SMGroup

Population Genetics of Omanies: A Review

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ABSTRACT

Oman being relatively small nation subjected to a fast progress from isolated medieval community to modern state within 40 years. A remarkable social and economic growth is best reflected in the well-organized and efficient health care system. With these achievements a shift in the pattern of disease became evident. There has been a great decrease in the incidence of communicable diseases and mortality rates of infants and children, and increase in the number of disadvantaged with birth defects and genetic conditions. The life expectancy is on the rise as well as the prevalence of non communicable diseases.

Revision of the literature on Oman's history assisted in understanding the pattern of population migrations and population structure in the past and present.

Published reports on genetic and non communicable disorders in Oman were reviewed to follow changes in disease pattern and study population genetics. Through comprehensive government-funded healthcare with a network of primary, secondary and tertiary care it was

possible to study population figures on consanguinity, birth defects, genetic disorders, diabetes and cancer. Studies on Hemoglobin disorders are the most instructive in view of the population genetics.

In addition to high levels of inbreeding large family size and presence of genetic isolates there are a number of unique factors in Oman, which make population especially useful for genetic studies and human population genetic research. This is due to the availability of the historical records of the population structure, cultural preservation of tribal aspects of the community, retention of the tribal names in Oman and inclusion of the tribal names in hospital records.

Keywords: Population genetics; Genetic disease; Birth Defects; Hemoglobin disorders; Non communicable diseases; Consanguinity; Sultanate of Oman

BACKGROUND

Oman is situated in the South East of the Arabian Peninsula along the East coast of the Persian Gulf (Figure 1). Oman is the second largest territory in the Arabian Peninsula with an area of 120,000 square miles and a coastline length of nearly 1,000 miles. Oman possesses a rich and varied terrain: with Rocky Mountains, deserts, flat plains and green oases. The coastal plains built up over the centuries by the outwash from the many wadis (valleys) which descend from the mountains. This forms the principle agricultural and date growing area and is also the most densely populated.

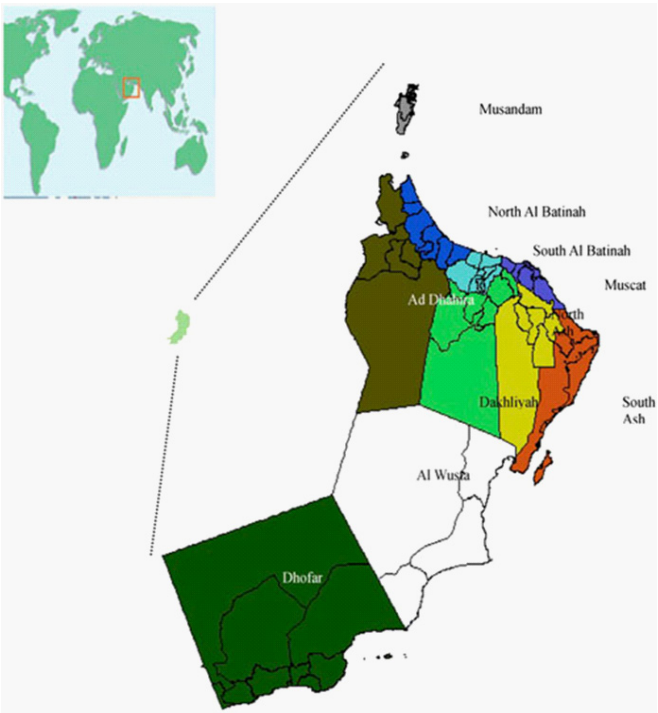

Figure 1: Map of Oman.

Oman divided into health regions and governorates.

After the accession of His Majesty Sultan Qaboos Bin Said in 1970, Oman opened the doors wide to the modern world after a long period of decline, debt and restrictions. Since 1970, progress has been extremely rapid. Schools, roads, hospitals, electricity and telecommunications have been brought to the remotest regions.

