	226 (35.6)	
Occupation	Business	43 (11.6)	68 (10.7)	
Not working/House wife		108 (29.2)	271 (42.7)	
	Sedentary	106 (28.6)	207 (32.6)	
Manual/Professional		79 (21.4)	57 (9.0)	<0.001
	Police/Army	34 (9.2)	32 (5.0)	
Consanguineous				
	Yes	109(29.5)	190(29.9)	0.887
	No	261(70.5)	445(70.1)	

Table 2. Inbreeding Characteristics of Cancer Patients (N= 370) and Controls (N= 635)

Variables	Cases	Controls	P Value
All Mean age	47.3±16.7	45.7±15.9	0.123
Consanguineous*	109 (29.5)	190 (29.9)	0.877
Coefficient**	0.0155±0.03	0.017±0.03	0.439
Males Mean age	46.2±21.7	44.2±19.2	0.392
Consanguineous	40 (35.4)	63 (30.4)	0.364
Coefficient	0.0189±0.03	0.0168±0.03	0.534
Females Mean age	47.8±14	46.4±14.1	0.205
Consanguineous	69 (26.8)	127 (29.7)	0.428
Coefficient	0.014±0.03	0.0171±0.03	0.177
Age <30 years			
All Consanguineous	22 (32.8)	48 (37.5)	0.519
Coefficient	0.0161±0.03	0.0207±0.03	0.345
Males Consanguineous	13 (38.2)	18 (29.5)	0.384
Coefficient	0.0191±0.03	0.0169±0.03	0.747
Females Consanguineous	9 (27.3)	30 (44.8)	0.092
Coefficient	0.013±0.03	0.0241±0.03	0.116
Age >30 years			
All Consanguineous	87 (28.7)	142 (28.0)	0.829
Coefficient g	0.0154±0.03	0.0161±0.03	0.742
Males Consanguineous	27 (34.2)	45 (30.8)	0.607
Coefficient	0.0189±0.03	0.0167±0.03	0.596
Females Consanguineous	60 (26.8)	97 (26.9)	0.982
Coefficient	0.0141±0.03	0.0158±0.03	0.491

* Parents Consanguineous; **Mean coefficient of inbreeding

Table 3. Inbreeding Category of Cancer Patients and Controls by More vs Less Inbred*

Variables		Cases	Controls	OR(95% CI)	P Value
All	Less	296 (80.0)	485 (76.4)		
	More	74 (20.0)	150 (23.6)	0.78 (0.56-1.08)	0.116
Male	Less	86 (76.1)	159 (76.8)		
	More	27 (23.9)	48 (23.2)	1.04 (0.58-1.84)	0.887
Female	Less	210 (81.7)	326 (76.2)		
	More	47 (18.3)	102 (23.8)	0.72 (0.48-1.07)	0.089
Age ≤30 years					
All	Less	54 (80.6)	94 (73.4)		
	More	13 (19.4)	34 (26.6)	0.67 (0.30-1.44)	0.268
Male	Less	26 (76.5)	48 (78.7)		
	More	8 (23.5)	13 (21.3)	1.14 (0.37-3.43)	0.804
Female	Less	28 (84.8)	46 (68.7)		
	More	5 (15.2)	21 (31.3)	0.39 (0.11-1.27)	0.084
Age >30 years					
All	Less	242 (79.9)	391 (77.1)		
	More	61 (20.1)	116 (22.9)	0.85 (0.59-1.22)	0.360
Male	Less	60 (75.9)	111 (76.0)		
	More	19 (24.1)	35 (24.0)	1.00 (0.50-2.00)	0.990
Female	Less	182 (81.3)	280 (77.6)		
	More	42 (18.8)	81 (22.4)	0.80 (0.51-1.23)	0.287

*Less inbred F<0.0625, More inbred F≥0.0625

Table 4. Inbreeding Characteristics of Patients with Most Common Cancers and Controls

