2 CONSANGUINEOUS MARRIAGES AND THEIR EFFECT ON COMMON DISEASES IN THE QATARI POPULATION

Abdulbari Bener[1,2,3]
[1]Department of Epidemiology and Medical Statistics, Hamad General Hospital, Hamad Medical Corporation
[2]Department of Public Health, Weill Cornell Medical College, Qatar
[3]Evidence for Population Health Unit, School of Epidemiology and Health Sciences, The University of Manchester, Manchester, United Kingdom

Summary

Since the consanguinity rate is very high in the Middle East countries compared to other countries, it is highly important to investigate the morbidity pattern of non-communicable diseases in this region. Few studies have been conducted in the State of Qatar examining the impact of consanguinity on most common diseases. Hence, this chapter reviews the extent and nature of consanguinity in the Qatari population and its effects on common diseases. This chapter is divided into three main sections which are:

Section 1: The Prevalence of Consanguineous Marriages in Qatar
Section 2: Effects of Consanguineous Marriages on Specific Illnesses
Section 3: Autosomal Recessive Disorders and Consanguineous Marriages

The study findings in Qatar show that in a population with a high rate of consanguinity there is a significant increase in the prevalence of common diseases, like cancer, mental disorders, heart diseases, blood disorders, gastro-intestinal disorders, hypertension and hearing deficit. In addition to these studies, action taken by the government and health authorities and suggestions for further action and research are also discussed.

Background

The State of Qatar lies on the western coast of the Arabian Gulf. The country is a peninsula from south to extreme north which is approximately 160 km in length and the total area including its islands is approximately 11,493 sq km. Oil revenue and gas constitute the cornerstones of the economy and have been used wisely to build a sophisticated social and health infrastructure. Investment in health and social development has resulted in dramatic gains in the health and well-being of the people. The estimated population of the State of Qatar during the year 2008 was 1,648,449 (75.72% males and 24.28% females) with expatriates comprising 70% of the total population. The Proportion of health expenditure, excluding the private sector, in the year 2008, as a percentage of GDP was 3.1 and GDP per capita was over US$ 67,000. Table 2.1 shows some of the selected health indicators and health services in the State of Qatar (*Annual Health Report, 2008*).

Table 2.1. Rates of health service performance in Qatar during a period of 1998-2008 (*Annual Health Report, 2008*).

Variables	1998	2003	2008
Leading Causes of Deaths (%)			
Cardiovascular	36.2	20.3	14.5
RTA and Poisoning	15.6	17.8	22.4
Cancer	10.1	9.2	9.0
Endocrine, Nutritional and Metabolic diseases	3.1	12.0	5.2
Congenital Malformation	6.2	5.8	3.1
Other Causes	28.8	35.0	45.9
Incidence Rates of Selected Infectious Diseases/10,000			
Measles	2.14	0.33	0.70
Rubella	0.68	0.48	0.85
Meningococcal Infection	0.15	0.79	0.85
Typhoid Para Typhoid	0.29	0.97	0.81
Malaria	4.88	1.28	1.49
Viral Hepatitis	1.80	21.17	12.32
Pulmonary T.B	2.56	2.18	2.11
Chicken Pox	29.01	31.31	39.07
Mumps	1.99	1.33	2.04
Shigellosis	0.0	0.76	0.33
Curative Medical Service			
Hospital Services			
No. of. PHC Centers	32	30	30
Population/Center	16979	24138	48,282
No. of. Hospitals	3	6	9
No. of Bed	1,253	1468	2023
Bed per 1000 Population	2.31	2.03	1.40
Rate of Bed Occupancy	78.0	75.5	81.3
Average Days of Stay	6.8	6.9	4.7
Discharge Daily Average	124	140	167
Population/Operation	34.01	36.96	51.53
Population/Daycare surgery	61.27	48.6	94.61
% Hosp. Deliveries	98.24	98.44	98.34
Consultation length in minutes/patient	5.8± 2.4	6.6±2.1	6.9±2.5
Manpower			
No. of Doctors	968	1624	3259
Doctors/Bed	0.8	1.1	1.6
Nurse/Bed	1.9	2.8	4.2
Population/Doctors	561	446	444
Population/Dentist	3528	2577	1786
Population/Pharmacist	1386	991	1099
Population/Nurse	226	179	172

The State of Qatar is in many respects characteristic of Arab Gulf countries in relation to its small population and historically high preference for consanguineous unions (*Bener and AlAli, 2006*). Qatar is a peninsula with a set of islands that consist of sparsely populated settlements, especially located on the coast. Rapid urbanization,

explosive population growth (due to a combination of immigration of foreign workers and natural increase through a high fertility among the local population), increases in wealth and the availability of most modern amenities, and excellent communication facilities and infrastructure development has transformed Qatar in a short period of time into a wealthy modern society.

Historically, there is a high prevalence of consanguineous marriages in many communities throughout the world; this is especially the case in countries of the Middle East and Arabian Gulf States (*Bener et al., 1996*; *Bener and AlAli, 2006*; *Al-Gazali et al., 2005*; *Bener et al., 2005c*; *Jaber et al., 1997*), South Asia (*Bittles et al., 2002*), and Northern Africa (*Mokhtar and Abdel-Fattah, 2001*). While within the Middle East region, the rate of consanguinity varies, the difference in such rates is usually related to religious, racial, ethnic and socio-cultural factors, including socially accepted norms of endogamy in tribal societies (*Bener et al., 1996*). Among the major populations studied, the highest rates of consanguineous marriages have been associated with low socioeconomic levels, illiteracy and rural residence (*Mokhtar and Abdel-Fattah, 2001*; *Khoury and Massad, 1992*; *Sueyoshi and Ohtsuka, 2003*; *El-Hazmi et al., 1995*; *Radovanovic et al., 1999*; *Bener and Hussain, 2006*).

Recent studies show that 68% of all marriages in Alexandria, Egypt are consanguineous (*Mokhtar and Abdel-Fattah, 2001*), while the prevalence in Jordan varies from 51-58% (*Khoury and Massad, 1992*; *Sueyoshi and Ohtsuka, 2003*), the prevalence is 58% in Saudi Arabia (*El-Hazmi et al., 1995*), 42.1% in Kuwait (*Radovanovic et al., 1999*), 50% in the United Arab Emirates (*Bener et al., 1996; Al-Gazali et al., 2005*), 38%-52% in Qatar (*Bener and AlAli, 2006*; *Bener and Hussain, 2006*), 40-47% in Yemen (*Jurdi and Saxsena, 2003*; *Gunaid et al., 2004*), 50% in Oman (*Rajab and Patton, 2000*), and 38.6% in Iran (*Saadat et al., 2004*).

