ELSEVIER

Cancer Detection and Prevention 31 (2007) 263–269

Cancer Detection and Prevention

www.elsevier.com/locate/cdp

Risk of cancer in an inbred population

Srdjan Denic MD[a,*], Chris Frampton PhD[b], M. Gary Nicholls MD[b]

[a] *Department of Internal Medicine, Faculty of Medicine and Health Sciences, UAE University, PO Box 17666, Al Ain, Abu Dhabi, United Arab Emirates*

[b] *Department of Medicine, Christchurch School of Medicine and Health Sciences, Christchurch Hospital, Christchurch, New Zealand*

Accepted 14 July 2007

Abstract

Background: In spite of a high prevalence of consanguineous marriages in Asia and Africa, there has been little epidemiological research on the effect of inbreeding on cancer risk. *Methods*: We conducted a case–control study of 391 native Arabs with cancer and 378 matched healthy controls. All cases had a histologic diagnosis of cancer. Participants were interviewed to collect information on the biological relatedness of their parents. Risk of cancer was determined in relation to the presence of parental consanguinity, coefficient of inbreeding (F), and whether subjects were more ($F \geq 0.0625$) or less ($F < 0.0625$) inbred, and was stratified by sex, age group, and cancer type. *Results*: Reduction of overall cancer risk was associated with increased F ($P < 0.001$). In men, F was significantly higher in healthy controls than cancer patients overall ($P = 0.001$) and in both younger (≤30 years) and older age groups ($P = 0.003$ and 0.013, respectively). In women, reduction of overall cancer risk by increased F was found only in the older age group ($P = 0.03$). Overall, being more inbred was associated with a reduction in overall cancer risk by about 25% (odds ratio (OR), 0.74; 95% confidence interval (CI), 0.64–0.86). For seven of the eight most common cancer types, the risk of cancer was reduced with increased F but these did not reach conventional statistical significance ($P > 0.05$). *Conclusions*: Inbreeding was associated with reduced overall risk of cancer in studied population. Reduction of cancer risk is greater in men than women and, in women, is restricted to those older than 30 years.

Keywords: Consanguinity; Inbreeding; Relative risk; Cancer; Homozygosity; United Arab Emirates

1. Introduction

Homozygosity of some low-penetrance cancer genes is associated with altered cancer risk [1–7]. Children of consanguineous parents have an increased likelihood of homozygosity by descent and their risk for malignancy may differ from that in children of biologically unrelated parents who are more often heterozygous. In spite of a large consanguineous population in Asia and Africa [8,9], the effect of human inbreeding on cancer risk in these regions is unclear.

The low-penetrance cancer genes are autosomal recessive genes that convert carcinogens into non-carcinogenic compounds or transform inactive substances into carcinogens. They are more numerous than rare high penetrance genes, their frequency varies between populations, and they work in a mutually dependent way and interact with environmental factors. For all these reasons their contribution to cancer susceptibility is difficult to determine although their public health importance is considerable since they are thought to be responsible for over 80% of all malignancies [10].

A double-dose of some gene variants (homozygosity) is associated with an increased risk of esophageal, oral, lung, bladder, and breast cancer and acute lymphocytic leukemia [1–7]. On the other hand, homozygosity for some low-penetrance genes is linked to a decreased risk of breast cancer [11]. Consanguinity, which increases the chances of homozygosity, is linked to an increased overall risk of cancer [12,13] and elevated risk of breast cancer, all leukemias, and acute lymphocytic leukemia in children [14–16]. However, studies conducted in some populations have shown that consanguinity does not affect, or may have a mild protective

* Corresponding author. Tel.: +971 3 7137677; fax: +971 3 7672995.
E-mail address: s.denic@uaeu.ac.ae (S. Denic).

0361-090X/$30.00
doi:10.1016/j.cdp.2007.07.006

effect on, breast cancer risk [17,18]. This suggests that the effect of inbreeding on cancer risk may differ for different tumors and, for the same tumor, may vary between populations. Consanguineous populations account for some 500–800 million individuals distributed over many countries most obviously located in subtropical and tropical Asia and Africa [8,9]. These various populations have different coefficients of inbreeding and may differ in the frequencies of their cancer-susceptibility alleles and in their exposure to cancer-modifying environmental factors. Consequently, the effect of inbreeding on the risk of cancer is likely to vary between ethnically different populations. We report here results of a case–control study exploring the effects of inbreeding on cancer risk in a local Arab population in the United Arab Emirates (UAE).