The present time Omani population is characterized by a rapid rate of growth, large family size, consanguineous marriages, and the presence of genetic isolates and semi-isolates. There are ten main geographical areas in Oman referred to as ''Manataq'' which are further divided into Districts referred as "Walayat" (Figure 1). Present days Demography and Health indicators presented in Figure 2 and Figure 3.

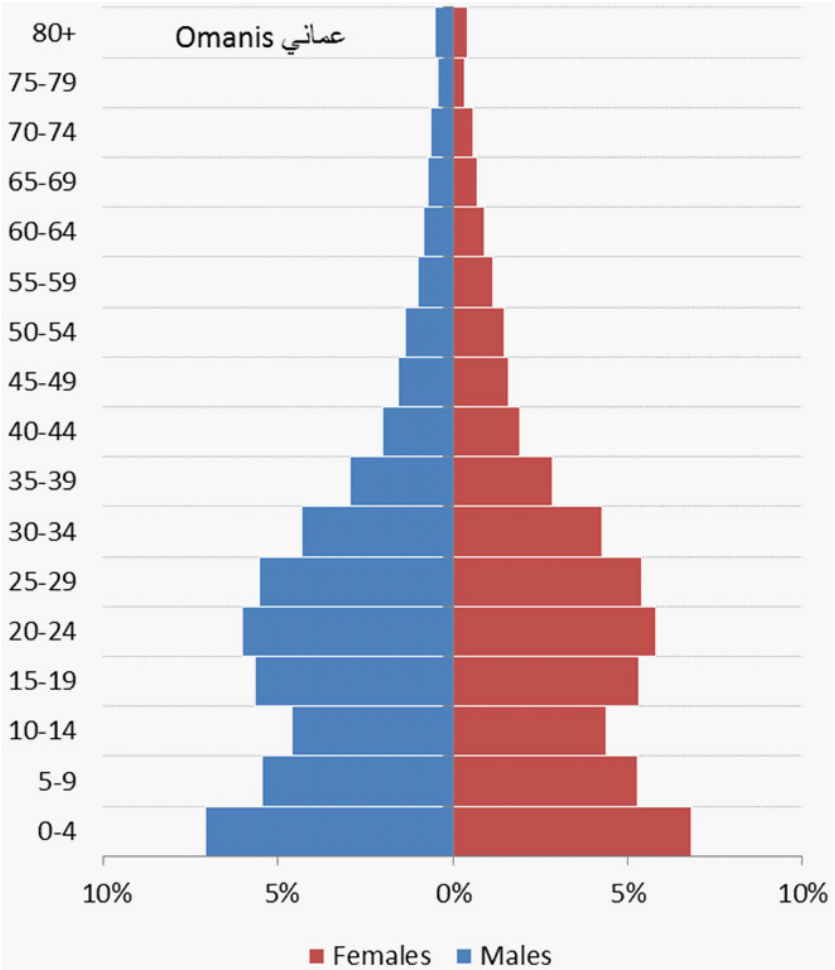

Figure 2: Population pyramid showing age and sex structure for the Omani population 2012. The total population size of Omani nationals is 2.450.000. Oman has a young population, about 11.58 and 36.2 % of the population are under 5 years and under15 years, respectively.

	Health Indicators (Ministry of Health Annual Report 2014)
1	Life expectancy at birth, 71.6 years (Ministry of National Economy Statistical Data [www.mone.gov.om]
2	The Crude Birth Rate (CBR) is estimated to be 33.9 per 1000 Omani population during 2014. The CBR showed a drop of 15.9% over the past twenty one years (1993 CBR= 40.3).
3	Perinatal mortality figures 7 per 1.000 live births (WHO)
4	Infant Mortality Rate (/1000 live births) declined from 16.7 in 2000 to 9.5 in 2012.
5	Under 5 Morality Rate (/1000 live births) declined from 21.7 in 2000 to11.5 in 2012.
6	About 63% of infant deaths take place during the first week of life and 79% during the first month, mainly due to congenital anomalies and malformations
7	About 25 out of 1000 births suffer congenital anomalies annually
8	Hypertension, hypercholesterolemia, obesity and diabetes mellitus are on the rise.
9	Cardiovascular diseases and neoplasm are the leading causes of deaths.
10	Crude Death Rate (CDR) from 7.3 in 1993 to 2.9 per 1000 Omani population in 2014. This represented a 60.3% decline in the past twenty one years.