Despite marked urbanization and modernization, the prevalence of consanguineous unions in the State of Qatar is still quite high and comparable to levels reported from other countries in the Middle Eastern region. The predominance of first cousin unions amongst the consanguineously married women is part of the pattern of consanguinity reported for across much of the Middle East and countries in West and South Asia including Jordan (*Khoury and Massad, 1992*; *Sueyoshi and Ohtsuka, 2003*), Iran (*Saadat et al., 2004*), Pakistan (*Bittles et al., 2002*), as well as in Muslim countries in North Africa, such as Egypt (*Mokhtar and Abdel-Fattah, 2001*).

There are several reasons why first cousin unions are preferential and perhaps the most important reason is ease of marriage decision-making when the potential spouse is well known and considered to be part of the 'extended family'. Such marriages also tend to reinforce social and kin bonds from one to the next generation (*Bener et al., 1996*; *Bener and AlAli, 2006*). Furthermore, the level of consanguinity in the parental generation was also high among consanguineous couples, with around a third of marriages in the parental generation being reported as consanguineous. It was found parental consanguinity, in both husband and wife's family, to be a strong predictor of consanguinity in their generation (*Bener and Hussain, 2006*).

Numerous reports on the effect of inbreeding on health have focused mainly on its impact on reproduction, childhood mortality and rare Mendelian disorders (*Bittles et al., 2002*; *Charlesworth et al., 1999*; *Ben Arab et al., 2004*; *Bittles, 2003*; *Wright and Hastie, 2001*). Nevertheless, very limited information is available on the possible role of consanguinity and recessive genes in multi-factorial or polygenic common adult diseases (*Bener et al., 2005c*; *Bener and Hussain, 2006*; *Bener et al., 2001*). This chapter will focus on the impact of high consanguinity on the prevalence of common diseases in the Qatari population.

The real life data that will be considered in this chapter will be divided into three main sections. The first section discusses the prevalence and the pattern of consanguineous marriages. The second section discusses the correlation between consanguineous marriages and specific illnesses. Also in this section, a detailed discussion of the relationship between consanguinity and type 2 diabetes mellitus (T2DM) and asthma respectively; these two diseases are discussed in detail, as the former, is the most common adult chronic disease among the Qatari population and the latter is the most prevalent disease among children. The third section describes a study done in Qatar by Hamad Medical Corporation in partnership with the University Children's Hospital in Heidelberg, Germany which examined the link between autosomal recessive disorders and consanguineous marriages.

Prevalence of Consanguineous Marriages in Qatar

The rate of consanguinity is relatively high in Qatar, with a rate of 51.0%, and predominantly first cousin marriages comprising 26.7% of all marriages. The most common pattern of first cousin unions was type 1 (paternal parallel first cousin), which constituted 17.6% of all marriages, and is similar to rates in other Arab countries (*Bener and Al-Ali, 2006*; *Khoury and Massad, 1992*; *Gunaid et al., 2004*; *Khlat and Khoury, 1991*; *Tamim et al., 2003*).

Consanguinity in current generation compared to parental generation and the associated coefficient of inbreeding are presented in Table 2.2 (*Bener et al., 2007b*). The mean age ±S.D. of the 876 women interviewed was 39.6 ±8.57 years. The rate of consanguinity in the present generation was 51% [95% CI = 47.7- 54.4]. The most common type of consanguineous marriage was first cousin marriage (26.7%). Of these, type I (patrilateral parallel cousin marriages) constituted marriages of first cousin unions, while type II (patrilateral cross cousin marriages) constituted 2.5% of all marriages, type III

Table 2.2. Consanguinity in current generation compared to parental generation (*n*= 876; *Bener et al., 2007b*).

Degree of Consanguinity	Current Generation			Husband's Parents			Wife's Parents		
	n	*%*	*IC**	*n*	*%*	*IC*	*n*	*%*	*IC*
No consanguinity	429	49.0		508	58.0		523	(59.7)	
Consanguinity	447	51.0		368	32.0		353	(40.3)	
Double first cousin	38	4.3	0.005375	25	2.9	0.003567	7	(0.8)	0.000999
First cousin (father's side uncle) Type I	154	17.6	0.016624	114	13.0	0.013413	121	(13.8)	0.014412
First cousin (mother's side aunt) Type II	22	2.5		27	3.1		21	(2.4)	
First cousin (mother's side uncle) Type III	25	2.9		16	1.8		20	(2.3)	
First cousin (Father's side aunt) Type IV	32	3.7		31	3.5		40	(4.6)	
Subtotal	233	26.7		188	21.4		202	(23.1)	
First cousins once removed	34	3.9	0.001215	21	2.4	0.00075	15	(1.7)	0.000463
Second cousin	26	3.0	0.000468	39	4.5	0.000695	26	(3.0)	0.01641
Less than second cousin	116	13.2		95	10.8		103	(11.8)	
Total coefficient of inbreeding**			**0.023724**			**0.018425**			**0.016410**

*Inbreeding coefficient; **Inbreeding coefficient up to 2nd cousins

2.9%, and type IV 3.7%. The second most common category of consanguineous marriages was double first cousin marriages (4.3%). The prevalence of first cousin once removed and second cousin marriages was 3.9% and 3.0% respectively, while 13.2% of all marriages were between more distant cousins (Table 2.2).

The rate of consanguinity in the parental generation was similar in the respondent's parents (51.0%) whereas the consanguinity rate among the respondent's husband's parents was 32.0% ($p<0.001$). The coefficient of inbreeding in the respondent, husband's parents and respondent's parents were 0.023724, 0.018425, and 0.016410, respectively. All types of consanguineous marriages were higher in the respondent's generation, particularly first cousin (26.7% versus 21.4% paternal and 23.1% maternal) and double first cousins (4.3% versus 2.9% paternal and 0.8% maternal; *Bener et al., 2007b*). A study conducted in an Eastern province of Saudi Arabia found the rate of consanguineous marriage to be 52.0% with an average inbreeding coefficient of 0.0312 which is slightly higher than the rate in Qatar (*Al-Abdulkareem and Ballal, 1998*).

Table 2.3. Consanguineous marriages and their effect on the most common diseases in the Qatari population.