2. Materials and methods

2.1. Study population

Between January 2001 and December 2003, 391 patients with cancer and 378 healthy controls were entered into a case–control study of consanguinity and cancer. Patients with a histological diagnosis of cancer were recruited from Tawam Hospital, which is the main cancer hospital in the UAE and is affiliated with the Faculty of Medicine and Health Sciences, UAE University, Al Ain. The hospital has an estimated catchment of 85% of all cancer patients in the country who have visited a hospital at some time during their illness. In this analysis we included only local Arab nationals: the much larger ex-patriot population was not considered. There were no restrictions on sex, age, type of malignancy, and the stage of disease. Healthy controls were local Arabs nationals group-matched to cases by sex, age (±5 years), and residence in one of the seven emirates. In assessing the effect of inbreeding on a particular cancer type, all controls (from the pool of controls) that could be matched were used for the analysis of each cancer subgroup. Controls were obtained from a random sample of citizens generated from the 1995 census, updated in 1998, and created for research purposes by the Ministry of Planning, Abu Dhabi. The study was approved by the Ethics Committees of both Tawam Hospital and the Faculty of Medicine and Health Sciences in Al Ain, Abu Dhabi, UAE, and all participants provided informed consent.

2.2. Consanguinity data

All patients and controls were interviewed over the telephone using a structured questionnaire by a trained nurse whose mother tongue (Arabic) was the same as the study participants. They were all asked if their parents are biologically related and, if so, how. When the subject was a minor or the patient had died, the closest family member provided information. All participants whose parents were second cousins once removed or biologically closer were considered to be of consanguineous parentage. The coefficient of inbreeding (F) is the probability of homozygosity by descent and was determined in the offspring from six types of consanguineous unions as follows: uncle–niece and double first cousin, 0.125; first cousin, 0.0625; first cousin once removed, 0.03125; second cousin, 0.015625; second cousin once removed, 0.0078125. All other types of unions were considered non-consanguineous and their F was assumed to be 0. The mean coefficient of inbreeding is the average of all Fs in the study population. The most common type of consanguineous marriages in the local UAE Arab population is between first cousins ($F = 0.0625$) [19] which is several times higher than that in the least inbred consanguineous union ($F = 0.0078125$). Pooling all data may, therefore, serve to obscure the effect of the degree of inbreeding on cancer risk. For this reason, we categorized all study subjects as ''more inbred'' if they had F of 0.0625 or greater, and as ''less inbred'' if their F was less than 0.0625. The exact F values for 13 cases and 8 controls were unavailable. In addition, in order to evaluate the effect of genetic factors on cancer risk before superimposition of environmental influences, we divided study subjects into a younger age group (30 years and less) and an older age group (above 30 years).

2.3. Statistical analysis

Statistical analyses were performed using Statistical Packages for Social Sciences (SPSS v13.0). The Student's t-test and Pearson's χ^2 test was used to ascertain the significance of differences in age, the coefficient of inbreeding and parental consanguinity. When the sample size was small, the Fisher exact test was performed instead of the χ^2 test. Odds ratios defining the association between the inbreeding categories and the presence of cancer were calculated using logistic regression models that included terms for age and gender. All statistical tests were two-tailed and P values of less than 0.05 were considered statistically significant.