Figure 3: Heath indicators 2014 Sultanate of Oman.

OMAN HISTORY

The earliest archaeological evidence of settlements in Oman dates back to about 12000 BC, towards the end of the Ice Age. The greater part of Oman was submerged by the sea in Upper Cretaceous or early Tertiary times [1]. The marine Gulf of Oman dates only from about 9000 BC, before which the area North of the Straits of Hormuz lay above sea level for several millennia [1]. Archaeologists have found well shaped flint hunting tools in 8000 year old settlements. The ancient burial mounds of Northern Oman ("beehive tombs") contained pottery, weapons, jewelry dated from about 3000 BC. A few settlements and burial grounds have been discovered which date from 4000 BC near Buraimi and Ibri which closely resemble the Temdet Nasr in Mesopotamia 3000-2800 BC.

Much remains obscure about the origins of the Omanies and how they became settled in their present areas. It is not unreasonable to think of the Australoid relic people as being the remainder of an ancient human bridge between Africa and Australia [2].

Few migration waves are known in history. Semitic migration from Northern Arabia, Western Asian stock in Pleistocene times, Northern Arab and Southern Arabs migrations in New Era.

For many centuries Omanies lived a disturbed life. During the early centuries of Islam, the country was invaded and devastated a number of times: by the Khalifsin 892 AD, later the Persians in 971 AD and the Turks in 1064 AD. In 1507 the Portuguese entered Oman and ruled it for almost a century and a half.

Oman lies along the trade routes between East and West, and Africa and India. Oman's sailors and merchants traded from one end of the monsoon to the other, from China to East Africa as far back as the 8th century AD and forged their ways in ancient times to the markets of India and the distant shores of China. In the 17th century Omanies had dislodged the Portuguese from East Africa

and established a trading empire in Zanzibar which flourished until 1964. Colonial expansion added to the Omani map and the Gwadar territory on the Pakistani Makran coast belonged to Oman until 1958. Seafaring and caravan roads were the principal way of communication in the early days.

RACIAL AND TRIBAL ORIGIN

As Oman lies on the cross-roads between East and West mixing with populations from neighbouring Asian and African countries occurred in centuries due to immigration, trade, introduction of slaves and mercenaries. Wind driven small ships and caravans were the only means of trade and communication with other countries before 1970. Until 1971 it is said that the life style of Omanies remain unchanged for many centuries.

Migration to East Africa was customary of Omanies. Baluchistan, once also a part of Oman's territory, was an important destination and provided mercenaries and slaves for centuries. Some more distant travels to Bahrain, Persia and the Far East took place on less regular basis.

In Dhofar province isolation was even greater as 600 miles distance lies between Central Oman. However it had ties in the history with neighboring Hadramaut and Yemen and trade connections with India and Indonesia. African slaves have been brought to Dhofar and Yemen from nearby Ethiopia.

The classical Arab division between town and desert dwelling people are Hadr (city dwellers) and Bedu or Bedouins (nomads). The Interior of Oman in the past had a tradition of a closed, isolated, self-sufficient community, tribal in its organisation, governed by an elected Imam (religious leader) [3,4]. The common characteristics of a tribal unit were: The existence of a leader (sheikh), wide measure of political and military autonomy, a well defined territory of pastures and water places, and identification element in the tribal brand mark for camels.