Disease	Consanguinity Rate	Reference
Hypertension	31.8%	*Bener et al., 2004*
Breast cancer	29.2%	*Denic and Bener, 2005*
Asthma	34.8%	*Bener et al., 2005a*
Hearing loss	60.5%	*Bener et al., 2005b*
Diabetes	47.6%	*Bener et al., 2005c*
Cardiomyopathy	57.1%	*El-Menyar and Bener, 2006*
Consanguinity in child health	54%	*Bener and Hussain, 2006*
Coronary artery disease	49.5%	*Daghash and Bener, 2007*
Diabetics	49%	*Bener et al., 2007a*
Consanguinity effect on diseases	51%	*Bener et al., 2007b*
Breast feeding	32.9% - 38.5%	*Ehlayel and Bener, 2008*
Vision loss	39.7%	*Bener et al., 2008a*
ADHD	33.9%	*Bener et al., 2008b*
Hearing loss	42.1%	*Bener et al., 2008c*
Type-1 diabetes and vitamin D deficiency	48.8%	*Bener et al., 2008d*
Vitamin D deficiency	44.1%	*Bener et al., 2008e*
Genetics of diabetics	31.9%	*Badii and Bener, 2009*
Diabetics	31.2%	*Bener et al., 2009a*
Cancer	29.5%	*Bener et al., 2009b*
Metabolic syndrome	36.1%	*Bener et al., 2009c*

Effects of Consanguineous Marriages on Specific Illnesses in Qatar

Consanguineous marriages and its effect on the most common diseases in the Qatari population are presented in Table 2.3. The frequency of specific illnesses in the offspring of all consanguineous and non-consanguineous couples is shown in Table 2.4. There was no statistically significant difference in the two groups in relation to sensory impairment such as blindness, deafness or other hearing problems. However, the offspring of all consanguineous couples had a significantly higher risk of mental retardation, epilepsy, asthma, leukemia, and diabetes mellitus. Although the risk ratios for leukemia appeared to be elevated, the difference was not statistically significant. Similarly, no consistent pattern was seen for other chronic conditions (Table 2.4).

The prevalence of common adult diseases among parents and the current generation and their offspring (*Bener et al., 2007b*) by consanguineous versus non-consanguineous mating in the Qatari population is presented in Table 2.5. The current generation of consanguineous parents had a significantly higher risk than the non-consanguineous parents for such diseases as: cancer, mental disorders, heart diseases, gastro-intestinal disorders, hypertension, hearing deficit, diabetes mellitus, blood disorders, and

Table 2.4. Specific illness in offspring of all consanguineous and non-consanguineous couples (*Bener and Hussain, 2006*).

Variables	Consanguineous *n= 818 (%)*	Non-Consanguineous *n= 697 (%)*	RR [95% CI]	p-Value
Parents consanguinity	**396 (48.4)**	**236 (33.9)**	**1.31 [1.20,1.44]**	**<0.001**
Spouse parents consanguineous	**365 (44.6)**	**183 (26.3)**	**1.42 [1.30,1.56]**	**<0.001**
Illness among offspring				
Blindness	10 (1.2)	8 (1.1)	1.03 [0.68,1.56]	0.894
Deafness	11 (1.3)	14 (2.0)	0.81 [0.52,1.27]	0.312
Other hearing problem	11 (1.3)	6 (0.9)	1.20 [0.84,1.71]	0.373
Mental retardation	30 (3.7)	3 (0.4)	1.71 [1.52,1.92]	<0.001
Epilepsy	45 (5.5)	6 (0.9)	1.67 [1.50,1.87]	<0.001
Asthma	189 (23.1)	84 (12.1)	1.37 [1.24,1.51]	<0.001
Anemia	38 (4.6)	29 (4.2)	1.05 [0.85,1.30]	0.647
Leukemia	17 (2.1)	4 (0.6)	1.51 [1.22,1.87]	0.013
Other neoplasm	4 (0.5)	6 (0.9)	0.74 [0.35,1.58]	0.373
Diabetes mellitus	45 (5.5)	17 (2.4)	1.36 [1.16,1.60]	0.003
Coronary heart disease	10 (1.2)	11 (1.6)	0.88 [0.56,1.38]	0.555
Cerebrovascular diseases	2 (0.2)	2 (0.3)	0.93 [0.35,2.47]	0.625
Hypertension	14 (1.7)	18 (2.6)	0.81 [0.54,1.20]	0.240
Chronic liver disease	9 (1.1)	11 (1.6)	0.83 [0.51,1.35]	0.417

Table 2.5. Prevalence of common adult diseases among current generation and their offspring by consanguineous (C) and non consanguineous (NC) unions (*Bener et al., 2007b*).

Current Generation	*C= 330*	*NC= 523*	OR	p-Value
Cancer	36	8	7.88 (3.46 - 18.64)	<0.001
Blood disorder	27	13	3.50 (1.70 - 7.27)	<0.001
Mental disorders	9	3	4.86 (1.20 - 22.78)	0.009
Heart diseases	27	17	2.65 (1.37 - 5.18)	0.002
Bronchial asthma	22	8	4.60 (1.92 - 11.38)	<0.001
GI disorders	10	6	2.69 (0.88 - 9.09)	0.048
Hypertension	27	5	9.23 (3.34 - 27.60)	<0.001
Hearing deficit	7	1	11.31 (1.40-245.78)	0.004
Diabetes mellitus	46	24	3.37 (1.96 - 5.82)	<0.001
Offspring	***C= 447***	***NC= 429***	**OR**	**p-Value**
Cancer	45	13	3.58 (1.84 - 7.10)	<0.001
Blood disorder	17	8	2.08 (0.84 - 5.31)	0.085
Mental disorders	1	3	0.32 (0.01 - 3.42)	0.364
Heart diseases	38	31	1.19 (0.71 - 2.01)	0.484
Bronchial asthma	17	22	0.73 (0.37 - 1.46)	0.342
GI disorders	15	7	2.09 (0.79 - 5.72)	0.103
Hypertension	22	14	1.53 (0.74 - 3.21)	0.217
Hearing deficit	7	1	6.81 (0.84-147.88)	0.070
Diabetes mellitus	47	36	1.28 (0.79 - 2.07)	0.283

bronchial asthma. There was also a significant difference in the prevalence between the offspring of consanguineous versus non-consanguineous mating for cancer cases. All reported diseases were more frequent in offspring of consanguineous marriages.