3. Results

Data from 391 cancer patients and 378 healthy controls were available for analysis. Participation rates of the patients and controls were 92.4% and 98.2%, respectively. Overall, there was no statistically significant difference in age between patients and controls but the female controls were slightly younger (mean 44.4 years) than female patients (48.2 years) ($P = 0.03$). The rate of parental consanguinity was 36% in both cancer patients and controls ($P = 0.98$). In males, the parental consanguinity rate was higher in the control group (45.6%) than in the patient group (40.0%) but the difference was not statistically significant ($P = 0.31$). Among females, the parental consanguinity rate was higher

Table 1
Inbreeding characteristics of cancer patients and controls

	Cancer				*P* value
	Yes ($N = 391$)	%	No ($N = 378$)	%	
All ($N = 769$)					
Mean age (range)	50.0 (1–95)		47.8 (1–95)		0.14[a]
Parents consanguineous	141	36.1	136	36.0	0.98[b]
Mean coefficient of inbreeding	0.0138		0.021		<0.001[a]
Females ($N = 231$)					
Mean age (range)	48.2 (1–95)		44.4 (1–92)		0.03[a]
Parents consanguineous	77	33.3	63	28.9	0.31[b]
Mean coefficient of inbreeding	0.0128		0.0169		0.11[a]
Males ($N = 538$)					
Mean age (range)	52.3 (1–95)		52.4 (1–95)		0.96[a]
Parents consanguineous	64	40.0	73	45.6	0.31[b]
Mean coefficient of inbreeding	0.0153		0.0273		0.001[a]

[a] Student's *t*-test.
[b] χ^2 test.

for patients (33.3%) than controls (28.9%) but again the difference was not statistically significant ($P = 0.31$) (Table 1). Overall, the mean coefficient of inbreeding was significantly higher in controls (0.021) than cancer patients (0.0138) ($P = 0.001$). In younger and older male groups, and in the older female group, the coefficient of inbreeding was significantly higher in controls than patients (Table 2).

When the proportions of more inbred subjects ($F \geq 0.0625$) were compared between cases and controls, controls were significantly ($P < 0.001$) more inbred than cases overall and among males (Table 3). In the older age group, significantly more inbred controls than patients were found among females, males, and overall ($P = 0.018$, 0.009, and 0.001, respectively). A summary of statistically significant findings of the protective effect of inbreeding against cancer is shown in Table 4.

Inbreeding characteristics of patients with the most common types of neoplasms and their controls, are shown in Table 5. The age of these patients and their respectively matched controls (not shown) was not significantly different.

Table 2
Inbreeding characteristics of younger and older cancer patients and controls

	Cancer				*P* value
	Yes	%	No	%	
Age ≤ 30	82		79		
All					
Parents consanguineous	42	51.2	34	43.0	0.30[b]
Mean coefficient of inbreeding	0.0190		0.0254		0.20[a]
Females					
Parents consanguineous	18	47.4	12	26.7	0.05[b]
Mean coefficient of inbreeding	0.0200		0.0147		0.42[a]
Males					
Parents consanguineous	24	54.5	22	64.7	0.37[b]
Mean coefficient of inbreeding	0.0180		0.0393		0.003[a]
Age > 30	309		299		
All					
Parents consanguineous	99	32.0	102	34.1	0.59[b]
Mean coefficient of inbreeding	0.0124		0.0202		0.001[a]
Females					
Parents consanguineous	59	30.6	51	29.5	0.82[b]
Mean coefficient of inbreeding	0.0113		0.0174		0.03[a]
Males					
Parents consanguineous	40	34.5	51	40.5	0.34[b]
Mean coefficient of inbreeding	0.0143		0.0241		0.013[a]

[a] Student's *t*-test.
[b] χ^2 test.

Table 3
More vs. less inbreed cancer patients and controls

	Cancer				Odds ratio	95% CI	*P* value[a]
	Yes	%	No	%			
All							
Less inbred	306	81.0	256	69.2			
More inbred	72	19.0	114	30.8	0.74	0.64–0.86	<0.001
Females							
Less inbred	187	82.4	164	76.3			
More inbred	40	17.6	51	23.7	0.83	0.67–1.03	0.11
Males							
Less inbred	119	78.8	92	59.4			
More inbred	32	21.2	63	40.6	0.66	0.53–0.81	<0.001
Age $\leq$ 30							
All							
Less inbred	58	73.4	50	65.8			
More inbred	21	26.6	26	34.2	0.84	0.60–1.16	0.30
Females							
Less inbred	26	70.3	36	83.7			
More inbred	11	29.7	7	16.3	2.17	0.74–6.25	0.185
Males							
Less inbred	32	76.2	14	42.4			
More inbred	10	23.8	19	57.6	0.23	0.09–0.62	0.004
Age > 30							
All							
Less inbred	248	82.9	206	70.1			
More inbred	51	17.1	88	29.9	0.71	0.61–0.84	<0.001
Females							
Less inbred	161	84.7	128	74.4			
More inbred	29	15.3	44	25.6	0.52	0.31–0.88	0.018
Males							
Less inbred	87	79.8	78	63.9			
More inbred	22	20.2	44	36.1	0.45	0.25–0.81	0.009