Site	N	CP*	p-value	Mean F	p-value	MI[$]	p-value
Breast							
Ca	167	40 (24)	0.637	0.014±0.03	0.610	30 (18)	0.266
Con	379	98 (26)		0.015±0.03		84 (22)	
Skin							
Ca	23	5 (22)	0.503	0.012±0.02	0.449	4 (17)	0.492
Con	87	25 (29)		0.017±0.03		21 (24)	
Leukemia and lymphoma							
Ca	66	21 (32)	0.637	0.018±0.03	0.686	15 (23)	0.860
Con	157	45 (29)		0.016±0.03		34 (22)	
Colorectal							
Ca	23	9 (39)	0.589	0.025±0.04	0.325	7 (30)	0.755
Con	132	44 (33)		0.019±0.03		36 (27)	
Thyroid							
Ca	13	4 (31)	0.705	0.008±0.02	0.455	1 (8)	0.436
Con	47	12 (26)		0.014±0.03		9 (19)	
Female genital							
Ca	25	9 (36)	0.369	0.014±0.02	0.939	5 (20)	0.929
Con	72	19 (26)		0.015±0.03		15 (21)	
Prostate							
Ca	10	5 (50)	0.156	0.017±0.02	0.601	2 (20)	0.999
Con	24	6 (25)		0.012±0.02		4 (17)	

*Consanguineous parents, N (%); [$]More inbred, N (%), F≥0.0625; Ca, cases; Con, controls

proportion of more inbred subjects was more in controls than cases for four common malignancies; breast (22.2%), skin (24.1%), thyroid (19.1%) and female genital organs (20.8%). The proportion of more inbred was among cases than controls for Leukemia and lymphoma (22.7%) colorectal (30.4%) and prostate (20%) cancer groups. However, there was no significant difference observed between cases and controls in the parental consanguinity, mean coefficient of inbreeding and proportion of more inbred subjects.

Discussion

Different types of consanguineous marriages impart to offspring a different probability of homozygosity by descent and their cancer risk may be different from that in children of biologically unrelated parents. The probability of homozygosity decreases exponentially from a more closely inbred to a less inbred offspring. Considering the high consanguinity rate among population of Qatar, it is important to examine whether parental consanguinity and different levels of inbreeding affect the cancer risk. The rate of parental consanguinity, the mean coefficient of inbreeding and more/less inbred category were the three indicators of inbreeding used to find the association between inbreeding and risk of cancer.

The present study findings revealed that inbreeding coefficient was higher among control groups (0.017) than cases (0.0155); with a similar parental consanguinity rate. This shows that the consanguinity in the studied Arab population has no impact on the development of cancer. Theoretically (Assie et al., 2008), the elimination of tumor genes would result in a lower incidence of cancer in a population with a high consanguinity rate than in a population where consanguineous marriages were rare. In United Arab Emirates (UAE), the data indicated that inbreeding in natives to the UAE (Denic et al., 2007; Abdulrazzaq et al., 1997) was associated with reduced overall risk of cancer, which is in line with our main study finding. Among Arab populations, few studies have shown an association between consanguinity and the increased risk of cancer overall (Bener et al., 2007). Another study among inbred populations in the Island off the coast of Croatia, the rates of cancer tended to be higher than in main landers from which the island populations implying that inbreeding is carcinogenic (Rudan, 1999). Among Pakistanis, increased inbreeding was associated with overall risk of cancer (Shami et al., 1991). Assie et al (2008) also reported an increased risk of cancer in inbred populations. These studies show opposite results from the present and UAE studies because in distinct ethnic groups, the risk differences may arise from different frequencies in different populations of the low-penetrance and tumor susceptibility alleles that Assie et al (2008) propose as the main mechanism of increased cancer risk. Although inbreeding was associated with reduced overall risk of cancer in studied population, parental consanguinity (35.4%) and risk of cancer (0.0189) was higher in male cancer patients than controls, but lower in female cancer patients (26.8% & 0.014). On the contrary in United Arab Emirates (Denic et al., 2007), the inbreeding coefficient was significantly lower in male cancer patients (0.0153) compared to controls (0.273). Also, among women of UAE, the inbreeding coefficient was lower among cancer patients (0.0128) than controls (0.0169) and this is in agreement with our results that inbreeding probably decreases the risk of cancer in women.