It has been reported that several genetic disorders, congenital malformations and reproductive wastage are more frequent in consanguineous marriages (*Bittles et al., 1991*). The risk for birth defects in the offspring of first cousin marriage has been estimated to increase sharply compared to non-consanguineous marriages (*Stoll et al., 1992*). In several countries, the occurrence of malignancies, congenital abnormalities, mental retardation and physical handicap was significantly higher in offspring of consanguineous than non-consanguineous marriages (*Bener et al., 1996*; *Bener and Hussain, 2006*; *Abdulrazzaq et al., 1997*), which are confirmative to the results in Qatar (*Bener et al., 2007b*).

Those findings showed that consanguinity did not result in reproductive wastage, but was an important factor in causing specific illnesses in offspring. Close consanguinity has probably been practiced in the Gulf countries (*El-*

Hazmi et al., 1995; *Bener et al., 1996*; *Bener and AlAli, 2006*; *Al-Gazali et al., 2005*; *Bener and Hussain, 2006*; *Al-Abdulkareem and Ballal, 1998*; *Radovanovic, 1999*), including Qatar for over 100 generations.

Over the last century, there has been rapid socio-economic development in many countries resulting in a move from a traditional to a modern way of life. The changes in diet and lifestyle habits combined with increased longevity have formed the basis for dramatic increases in the prevalence of type 2 diabetes mellitus (T2DM) in both developed and developing countries. The prevalence of diabetes varies widely among populations according to race, lifestyle and urbanization (*Bener et al., 2005c*; *Bener et al., 2009b*). The State of Qatar is a rapidly developing country with a change that influenced the lifestyle of the people towards urbanization, particularly over the recent decades. This has led to diabetes becoming the most prevalent chronic disease among adults in Qatar. Thus, conducting a study on diabetes mellitus and its associated risk factors is of paramount importance. The possible causes of this 'diabetic epidemic' are population growth, longer survival, urbanization, low physical activity, obesity, excessive energy intake and other factors as is reported recently by *Bener et al. (2005c*; *2007a*; *2009b)*. Another possible cause, which will be discussed in this chapter, is the inheritance of this disease from the parental generation.

The presence of maternal and paternal history of T2DM in relatives of 586 T2DM patients from Qatar was investigated to evaluate its influence on the clinical characteristics of this disease. A questionnaire was distributed to examine this relationship. The maternal and paternal history was scrutinized over two generations and confirmed by medical records. Table 2.6 shows the frequencies of patients who reported diabetic relatives.

In summary, 45.2% of the patients reported at least one first-degree affected familial member. History of T2DM among mothers was reported by a higher percentage of the diabetic patients compared to the history of T2DM among fathers (36.3% versus 17.8%; $p< 0.001$). The same pattern was observed for history of T2DM among maternal aunts or uncles compared to the paternal relatives (16.9% versus 10.6%; $p< 0.001$); thus, suggesting an excess of maternal transmission in this generation. In addition, the excess of maternal history was reinforced by results found in the second generation: 18.4% of the diabetic mothers had diabetic children when compared to 11.2% of the diabetic fathers ($p<0.001$).

Another highly prevalent disease, Asthma is one of the most common disorders in childhood (*Bener and Janahi, 2005*). Accumulating evidence indicates that asthma is becoming increasingly common and is the most common chronic illness of childhood and there is a wide consensus that asthma and allergies have become more prevalent among children, especially in developed societies. The environmental factors responsible for asthma are not well understood, but changes in lifestyle leading to changes in

Table 2.6. Distribution of type 2 diabetes mellitus (T2DM) among first degree relatives with their family history prevalence rate (*n*= 586; *Bener et al., 2005c*; *Badii et al., 2008*; *Bener et al., 2009b*).

Family Relationship	*n*	%	p-Value
At least one first degree relative	265	45.2	
Mother	212	36.3	p<0.001
Father	104	17.7	
Siblings	195	33.2	
Maternal aunt / uncle	99	16.9	p<0.001
Paternal aunt / uncle	62	10.6	
Offspring			
When the patient is male	126	21.5	p<0.001
When the patient is female	87	14.8	
Second Generation			
Clear maternal history (with diabetic mother)	108	18.4	p<0.001
Clear paternal history (with diabetic father)	66	11.2	

immediate environment may have an adverse effect on the prevalence of asthma. More than the environmental factors, it is understood that the genetic factors got more influence on Asthma. A recent study of *Bener and Janahi (2005)* investigated the familial and environmental risk factors associated with asthma among Qatari school children aged 6-12 years.

The transition of asthma via each parent to the next generation was focused and it was found that unlike T2DM, the prevalence of asthma in fathers was found to effect the next generation to a similar degree of that of mothers. Thus, while, the prevalence of asthma in fathers of non-asthmatic children was 6.8%, it reached 18.2% among asthmatic children [relative risk 2.2 (95% CI 1.9-2.6; $p<0.001$)]. Similar values were observed for asthma in mothers (Table 2.7). It was found that 35.0% had either parent with the above condition and this contrasted with 14.8% of non-asthmatic children who had either parent with asthma and the difference being statistically significant ($p<0.001$).

A similar pattern was observed when parent-child association of allergic rhinitis, symptoms was investigated, where 25.3% and 26.5% of asthmatic children had fathers and mothers with allergic rhinitis, respectively. It was also found that 41.8% of asthmatic children had either parents with allergic rhinitis, and 10.0% of asthmatic children had both parents with allergic rhinitis. The prevalence rates of eczema in fathers, mothers, either parents and both parents of children who were asthmatic were 17.7%, 19.6%, 31.6%, and 5.4%, respectively.

Impact of Consanguinity on Cancer in a Highly Endogamous Population

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. Among Arab populations, an association between consanguinity and the increased risk of cancer overall was reported *(Bener et al., 2007b)*. Considering the high consanguinity rate among population of Qatar, it was examined whether parental consanguinity and different levels of inbreeding affect the cancer risk. Inbreeding characteristics of cancer patients and controls presented in Table 2.8 revealed that overall consanguinity has no impact on the development of cancer in the Arab population in Qatar. Although inbreeding was associated with reduced overall risk of cancer in Qatar 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% and 0.014). Theoretically, it was reported that 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 are rare (*Assie et al., 2008*). These results show that inbreeding probably decreases the risk of cancer in women.