Less inbred, $F < 0.0625$; more inbred, $F \geq 0.0625$.
[a] χ^2 test.

Table 4
Summary of statistically significant findings of protection against cancer by increased inbreeding (gray area)

	All ages			**Younger age (≤30 years)**			**Older age (>30 years)**		
	All	**Males**	**Females**	**All**	**Males**	**Females**	**All**	**Males**	**Females**
Parental consanguinity	NS	NS	NS	NS	NS	NS	NS	NS	NS
Coefficient of inbreeding	<0.001	0.001	NS	NS	0.003	NS	0.001	0.013	0.03
More inbred vs. less inbred	<0.001	<0.001	NS	NS	0.004	NS	<0.001	0.018	<0.009

NS: not statistically significant.

Table 5
Inbreeding characteristics of patients with common malignancies and controls

Tumor pathology	*N*	Consanguineous parentage, *N* (%)	*P* value[a]	Mean *F*	*P* value[b]	More inbred, *N* (%)	*P* value[a]
Breast cancer							
Cases	72	20 (27.8)		0.0110		10 (14.1)	
Controls	145	40 (27.6)	0.98	0.0166	0.16	35 (24.1)	0.09
Thyroid carcinoma							
Cases	25	13 (52.0)		0.01812		6 (24.0)	
Controls	78	24 (30.8)	0.05	0.0180	0.98	19 (24.7)	0.95
Colorectal carcinoma							
Cases	24	8 (33.3)		0.0121		4 (18.2)	
Controls	79	32 (40.5)	0.53	0.0230	0.14	26 (33.8)	0.20
Cervical carcinoma							
Cases	24	8 (33.3)		0.0078		2 (9.1)	
Controls	82	25 (30.5)	0.79	0.0174	0.13	22 (26.8)	0.09
Head and neck carcinomas							
Cases	22	5 (22.7)		0.0096		3 (13.6)	
Controls	78	30 (38.5)	0.17	0.0243	0.057	27 (35.5)	0.05
Lung cancer							
Cases	22	8 (36.4)		0.0206		6 (27.3)	
Controls	104	43 (41.3)	0.67	0.0231	0.73	36 (36.0)	0.44
Non-Hodgkin's lymphoma							
Cases	22	5 (22.7)		0.0187		5 (27.8)	
Controls	78	30 (38.5)	0.17	0.0182	0.95	14 (25.5)	0.85
Acute lymphocytic leukemia							
Cases	22	12 (54.5)		0.0195		6 (27.3)	
Controls	43	22 (51.2)	0.80	0.0327	0.14	19 (45.2)	0.16

[a] χ^2 test.
[b] Student's *t*-test.

For seven of the eight most common malignancies, the proportion of cases that were more inbred was less than among the controls, and in the head and neck cancer group this difference almost reached statistical significance ($P = 0.054$). Six of the eight cancer groups also had higher mean inbreeding coefficients among controls compared to cases.

Parental consanguinity was more frequent in patients with thyroid cancer (50.0%) than controls (30.8%) ($P = 0.05$). However, neither the mean coefficient of inbreeding nor the proportion of more inbred subjects differed significantly between cases and controls ($P = 0.98$ and 0.95, respectively) for this thyroid cancer group (Table 5).

4. Discussion

Because homozygotes for some cancer-susceptibility genes have different risks of cancer compared with heterozygotes, and since previous research has shown that inbreeding may alter the risk of developing some neoplasms, we used three indicators of inbreeding in our study—the rate of parental consanguinity, the mean coefficient of inbreeding, and the category of more (versus less) inbred ($F \geq 0.0625$) subjects in an attempt to determine the form of any association between inbreeding and the risk of cancer. Our main finding is that inbreeding in this Arab population had a protective effect against the development of cancer in males, and in females older than 30 years.