Bedouins in Oman in the past represented not only the most numerous, but also politically and economically the most important group of autonomous population. They were believed to be the indigenous inhabitants of the country. The way of life and economy of the Bedouins is characterized by a mobility which allows them to change their dwelling place frequently and to cover great distances to look for fresh pastures. The tribes that took possession of Arabia in the beginning of the New Era were composed of two main stocks. One of these stocks was BaniHina (Qahtan), who colonized the Yemen and moved up North into Oman territories after collapse of the Mareb dam in Yemen in 5th century AD. The other was Adnan, Northern Arabian descendant from BaniGhafir who occupied the Northern part of Arabian Peninsula [5]. Thus BaniHina and BaniGhafir have been opponents and have been competing for the territories as pastures and watering places for the last two centuries (Figure 4). This fact is interesting from a genealogical point of view as it was most unlikely that marriages took place between the members of the two clans.

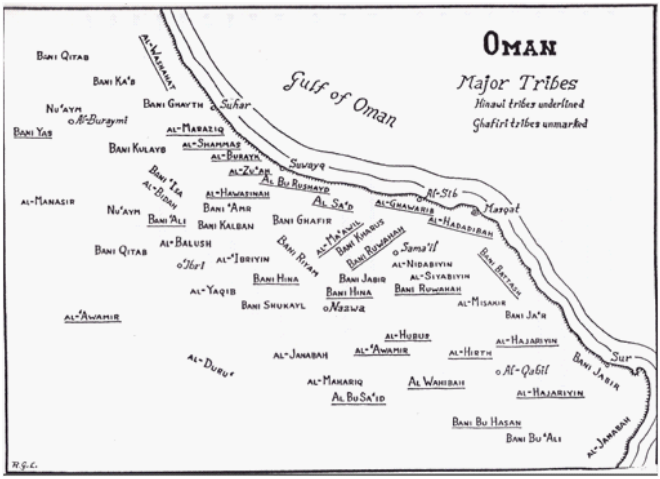

Figure 4: Historical map of omani tribes.

From Miles SB. Countries and the Tribes of the Persian Gulf. 1919 First Edition.Frank Cass & Co. Ltd, London.

Historically the survival of the tribes largely depended on the water sources available. Water has been the most important factor for survival in the tropical desert, crucial for agriculture and animal breeding. It was also vital for the survival of the tribes to control and protect their water sources and pastures. The reason for most of the tribal wars in the past has been due to competition for the control of the valley where pastures and water sources are located.

There are several important sedentary tribes in central Oman where traditionally each one controls the territory of the Wadi (valley) and may take its name. For its members a tribe represents the supreme cultural, political and social unit. All those belonging to a tribe derive their descent from a common ancestor who cannot be accurately traced in genealogical terms but who lived a very long time ago, possibly in pre-Islamic days.

Oman had relatively small population in the past. There was less than quarter of a million inhabitants in the beginning of 19th century [6].

Tribes of Oman may be found in the same areas as centuries ago and can be identify geographically by tribal maps (Figure 3). A tradition of tribal organisation and a Sheikh's leadership of the tribe are still preserved in Oman, but became directed towards justice and care of those in need rather than historical inter-tribal politics. Preferred type of marriage is still within the tribal members.

ANALYSIS OF THE POPULATION STRUCTURE

The analysis of the population structure [7] was based on documents of travelers of the last century (3,5,6). The total number of tribal names found was approximately 700 and includes the names of main tribes, tribal sections and subsections. After tribal sections and subsections incorporated within the main tribal name the number of the names was reduced to 198.

A quarter of the tribes in 1908 were of small size (<100 individuals) and only 2.5% were of large size with 15000-25000 members. The number of tribal sections varied from one to thirty eight per tribe. More than half of all tribes had just one or two sections. In history a typical picture of the Bedouin way of life was the prevalence of a small camp and travel groups. The small nomadic group represents an optimal adaptation to the prevailing ecological condition, where limited pastures will be quickly consumed by larger number of livestock, thereby necessitating a frequent change of location. It is often a household of a father and his married sons which make up a travel or camp group [8].

CONSANGUINITY

Table 1: Consanguinity figures in Oman (1994 - 1996) [Rajab and Patton, 2002].