The inbreeding characteristics of patients with most common cancers and controls were further investigated in Qatar population (Table 2.9). It has been reported that the inbreeding coefficient was higher in leukemia and lymphoma, colorectal and prostate cancer groups. This shows that inbreeding has an effect in the development of leukemia and lymphoma, colorectal and prostate cancers. Also, a previous population based study reported an increased incidence of leukemia and tumors in consanguineous families (*Bener et al., 2001*). In populations where consanguinity is common, leukemia, lymphoma and other tumors are frequent. In few types of cancer, there is a striking evidence of familial aggregation (*Goldgar et al., 1994*). The most frequently cited are colorectal cancer, breast and ovarian cancer and thyroid cancer. Parents of colorectal cancer patients had a 75% increased risk of developing disease, in comparison with general population (*Sonderguard et al., 1991*). Since colon cancer is inherited as an autosomal dominant manner, consanguinity increases its potential incidence. At the same time for breast, skin, thyroid and female genital cancer groups, the inbreeding coefficient was lower in cancer groups. This reveals the lack of association between the risk of breast, skin, thyroid and female genital cancers and inbreeding.

A recent case-control study (*Bener et al., 2010a*) on the impact of family history and life style habits on colorectal cancer risk supported the above study findings that family history and parental consanguinity to be strongly associated with the development of colorectal cancer among the Arab population in Qatar (Table 2.10). This study revealed that family history of colorectal cancer was significantly higher in cases (41.8%) than in healthy subjects (29.1%), particularly in the first degree (22.6%) and second-degree (11.6%) relatives. This study suggests that a family history of colorectal cancer is an important risk factor for the development of colorectal cancer in this population and confirms the observation reported by others that a family history of colorectal cancer increases

Table 2.7. Relationship of parental asthma, allergic rhinitis, and eczema to children's asthma (*Bener et al., 2005a*).

	Father			Mother			Either Parent			Both Parents		
	A	*NA*	*RR (95% CI)*	*A*	*NA*	*RR (95% CI)*	*A*	*NA*	*RR (95% CI)*	*A*	*NA*	*RR (95% CI)*
Asthma	118 (18.2)	179 (6.8)	2.2 (1.9-2.6)*	140 (21.6)	248 (9.4)	2.1 (1.8-3.4)*	227 (35.0)	390 (14.8)	2.3 (2.0-2.7)*	31 (4.8)	37 (1.4)	2.4 (1.8-3.1)*
Allergic rhinitis	164 (25.3)	411 (15.6)	1.6 (1.4-1.9)*	172 (26.5)	436 (16.6)	1.6 (1.4-1.8)*	271 (41.8)	728 (27.6)	1.6 (1.4-1.9)*	65 (10.0)	119 (4.5)	1.9 (1.5-2.3)*
Eczema	115 (17.7)	329 (12.5)	1.4 (1.2-1.6)*	127 (19.6)	359 (13.6)	1.4 (1.2-1.7)*	205 (31.6)	583 (22.1)	1.5 (1.3-1.7)*	35 (5.4)	104 (3.9)	1.3 (0.9-1.8)†

A = Asthmatic; NA = Non-asthmatic; RR = Relative risk; CI = Confidence interval; * p<0.001; † Not significant

Table 2.8. Inbreeding characteristics of cancer patients and controls.

Variables	Case *n= 370*	Control *n= 635*	p-Value
All			
Mean age	47.3±16.7	45.7±15.9	0.123
Parents consanguineous	109(29.5)	190(29.9)	0.877
Mean coefficient of inbreeding	0.0155±0.03	0.017±0.03	0.439
Males			
Mean age	46.2±21.7	44.2±19.2	0.392
Parents consanguineous	40(35.4)	63(30.4)	0.364
Mean coefficient of inbreeding	0.0189±0.03	0.0168±0.03	0.534
Females			
Mean age	47.8±14	46.4±14.1	0.205
Parents consanguineous	69(26.8)	127(29.7)	0.428
Mean coefficient of inbreeding	0.014±0.03	0.0171±0.03	0.177

Table 2.9. Inbreeding characteristics of patients with most common cancers and controls.

Variables	*n*	Consanguineous Parents *n*(%)	p-Value	Mean F	p-Value	More Inbred* *n*(%)	p-Value
Breast							
Cases	167	40(24.0)	0.637	0.014±0.03	0.610	30(18)	0.266
Controls	379	98(25.9)		0.015±0.03		84(22.2)	
Skin							
Cases	23	5(21.7)	0.503	0.012±0.02	0.449	4(17.4)	0.492
Controls	87	25(28.7)		0.017±0.03		21(24.1)	
Leukemia and lymphoma							
Cases	66	21(31.8)	0.637	0.018±0.03	0.686	15(22.7)	0.860
Controls	157	45(28.7)		0.016±0.03		34(21.7)	
Colorectal							
Cases	23	9(39.1)	0.589	0.025±0.04	0.325	7(30.4)	0.755
Controls	132	44(33.3)		0.019±0.03		36(27.3)	
Thyroid							
Cases	13	4(30.8)	0.705	0.008±0.02	0.455	1(7.7)	0.436
Controls	47	12(25.5)		0.014±0.03		9(19.1)	
Female genital							
Cases	25	9(36.0)	0.3691	0.014±0.02	0.939	5(20)	0.929
Controls	72	19(26.4)		0.015±0.03		15(20.8)	
Prostate							
Cases	10	5(50.0)	0.156	0.017±0.02	0.601	2(20)	0.999
Controls	24	6(25.0)		0.012±0.02		4(16.7)	

*More inbred F≥0.0625

Table 2.10. Characteristics of consanguinity and family history of colorectal cancer among patients and controls (*n*= 428).

Variables	Cases	Controls	p-Value
Overall frequency	146	282	
Parents consanguineous			
Yes	52(35.6)	83(29.4)	0.231
No	94(64.4)	199(70.6)	
Mean coefficient of inbreeding	0.019	0.016	0.440
Age <50 years frequency	55	100	
Parents consanguineous			
Yes	16(29.1)	31(31.0)	0.948
No	39(70.9)	69(69.0)	
Mean coefficient of inbreeding	0.016	0.019	0.464
Age ≥50 years frequency	91	182	
Parents consanguineous			
Yes	36(39.6)	52(28.6)	0.090
No	55(60.4)	130(71.4)	
Mean coefficient of inbreeding	0.020	0.015	0.112
Family history of cancer			
Yes	61(41.8)	82(29.1)	<0.011
No	85(58.2)	200(70.9)	
Cancer in type of relatives			
1st Degree	33(22.6)	39(13.8)	0.030
2nd Degree	17(11.6)	9(3.2)	0.001
3rd Degree	11(7.5)	4(1.4)	0.002

the risk of colorectal cancer (*Slattery et al., 2003*; *Martinez, 2005*). First degree relative of individuals with colorectal cancer are known to have an approximately two fold increased risk of sporadic colorectal cancer (*Kerber et al., 1998*). Furthermore, parental consanguinity was higher in colorectal patients with a higher inbreeding coefficient (35.6%; 0.019), compared to healthy subjects (29.4%; 0.016). This shows that increased evidence of colorectal cancer is among persons with a family history of colorectal cancer and families in which multiple family members affected with colorectal cancer. These study findings confirm that inheritance plays a special role in colorectal cancer development.