With 391 cancer patients and 378 healthy controls, this study had a reasonable power to detect moderate changes of cancer risk. Of the three indicators of inbreeding, the mean coefficient of inbreeding (F) and categorization into more versus less inbred individuals appeared to be more sensitive indicators of the effect of inbreeding on cancer than parental consanguinity (Table 4). This is to be expected because the former two indices (F and categorization) appropriately place more weight on unions that produce more inbred children, whereas parental consanguinity alone, as an indicator of inbreeding, does not discriminate unions that produce more and less inbred children. For example, parental consanguinity places the same weight on those with an F of 0.125 (e.g., children of double first cousins) and an F of 0.0078125 (children of second cousin once removed) although the former are 16 times more inbred than the latter.

One mechanism by which inbreeding potentially affects the risk of cancer is through an increased rate of homozygosity. The number of homozygotes in a population depends on the coefficient of inbreeding (which determines the number of homozygotes by descent) and the frequency of allele of interest in that population. When the frequency of

an allele is very low, the relative contribution of consanguinity to the risk of cancer is substantial and the relative contribution of homozygosity by chance is small. In this situation, a large study sample is required to detect any effect of inbreeding on cancer risk because the number of counted events (cancer) is very small. On the other hand, when the frequency of an allele is high, the relative contribution of consanguinity to the total number of homozygotes is small and that of homozygosity by chance is high. In this situation, a large study sample is also needed in order to detect a small contribution of inbreeding to the total number of homozygotes. In a third scenario, when the frequency of an allele is moderately low, the number of homozygotes by common descent and those by chance strike a balance that permits detection of the effect of inbreeding in a moderate sized study sample. Our study was perhaps most suited to detect the effect of homozygosity of cancer-susceptibility alleles with moderately low frequencies in the population. Nonetheless, the study was not large enough to detect any effect of inbreeding on individual tumor types although a trend toward protection by inbreeding was noted in seven of the eight most common malignancies and, for the head and neck cancers, closely approached statistical significance (Table 5).

The long-term practice of consanguinity, as documented for populations in India and the Middle East, will decrease the frequency of those alleles that increase the chances of deaths among younger individuals before they reach reproductive age (relatively lethal genes, e.g., BRCA1) [20,21]. Here, with the death of each homozygote, individual alleles are permanently removed from the gene pool. Therefore, the effect of inbreeding on cancer risk in younger individuals could be different due to a decreased allele frequency. Alternatively, when the coefficient of inbreeding in a population decreases, the detrimental effect of inbreeding in younger age groups may not be detectable any more at the given sample size. These mechanisms may explain the absence of a protective effect of inbreeding in the younger female age group in our study.

The differential effect of inbreeding on males and females is best explained by negative heterosis. Our findings indicate that increased heterozygosity (lower levels of inbreeding) is associated with an increased risk of cancer in younger females (Tables 3 and 4). When heterozygote (hybrid) offspring display a phenotype characteristic that is significantly different from either parent, the phenomenon is called heterosis. Because the cancer phenotype is harmful, we call it negative heterosis as opposed to a beneficial phenotype, which is characteristic of some heterozygotes: this is called positive heterosis, also known as hybrid vigor [22]. At the molecular level, heterosis develops when one allele is inactivated by methylation of cytosine in its promoter region. Methylation is triggered by gender (through the presumed effect of hormones), stress, environment, or other genes [22,23]. Our finding of an increased risk of cancer in younger heterozygote females could be caused by inactivation of some cancer-susceptibility gene that is triggered by female gender. An alternative explanation is the inactivation of a tumor-suppressor allele [23], which could be behind the differential effect of inbreeding on cancer risk in different subgroups of a population [19]. In the UAE, the frequency of inter-tribal marriages, where offspring are more likely to be heterozygous, has apparently increased in the last 20–30 years.