TYPE OF UNION	NO. OF COUPLES STUDIED, % OF TOTAL	COEFFICIENT OF INBREEDING
Double first cousins	2945 (4.8%)	0.006
First cousins	10205 (16.8%)	0.0104
First cousins once removed	1575 (2.6%)	0.0008
Second cousins	7186 (11.8%)	0.0018
Marriages within the same tribe	12459 (20.4%)	0.0008
Unrelated	26525 (43.6%)	-
Total	60895 (100%)	0.0198

Note: The figures are similar to the rates seen in other parts of the Middle East.

The first study of the frequency of consanguineous marriages in Oman 1994-1996 [9] was designed to combine a large-scale survey based on 60.895 national birth registration records in delivery units across the country with a smaller but detailed verification study based on 500 three generations pedigree analysis.

The coefficient of inbreeding (F) may be defined as the probability that an individual will have, at a given locus, two genes identical by descent from a common ancestor.

The proportion of consanguineous unions in 60995 couples based on the delivery registers presented in Table 2.

Table 2: Comparison of consanguinity levels 1994 and 2012.

Publication Year	First Cousins	Second Cousins	Same Tribe Members	Unrelated-Consequently	No studied
Rajab and Patton, 2000	(24.2%)	(11.8%)	(20.4%)	(43.6%)	60.895
Rajab et al., 2014	(25.5%)	(14.6%)	(12.7%)	(47.3%)	3063

Note: No major changes in the rates of consanguineous unions noted in two decades.

The amount of consanguinity in a population is expressed as the average inbreeding coefficient (F). F = Σpifi where "Σ" stand for sum of PiFi, Pi is the proportion of marriages with inbreeding coefficient of Fi. The inbreeding coefficient for Omani nationals derived from data of the delivery registers 1994-1996 was 0.0176.

Through verification process based on the analysis of 500 three- generation pedigrees it was possible to make more precise estimation of F. As expected, the F value calculated from pedigrees greatly exceed the estimated by standard questionnaire value of 0.0176. It was due to the presence of double first cousin and first cousin once removed among labeled as "first cousin" marriages, and "distant relatives" found to be cousins.

Taking into account verified from pedigrees figures Cumulative inbreeding for Oman -Coefficient -F^{oman} was 0.0208.

Coefficient of inbreeding can reach high values. It was 0.1 measured in8 nomadic families. The average coefficient of inbreeding among 285 omani patients with inborn errors of metabolism [10] (F) was 0.081.

Resent figures on consanguinity derived from 2010-2012 population-based study (Table 2) indicated no major changes in the rates of consanguineous unions in two decades [11]. It indicates the custom of consanguineous marriages is deeply rooted in Arab culture, and the balance of opinion in the Middle East still remains in favor of consanguinity irrespective of increased risk of autosomal recessive diseases and birth defects.

GENETIC TRAITS

The Sources of knowledge about disorders and traits in Oman can be derived from publications and Annual Health Report of the Ministry of Health.

ABO and HLA

ABO and HLA types in Omani population matches historical population mix pattern. The distribution of the ABO and Rh genes in Oman configured from Oman Blood Transfusion services [12]. The data from 26930 donors summarized in Table 3.

Table 3: The distribution of the ABO in Oman.

ABO	%
O	51.5%
A	27.5%
B	17.5%
AB	3.5%

Note: The proportion of Blood Group O was higher in coastal regions compared with interior regions of Oman. Rh system reports were 93.7% positive.

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Recently blood group diversity of the ABO and Rh loci in Middle Eastern populations studied by AlSuhaibani [13]. The conformity with Hardy-Weinberg equilibrium at the ABO locus in 6 Arab populations and low heterozygosity in samples from Oman was found. High affinities between Oman and Yemen at Nei's genetic distance could be influenced by sampling from adjacent to Yemen regions.