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.

A further study on the possible effect of consanguinity on the risk of breast cancer also confirmed that there is no association between the risk of breast cancer and the parental consanguinity among Arab women residing in Qatar (*Bener et al., 2010b*). The coefficient of consanguinity was higher in healthy women than in breast cancer patients (Table 2.11). The consanguinity rate does not appear to be an intensive indicator of the effect of consanguinity on the risk of developing breast cancer. The family history of breast cancer was positive more often in cases.

Autosomal Recessive Disorders and Consanguineous Marriages

Inbreeding over centuries along with high rates of consanguinity among the Qatari population and some groups of expatriates, in addition to large family sizes

Table 2.11. Characteristics of consanguinity and family history of breast cancer patients and controls (*n*= 508).

Variables	Cases	Controls	Odd Ratio [95% CI]	p-Value
Overall frequency	167	341		
Parents consanguineous				
Yes	40(24.0)	110(32.3)	0.66 [0.42 – 1.03]	0.068
No	127(76.0)	231(67.7)		
Mean coefficient of inbreeding	0.014	0.018		0.125
Age <50 years frequency	97	218		
Parents consanguineous				
Yes	25(25.8)	72(33.0)	0.70 [0.40 -1.24]	0.198
No	72(74.2)	146(67.0)		
Mean coefficient of inbreeding	0.015	0.019		0.340
Age ≥50 years frequency	70	123		
Parents consanguineous				
Yes	15(21.4)	38(30.9)	0.61[0.29 – 1.28]	0.157
No	55(78.6)	85(69.1)		
Mean coefficient of inbreeding	0.013	0.018		0.052
Family history of breast cancer				
Yes	24(14.4)	21(6.2)	2.56 [1.32 – 4.96]	0.002
No	143(85.6)	320(93.8)		
Breast cancer in family				
Mother	7(4.2)	7(2.1)		0.246*
Sister	6(3.6)	2(0.6)		0.018*
Grand mother	3(1.8)	3(0.9)		0.400
Aunt	8(4.8)	11(3.2)		0.383

*Fisher Exact Test used

and rapid population growth, have contributed to a high frequency of autosomal recessive disorders. In December 2003, Hamad Medical Corporation in Doha, Qatar, and the University Children's Hospital of Heidelberg in Germany started an extended state-wide neonatal screening program for metabolic and endocrine disorders.

The laboratory for this joint venture was situated in Heidelberg, Germany (*Elsaid et al., 2007*). All aspects of the screening process had to be adapted to the unique situation of the laboratory being 6000 km away from the birthplace of the neonates. Within 32 months, samples of 25,214 neonates were screened. In 28 cases, an endocrine or metabolic diagnosis was identified (incidence 1:901, in Germany 1:1728). In particular, a variety of monogenic metabolic diseases were prevalent, with 19 patients detected, giving an incidence of metabolic diseases of 1:1327 (Germany 1:2517).

Each Euro spent on the screening program saved more than 25 Euros in health and social costs. The program revealed a high incidence of treatable inborn metabolic diseases in the population of Qatar. A reliable screening for classical homocystinuria, which showed a unique incidence of >1:3000, and for sickle cell disease, has now been added.

The detection, treatment and possible prevention of disease for individually rare genetic diseases has developed into one of the major health problems of the 21st century (*Christianson et al., 2006*; *Fang-Hoffmann et al., 2006*). The success of the joint project presented in this paper shows that it is possible to implement an effective and efficient extended newborn screening program covering the complete population of a small country within months. From the beginning, this program provided immediate benefit to the patients and their families. A child with a severe handicap because of a late diagnosed metabolic disorder in Germany requires 30,000–50,000 Euros per year just for direct health care costs. In Qatar, excellent facilities for care of the chronically ill and handicapped people have been established. They entail similar or even higher costs. In addition, the effectiveness of neonatal screening is greater than in Germany owing to the increased incidence of metabolic disorders in this population.

The excess risk that an autosomal recessive disorder could be expressed in the progeny of a consanguineous union is inversely proportional to the frequency of the disease allele in the total gene pool (*Bittle et al., 2002*). For this reason, during the last decade many rare disease genes have been identified and their chromosomal locations mapped by studying highly inbred families with multiple affected members (*Moynihan et al., 1999*; *McHale et al., 2000*). The main impact of inbreeding is an increase in the rate of homozygotes for recessive disorders (*Bener et al., 1996*; *Bener and Hussain, 2006*; *Bittles, 2003*; *Robert and Pembrey, 1978*). It is believed, although not proven, that high rates of inbreeding over multiple generations lead to elimination of deleterious recessive genes from the gene pool (*Robert and Pembrey, 1978*). However, studies from South India where inbreeding has been practiced for more than 2000 years showed that there has been no appreciable elimination of recessive lethals and sub-lethals in the gene pool (*Devi et al., 1987*).

Limitations and Suggestions for Further Research and Action

The quality of health services in Doha and semi-urban areas of Qatar is high, and access to good quality medical care is not an issue for most of the population. The absence of a comprehensive disease registry and database makes it difficult to make a sound assessment of the health impact of consanguinity at the community level. Furthermore, it is worth noting that there might be some bias in data associated with the ages of participants and reporting of diseases such as cancer, hypertension, diabetes, and coronary heart diseases, which may arise later in life (in both cases and controls). Further in-depth studies are needed to determine the consanguinity rates in relation to morbidity and mortality in this population because consanguinity is increasing in the current generation, in spite of better education. The overall conclusion is that Qatar's health system has been improved after the Joint Commission International (JCI) accreditation. Still, there is a need for specific planning for an increased medical workforce in PHC, which is specifically trained for the area. There is an urgent need to acquire more accurate data from PHC Centers in Qatar and some attempts should be made to obtain reliable diseases registry and to assess outcome in relation to services in addition to process.

Conclusion

This study shows a higher incidence of certain diseases in consanguineous couples and that in a population with a high rate of consanguinity, there is a significant increase in the prevalence of common adult diseases such as: cancer, mental disorders, heart diseases, gastro-intestinal disorders, hypertension, congenital abnormalities, vision loss, hearing deficit, and diabetes mellitus.