Results, differing from ours, have shown a positive association between increased inbreeding and risk of cancer in other populations. Among Pakistanis, increased inbreeding was reportedly associated with a heightened overall risk of cancer and risk of breast cancer [12,14]. Among inbred populations on the islands off the coast of Croatia, the rates of cancer tended to be higher than in mainlanders from which the island populations originated, implying that inbreeding is carcinogenic [13]. Differences in the gene frequencies between populations, with or without the interaction of specific environmental factors, may explain contrasting effects of inbreeding on the risk of cancer in different populations. Nonetheless, previous studies in the same Arab population as ours have linked parental consanguinity with an increased risk of cancer overall (of borderline statistical significance) and for all leukemias and childhood acute lymphocytic leukemia [15,16]. However, the coefficient of inbreeding was not calculated and the degree of inbreeding was not correlated with cancer risk in these earlier studies [15,16] whereas both of these indices appeared to be more sensitive risk predictors in the present study. Along this line of argument, in our study, parental consanguinity was associated with an increase in the risk of thyroid cancer (of borderline of statistical significance) but determination of the coefficient of inbreeding and the correlation of cancer risk with more and less inbred groups, failed to confirm that inbreeding is a risk factor (Table 5). In our breast cancer patients (also separately reported [17]), inbreeding may have a protective effect (which did not reach statistical significance), but the results are similar to those of another study carried out in the same population [18].

Although this is, to our awareness, the first study that reports the quantified association between human inbreeding (using the coefficient of inbreeding and categories of more and less inbred groups) and overall risk of cancer in one population, there are limitations in such epidemiological analyses. First, we should, ideally, have matched cases and controls by tribe within each emirate. This, however, is impractical since there are a number of tribes and many subtribes within each emirate. Furthermore, as mentioned already, there has been considerable inter-tribal inbreeding within recent decades. Second, selection and recall bias, as well as confounding variables, are of potential concern in case–control studies. We attempted to avoid selection bias by collecting patients from the country's main cancer hospital with an estimated catchment of 85% of all cancer cases, and for control selection we used a random sample from the national census database. Although participation

rate was high, more patients than controls for variety of reasons could not be entered in the study. In the UAE, up to 80% of the population is made up of recent temporary immigrants and we restricted our analysis to the local native Arab population. Furthermore, we used structured personal interviews as opposed to self-administered forms to collect vital information. Nonetheless, the mean age of females was lower in controls than among patients which could be related to the recognized problem of inaccurate assessment of age and terminal-digit preference for ''5'' and ''0'' in populations from developing countries in general and in our population in particular [24]. For common types of malignancies, therefore, we matched controls to each patient age within a 5-year age grouping (using 2.5 and 7.5 terminal digits for age-group separation to ameliorate documented age preference). Education level may correlate with consanguinity and could potentially confound the results although this was not observed in a prior study in our population [25].

In summary, our data indicate that inbreeding in natives to the UAE is protective overall against cancer. Reduction of cancer risk is more obvious in men then women and, in women, is restricted to those older than 30 years. Consanguinity rate appears to be an insensitive indicator of the effect of inbreeding on the risk of developing cancer. The coefficient of inbreeding and categories of more and less inbred subgroups may provide more meaningful and more sensitive predictors of the effect of homozygosity on cancer risk. By extension, this applies to other diseases with complex pathogeneses to which genetics is a contributing factor. With around 10% of the world population being of consanguineous parentage, the effects of inbreeding on cancer risk in ethnically different populations requires further study.

Acknowledgment

Supported by the grant (NP/01/1) from the Faculty of Medicine and Health Sciences, UAE University, Al Ain, Abu Dhabi, UAE.

Conflict of interest

None.

References

[1] Gao CM, Takezaki T, Wu JZ, Li ZY, Liu YT, Li SP, et al. Glutathione-*S*-transferases M1 (GSTM1) and GSTT1 genotype, smoking, consumption of alcohol and tea and risk of esophageal and stomach cancers: a case–control study of a high-incidence area in Jiangsu Province, China. Cancer Lett 2002; 188:95–102.

[2] Buch SC, Notani PN, Bhisey RA. Polymorphism at GSTM1, GSTM3 and GSTT1 gene loci and susceptibility to oral cancer in an Indian population. Carcinogenesis 2002; 23:803–7.