Histocompatibility antigens in Omanis in comparison with other Gulf populations' study [14] concluded Omani population was characterized by a very high incidence of HLA-DR2 (66%), with associated HLA-DQ1 (76%) and a reduced incidence of DR4, DR7 and DR53. The frequency of many HLA antigens in Omanis differs significantly from frequencies found in the populations of Kuwait and Saudi Arabia, possibly reflecting different migration patterns.

Mendelian Disorders

There is a wealth of the data on genetic diseases available through publications [15-18] and the Ministry of Health **(MOH)** information system. In 2008 MoH reported that 39% of perinatal deaths in hospitals were caused by malformations and genetic diseases. A number of new genetic diseases and genetic variants have been described for the first time among Omanies [16-18].

In the past, the scale of the problem of congenital and genetic disorders was hidden in the high infant mortality rate because most affected infants died without being diagnosed. Changes in mortality rates presented in Figure 5. At present, the majority are diagnosed and provided with the best possible treatment. As a result, the number of surviving affected children increases every year causing a considerable burden on the health care services [19,20,11].

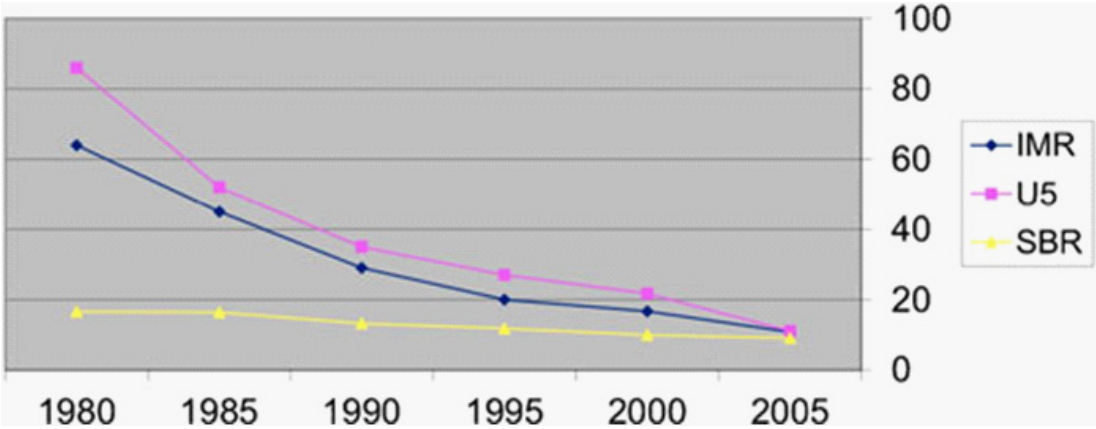


Figure 5: Changes in mortality rates in Oman (per 1,000 live births).

Infant mortality rates (IMR), mortality rates under 5 (U5) and stillbirth rates (SBR) at 5 year intervals from the years 1980-2005. Data from the Ministry of Health Information System.

Hemoglobinopathies

The Haemoglobinopathies is an important subject in Oman and other Middle Eastern countries because the high incidence drains health resources and they drastically affect family and personal life. The frequency of haemoglobinopathies in the Arabian peninsula is amongst the highest in the world [21-23].

Data confirmed that Haemoglobinopathies are a major health problem in Oman with birth prevalence of Sickle Cell Anemia (SCA) 1 in 370 or 2.7 per 1000 and Beta-thalassaemia was 1 in 2594 or 0.38 per 1000 [24-26].

The only way the SCA gene can be maintained at high frequency in a population in the face of the genetic unfitness of homozygotes is by selective advantage (new mutation are extremely rare) and natural selection.

Age distribution of SCA patients in 1995 (Figure 6) shows a sharp decline in the frequency of sickle cell disease patients over 18 years. It would suggest natural selection with increased mortality associated with SCA in the years before specialized medical services were available in Oman.