References

Abdulrazzaq YM, Bener A, al-Gazali LI, al-Khayat AI, Micallef R, Gaber T. A study of possible deleterious effects of consanguinity. *Clin Genet*. 1997; 51(3):167-73.

Al-Abdulkareem AA, Ballal SG. Consanguineous marriage in an urban area of Saudi Arabia: rates and adverse health effects on the offspring. *J Community Health*. 1998; 23(1):75-83.

Al-Gazali LI, Alwash R, Abdulrazzaq YM. United Arab Emirates: communities and community genetics. *Community Genet*. 2005; 8(3):186-96.

Annual Health Report. *Vital Health Statistics*. Doha, State of Qatar, 2008.

Assie G, LaFramboise T, Platzer P, Eng C. Frequency of germline genomic homozygosity associated with cancer cases, *JAMA*. 2008; 299:1437-45.

Badii R, Bener A, Zirie M, Al-Rikabi A, Simsek M, Al-Hamaq AO, Ghoussaini M, Froguel P, Wareham NJ. Lack of association between the Pro12Ala polymorphism of the PPAR-gamma 2 gene and type 2 diabetes mellitus in the Qatari consanguineous population. *Acta Diabetol*. 2008; 45(1):15-21.

Ben Arab S, Masmoudi S, Beltaief N, Hachicha S, Ayadi H. Consanguinity and endogamy in Northern Tunisia and its impact on non-syndromic deafness. *Genet Epidemiol*. 2004; 27(1):74-9.

Bener A, Abdulrazzaq YM, al-Gazali LI, Micallef R, al-Khayat AI, Gaber T. Consanguinity and associated socio-demographic factors in the United Arab Emirates. *Hum Hered*. 1996; 46(5):256-64.

Bener A, Al Qahtani R, Teebi AS, Bessisso M. The prevalence of attention deficit hyperactivity symptoms in schoolchildren in a highly consanguineous community. *Med Princ Pract*. 2008b; 17(6):440-6.

Bener A, Alali KA. Consanguineous marriage in a newly developed country: the Qatari population. *J Biosoc Sci*. 2006; 38(2):239-46.

Bener A, Al-Ali M, Hoffmann GF. Vitamin D deficiency in healthy children in a sunny country: associated factors. *Int J Food Sci Nutr*. 2009a; 60 Suppl 5:60-70.

Bener A, Al-Mahdi H, Warid F, Darwish S. Correlation between Vision Loss and its risk factors in elderly people in a rapidly developed Arabian society. *Asian J Ophthal*. 2008a; 10:126-9.

Bener A, Alsaied A, Al-Ali M, Hassan AS, Basha B, Al-Kubaisi A, Abraham A, Mian M, Guiter G, Tewfik I. Impact of lifestyle and dietary habits on hypovitaminosis D in type 1 diabetes mellitus and healthy children from Qatar, a sun-rich country. *Ann Nutr Metab*. 2008d; 53(3-4):215-22.

Bener A, Al-Suwaidi J, Al-Jaber K, Al-Marri S, Dagash MH, Elbagi IE. The prevalence of hypertension and its associated risk factors in a newly developed country. *Saudi Med J*. 2004; 25(7):918-22.

Bener A, Denic S, Al-Mazrouei M. Consanguinity and family history of cancer in children with leukemia and lymphomas. *Cancer*. 2001; 92(1):1-6.

Bener A, El Ayoubi HR, Ali AI, Al-Kubaisi A, Al-Sulaiti H, Does Consanguinity lead to decreased incidence of breast cancer. *Cancer Epidemiol*. 2010a; 34:413-418.

Bener A, El Ayoubi HR, Chouchane L, Ali AI, Al-Kubaisi A, Al-Sulaiti H, Teebi AS. Impact of consanguinity on cancer in a highly endogamous population. *Asian Pac J Cancer Prev*. 2009c; 10(1):35-40.

Bener A, Elhakeem AA, Abdulhadi K. Is there any association between consanguinity and hearing loss. *Int J Pediatr Otorhinolaryngol*. 2005b; 69(3):327-33.

Bener A, Hussain R, Teebi AS. Consanguineous marriages and their effects on common adult diseases: studies from an endogamous population. *Med Princ Pract*. 2007b; 16(4):262-7.

Bener A, Hussain R. Consanguineous unions and child health in the State of Qatar. *Paediatr Perinat Epidemiol*. 2006; 20(5):372-8.

Bener A, Janahi I. Association between childhood atopic disease and parental atopic disease in a population with high consanguinity. *Coll Antropol*. 2005a; 29(2):677-82.

Bener A, Moore MA, Ali R, El Ayoubi HR. Impacts of Family History and Life style Habits on Colorectal Cancer Risk: A Case-Control study in Qatar, *Asian Pacific J Cancer Prev*. 2010b; 11:1-6.

Bener A, Salahaldin AH, Darwish SM, Gansan L. Association between hearing loss and type 2 diabetes mellitus in elderly people in rapidly developed society. *Biomed Res*. 2008c; 19(3):187-93.

Bener A, Zirei M, Daghash M, Al-Hamaq AOA, Heller R. Lipids, lipoprotein (a) profile and HbA1c in Qatari Type 2 diabetic patients. *Biomed Res*. 2007a; 18:97-102.

Bener A, Zirie M, Al-Rikabi A. Genetics, obesity, and environmental risk factors associated with type 2 diabetes. *Croat Med J*. 2005c; 46(2):302-7.

Bener A, Zirie M, Janahi IM, Al-Hamaq AO, Musallam M, Wareham NJ. Prevalence of diagnosed and undiagnosed