[3] Engel LS, Taioli E, Pfeiffer R, Garcia-Closas M, Marcus PM, Lan Q, et al. Pooled analysis and meta-analysis of glutathione *S*-transferase M1 and bladder cancer: a HuGE review. Am J Epidemiol 2002; 156:95–109.

[4] Benhamou S, Lee WJ, Alexandrie AK, Boffetta P, Bouchardy C, Butkiewicz D, et al. Meta- and pooled analyses of the effects of glutathione *S*-transferase M1 polymorphisms and smoking on lung cancer risk. Carcinogenesis 2002; 23:1343–50.

[5] Cascorbi I, Brockmoller J, Mrozikiewicz PM, Bauer S, Loddenkemper R, Roots I. Homozygous rapid arylamine *N*-acetyltransferase (NAT2) genotype as a susceptibility factor for lung cancer. Cancer Res 1996; 56:3961–6.

[6] Weber BL, Nathanson KL. Low penetrance genes associated with increased risk for breast cancer. Eur J Cancer 2000; 36:1193–9.

[7] Sinnett D, Krajinovic M, Labuda D. Genetic susceptibility to childhood acute lymphoblastic leukemia. Leuk Lymphoma 2000; 38:447–62.

[8] Bittles A. Consanguinity and its relevance to clinical genetics. Clin Genet 2000; 60:89–98.

[9] Consang.net [database on Internet]. Global prevalence of consanguinity [updated 2007, cited 2007 Sep 25]. Perth: Edith Cowan University; c2007. Available from: http://www.consang.net/index.php/global_prevalence.

[10] Balmain A, Gray J, Ponder B. The genetics and genomics of cancer. Nat Genet 2003; 33:238–44.

[11] Ambrosone C, Moysich K, Furberg H, Freudenheim J, Bowman E, Ahmed S, et al. CYP17 genetic polymorphism, breast cancer, and breast cancer risk factors. Breast Cancer Res 2003; 5:R45–51.

[12] Shami SA, Qaisar R, Bittles AH. Consanguinity and adult morbidity in Pakistan. Lancet 1991; 338:954–5.

[13] Rudan I. Inbreeding and cancer incidence in human isolates. Hum Biol 1999; 71:173–87.

[14] Liede A, Malik IA, Aziz Z, Rios Pd PL, Kwan E, Narod SA. Contribution of BRCA1 and BRCA2 mutations to breast and ovarian cancer in Pakistan. Am J Hum Genet 2002; 71:595–606.

[15] Bener A, Denic S, Al Mazrouei M. Consanguinity and family history of cancer in children with leukemia and lymphomas. Cancer 2001; 92:1–6.

[16] 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; 51:167–73.

[17] 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:CR415–9.

[18] Denic S, Bener A. Consanguinity decreases risk of breast cancer–cervical cancer unaffected. Br J Cancer 2001; 85:1675–9.

[19] Al-Gazali LI, Bener A, Abdulrazzaq YM, Micallef R, Al-Khayat AI, Gaber T. Consanguineous marriages in the United Arab Emirates. J Biosoc Sci 1997; 29:491–7.

[20] Denic S, Al-Gazali L. Breast cancer, consanguinity, and lethal tumor genes: simulation of BRCA1 and BRCA2 prevalence over 40 generations. Int J Mol Med 2002; 10:713–9.

[21] Denic S, Al-Gazali L. BRCA1 and BRCA2 mutations in breast cancer patients from Saudi Arabia. Saudi Med J 2003; 24:696.

[22] Comings DE, MacMurray JP. Molecular heterosis: a review. Mol Genet Metab 2000; 71:19–31.

[23] Herman GJ, Baylin BS. Gene silencing in cancer in association with promoter hypermethylation. N Engl J Med 2003; 349:2042–54.

[24] Denic S, Khatib F, Saadi H. Quality of age data in patients from developing countries. J Public Health (Oxf) 2004; 26:168–71.

[25] Bener A, Rizk DE, Ezimokhai M, Hassan M, Micallef R, Sawaya M. Consanguinity and the age of menopause in the United Arab Emirates. Int J Gynaecol Obstet 1998; 60:155–60.