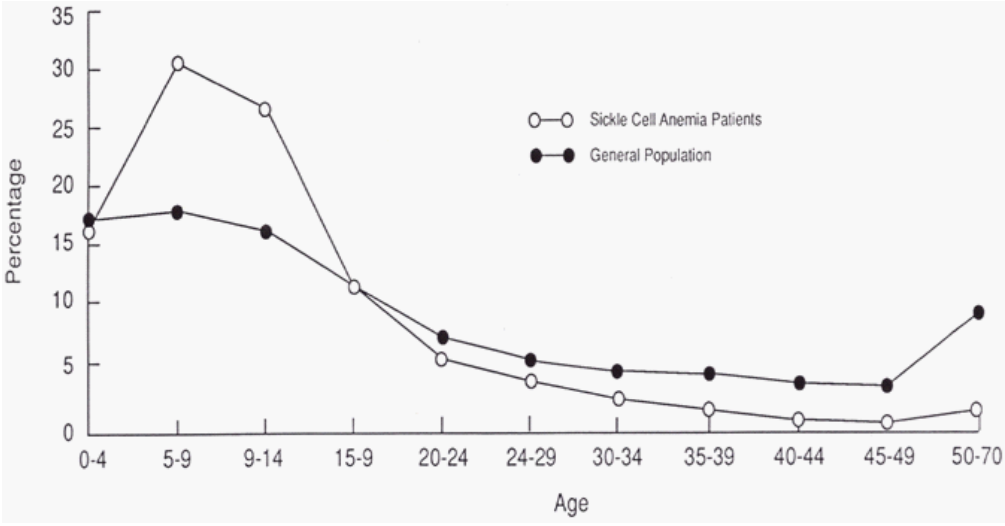


Figure 6: Percentage distribution by age of Sickle Cell Anemia patients in 1995 indicate decreased survival in patients which were born before modern healthcare became available.

On the global scale, a close positive correlation between rates of malaria transmission, βS and β-thal gene frequency are seen. The βS gene found at high frequency in populations living in areas where P. Falciparum is endemic. Until recently Oman was a hyper endemic malarial area. Extensive malaria eradication activities in Oman from 1971 were followed by complete eradication.

The considerable variation in prevalence of SCA in Oman generally coincides with the incidence of malaria indicating that malaria endemicity played a major role in maintaining high frequencies of heterozygotes. Most of SCA cases in Oman are found in agricultural areas where a continuous chain of villages situated along well-watered walleyes provide favorable conditions for malaria transmission. The exceptions were two Regions (Sharqiya and Capital Regions) with high incidence of SCA (17.5% of heterozygotes) in spite of a relatively low malaria incidence. The history of previous migration to East Africa and the discovery of Bantu and Benin Beta Globin haplotypes support gene flow hypothesis [24].

Detailed study of Beta Globin haplotypes [23] confirmed the presence of Benin, Arab-Indian and Bantu haplotypes in Oman originated trough ancient contacts between Oman, Africa and Asia.

The environmental diversity may have its affect on gene frequency. It was surprising to discover complete absence of SCA from the Al Wusta Region, a large nomadic territory with a small population of 16000. Malaria transmission is expected to be interrupted in migrating populations and in desert weather conditions.

The absence of SCA patients in Dhofar region was unexpected since it receives a higher rain fall, and has an abundance of mosquitoes and tropical vegetations. One of the reasons for low level of malaria is a different strain of mosquito (Anopheles coustiani) in which the malarial parasite is not able to complete its life cycle (sporogony) to undergo full replication. The second reason could be greater isolation of Dhofar in the past as a factor in preventing population admixture with neighboring regions of Oman. There is historic evidence of massive migration into Dhofar from Yemen in the 16th century after the collapse of the Mareb dam. Yemen is known as highly endemic malarial area. It is now recognized that alleles and genotypes within the gene pool are prone to variation, and the variation may change from one generation to the next. The sickle-cell trait, though inherited through a single gene, does not necessarily maintain a constant frequency in a population from generation to generation, but that it's frequency is the result of two opposing processes of natural selection. The gene of SCA tends to be eliminated from the population because of the death of homozygotes from SCA (Figure 6), while, in the presence of endemic Falciparum malaria, homozygotes for normal adult haemoglobin (A) have a higher mortality than heterozygotes with genes for both A and S. The sickle -cell mutation is thus maintained from generation to generation from the pool represented by the favored heterozygotes. So long as malarial incidence remains constant, a state of balanced polymorphism will eventually be reached; but if the former changes, there will be gradual shift towards a new balance of genes. There can, therefore, be no doubt that the frequency of SCA trait in a population is, at least in part, related to the recent malaria history of that population.