In the study sample, controls were more inbred in all studied subjects (23.6%) and women (23.8%), but the proportion of inbred was similar in male cancer patients (23.9%) and controls (23.2%). In United Arab Emirates (Denic et al., 2007), the proportion of more inbred subjects

was significantly higher in controls than cases among all studied subjects, men and women. These two similar population based case-control studies confirm the lack of association between cancers overall and parental consanguinity in the Arab population.

In the present population based study, the inbreeding coefficient was higher in controls for breast, skin, thyroid and female genital cancer groups. This reveals the lack of association between the risk of breast, skin, thyroid and female genital cancers and the inbreeding. On the other hand, in Pakistan (Liede et al., 2002), daughters of parents who were first cousins were at approximately twice the risk of breast and ovarian cancer than were daughters of unrelated parents. The effects of consanguinity were significant for case subjects with early onset of breast and ovarian cancer. Similar findings were seen in previous studies (Denic and Bener, 2001; Denic et al., 2005), showing that the coefficient of inbreeding was lower in breast cancer patients

At the same time for leukemia and lymphoma, colorectal and prostate cancer groups, the inbreeding coefficient was higher in cases. This shows that inbreeding has an effect in the development of leukemia and lymphoma, colorectal and prostate caners. In a recent population based study by Bener et al (2001), an increased incidence of leukemia and tumors was found in consanguineous families. In an early study (Abramson et al., 1978), an increased frequency of consanguinity was detected in Hodgkin lymphoma patients. A previous study performed by Bener (2001) provided evidence that consanguinity has no effect on leukemia and lymphomas. In populations where consanguinity is common, leukemia, lymphoma and other tumors are common, although the specific type of disease associated with inbreeding is neither well documented nor clearly defined. In few types of cancer (Goldgar et al, 1994), there is a striking evidence of familial aggregation. Among these types, the most frequently cited are colorectal cancer, breast and ovarian cancer and thyroid cancer. In a population based prospective study, we found that parents of colorectal cancer patients, in comparison with the general population, had a 75% increased risk of developing disease (Sonderguard et al., 1991).

The cultural practice may create different gene frequencies in consanguineous and non consanguineous families and result in a different family history of diseases. The leading hypothesis is that if there were genes or gene complexes especially with recessive inheritance responsible for genetic susceptibility to certain types of cancer, then the incidence of those cancer types should be greater in reproductively isolated population than in a control population because of prominent manifestations of such genes or genes complexes caused by inbreeding. Overall, the effect of inbreeding on the occurrence of different neoplasms is presently unknown.

The study findings emphasize that genetic counseling has to become both available and mandatory for families. Pre-marital genetic counseling could be of great importance in helping young couples to understand the high risk associated with consanguineous marriages.

The study findings revealed that although the consanguinity rate is high in the Arab population, it has no effect on the incidence of cancers overall. The inbreeding coefficient was lower in female and overall cancer patients, but higher in male cancer group. Overall, Parental consanguinity was similar in controls and cases, but it was more frequent among five most common malignancies. Although inbreeding was associated with reduced overall risk of cancer, the data revealed that among the most common types of neoplasms, the coefficient of inbreeding was higher in leukemia and lymphoma, colorectal and prostate cancer groups, but inbreeding coefficient was lower in breast, skin, thyroid and female genital cancer groups. The incidence of cancer in cases of inbreeding prompt the necessity of establishing programs to avoid the complications in the offspring.

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