diabetes mellitus and its risk factors in a population-based study of Qatar. *Diabetes Res Clin Pract*. 2009b; 84(1):99-106.
Bener A, Zirie M, Musallam M, Khader YS, Al-Hamaq AO. Prevalence of metabolic syndrome according to Adult Treatment Panel III and International Diabetes Federation criteria: a population-based study. *Metab Syndr Relat Disord*. 2009d; 7(3):221-9.
Bittles AH, Grant JC, Sullivan SG, Hussain R. Does inbreeding lead to decreased human fertility? *Ann Hum Biol*. 2002; 29(2):111-30.
Bittles AH, Mason WM, Greene J, Rao NA. Reproductive behavior and health in consanguineous marriages. *Science*. 1991; 252(5007):789-94.
Bittles AH. Consanguineous marriage and childhood health. *Dev Med Child Neurol*. 2003; 45(8):571-6.
Charlesworth B, Hughes KA. The maintenance of genetic variation in life history traits. In: Singh RS, Krimbas CB (editors). *Evolutionary genetics: from molecules to morphology*. Vol. 1, Cambridge University Press, 1999.
Daghash MH, Bener A, Zirie M, Dabdoob W, Al-Hamaq AO, Al-Arabi ZA. Lipoprotein profile in Arabian type 2 diabetic patients. Relationship to coronary artery diseases. *Int J Cardiol*. 2007; 121(1):91-2.
Denic S, Bener A, Sabri S, Khatib F, Milenkovic J. Parental consanguinity and risk of breast cancer: a population-based case-control study. *Med Sci Monit*. 2005; 11(9):CR415-9.
Devi AR, Rao NA, Bittles AH. Inbreeding and the incidence of childhood genetic disorders in Karnataka, South India. *J Med Genet*. 1987; 24(6):362-5.
Ehlayel MS, Bener A. Duration of breast-feeding and the risk of childhood allergic diseases in a developing country. *Allergy Asthma Proc*. 2008; 29(4):386-91.
El-Hazmi MA, Al-Swailem AR, Warsy AS, al-Swailem AM, Sulaimani R, al-Meshari AA. Consanguinity among the Saudi Arabian population. *J Med Genet*. 1995; 32(8):623-6.
El-Menyar AA, Bener A, Numan MT, Morcos S, Taha RY, Al-Suwaidi J. Epidemiology of idiopathic cardiomyopathy in Qatar during 1996-2003. *Med Princ Pract*. 2006; 15(1):56-61.
Elsaid MF, Bener A, Lindner M, Alzyoud M, Shahbek N, Abdelrahman MO, Abdoh G, Bessisso MS, Zschocke J, Hoffmann GF. Are heterocygotes for classical homocystinuria at risk of vitamin B12 and folic acid deficiency? *Mol Genet Metab*. 2007; 92(1-2):100-3.
Emery A. Methodology in medical genetics. In: *Introduction to Statistical Methods*. Churchill Livingstone, Edinburgh, 1976.
Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. Systematic population based assessment of cancer risk in first-degree relatives of cancer probands. *J Natl Cancer Inst*. 1994; 86:1600-8.
Gunaid AA, Hummad NA, Tamim KA. Consanguineous marriage in the capital city Sana'a, Yemen. *J Biosoc Sci*. 2004; 36(1):111-21.
Jaber L, Shohat T, Rotter JI, Shohat M. Consanguinity and common adult diseases in Israeli Arab communities. *Am J Med Genet*. 1997; 70(4):346-8.
Jurdi R, Saxena PC. The prevalence and correlates of consanguineous marriages in Yemen: similarities and contrasts with other Arab countries. *J Biosoc Sci*. 2003; 35(1):1-13.
Kerber RA, Slattery ML, Potter JD, Caan BJ, Edwards SL. Risk of colon cancer associated with a family history of cancer or colorectal polyps: the diet, activity, and reproduction in colon cancer study. *Int J Cancer*. 1998; 78(2):157-60.
Khlat M, Khoury M. Inbreeding and diseases: demographic, genetic, and epidemiologic perspectives. *Epidemiol Rev*. 1991; 13:28-41.
Khoury SA, Massad D. Consanguineous marriage in Jordan. *Am J Med Genet*. 1992; 43(5):769-75.
Lindner M, Abdoh G, Fang-Hoffmann J, Shabeck N, Al-Sayrafi M, Al-Janahi M, Ho S, Abdelrahman MO, Ben-Omran T, Bener A, Schulze A, Al-Rifai H, Al-Thani G, Hoffmann GF. Implementation of extended neonatal screening and a metabolic unit in the State of Qatar: developing and optimizing strategies in cooperation with the Neonatal Screening Center in Heidelberg. *J Inherit Metab Dis*. 2007; 30(4):522-9.
Martinez ME. Primary prevention of colorectal cancer: lifestyle, nutrition, exercise. *Recent Results Cancer Res*, 2005; 166:177-211.
McHale DP, Jackson AP, Campbell, Levene MI, Corry P, Woods CG, Lench NJ, Mueller RF, Markham AF. A gene for ataxic cerebral palsy maps to chromosome 9p12-q12. *Eur J Hum Genet*. 2000; 8(4):267-72.
Mokhtar MM, Abdel-Fattah M. Major birth defects among infants with Down syndrome in Alexandria, Egypt (1995-2000): trends and risk factors. *East Mediterr Health J*. 2001; 7(3):441-51.
Moynihan L, Houseman M, Newton V, Mueller R, Lench N. DFNB20: a novel locus for autosomal recessive, non-syndromal sensorineural hearing loss maps to chromosome 11q25-qter. *Eur J Hum Genet*. 1999; 7(2):243-6.
Radovanovic Z, Shah N, Behbehani J. Prevalence and social correlates to consanguinity in Kuwait. *Ann Saudi Med*. 1999; 19(3):206-10.
Rajab A, Patton MA. A study of consanguinity in the Sultanate of Oman. *Ann Hum Biol*. 2000; 27(3):321-6.
Robert F, Pembrey ME. Cousin marriage. In: *An Introduction to Medical Genetics*. Oxford University Press, New York, 1978.
Saadat M, Ansari-Lari M, Farhud DD. Consanguineous marriage in Iran. *Ann Hum Biol*. 2004; 31(2):263-9.
Slattery ML, Levin TR, Ma K, Goldgar D, Holubkov R, Edwards S. Family history and colorectal cancer: predictors of risk. *Cancer Causes Control*. 2003; 14(9):879-87.
Sonderguard J, Bulow S, Lynge E. Cancer incidence among parents of patients with colorectal cancer. *Int J Cancer*.1991; 7:202-6.
Stoll C, Alembik Y, Roth MP, Dott B. Parental consanguinity as a cause for increased incidence of births defects in a study of 238,942 consecutive births. *Ann Genet*. 1999; 42(3):133-9.
Sueyoshi S, Ohtsuka R. Effects of polygyny and consanguinity on high fertility in the rural Arab population in South Jordan. *J Biosoc Sci*. 2003; 35(4):513-26.
Tamim H, Khogali M, Beydoun H, Melki I, Yunis K; National Collaborative Perinatal Neonatal Network. Consanguinity and apnea of prematurity. *Am J Epidemiol*. 2003; 158(10):942-6.
Wright AF, Hastie ND. Complex genetic diseases: controversy over the Croesus code. *Genome Biol*. 2001; 2(8):COMMENT2007.