If it is assumed that the migrating population from Yemen introduced SCA trait into Dhofar and that the trait disappeared in Dhofar because of absence of malaria, it is possible to make some estimate of the number of generations which are needed for the trait to disappear. The rate of loss or gain of alleles in a population will depend on the size of the breeding population (see below).

The process of allele frequency change in a population is termed random genetic drift. The basic calibrator of drift is effective population size (Ne) which is the size of a homogenous population of equally reproductive individuals that would generate the same rate of genetic drift as is observed in the real population of total census size "N" [27]. In reality human population has individuals of different ages and sexes with difference in geographical and social subdivisions. Those factors affect the rate of genetic drift, therefore Ne estimated indirectly or assumed to be for humans:

Ne =N/2-N/3 [27]. N= total census size of population.

The new mutation introduced has probability of 1-(1/2 N) of becoming extinct, and in situation where there is no advantage of heterozygotes (N=diploid population size). For the

mutation that does eventually become fixed, the average fixation time is about 4Ne generations. For the remainder that eventually becomes lost, the average survival time is about 2 Ne/N in 2N generations: for population of 10,000 the mean survival time before all copies are lost, is only about 10 generations, approximately 250 years. It is difficult to estimate the population size of Dhofar in the 16th century, but if one assumes that it was approximately same size as in the end of 18th century (around 10,000), it is possible that the sickle gene could disappear in about 10 generations (250 years) in the absence of selective advantage of heterozygotes.

The consanguinity can be an important catalyst in unmasking the recessiveness of numerous potential mutations across Beta -Globin loci [18].

The Hardy Weinberg's uncorrected equation gives a heterozygote frequency of AS in Oman of 1 in 10 or 9.86% (q^2= 1/370; q= 1/19.2 or 0.052; p=0.948; 2pq=0.0986). It is known that non-random mating patterns (consanguineous unions in Oman) disturb the genotype frequencies expected on the basis of Hardy-Weinberg's equilibrium by increasing the frequency of homozygotes while decreasing that of heterozygotes. Therefore a correction was carried out (Emery, 1986) for the observed "F" in Oman (P=0.0001): HF = (1-F) x HO = (1-0.0175) x 0.0968 = 0.097 or 9.87%.

(HF, HO = rates of heterozygotes in consanguineous and a non-consanguineous community respectively; F = coefficient of inbreeding).

The percentage of the heterozygotes carriers for sickle cell disease in Oman is 9.87%.

For quantifying genetic effects of inbreeding the population Attributable risk, or Attributable fraction was calculated to denote the proportionate excess risk of morbidity from SCA and BTM associated with inbreeding [28]. Consanguinity in 150 families with SCA and 150 controls presented in Table 4.

Table 4: Consanguinity levels in the families of 150 SCA patients and 150 control families.

Type of unions	SCA patients	Controls matched for age, place of residence.
First cousins	60 (40%)	55 (36.7%)
Second cousins	16 (10.7 %)	11 (7.3%)
Same tribe members	25 (16.6%)	12 (8%)
Unrelated	49 (32.7 %)	72 (48%)
Total	150 (100%)	150 (100%)

Note: Data used for quantifying genetic effects of inbreeding the population(**Attributable fraction)**.

From 2 and 2 tables:

a=sum of consanguineous unions among 150 SCA cases.

b= unrelated parents among 150 SCA cases.

c= sum of consanguineous unions among 150 controls.

d= unrelated parents among 150 controls.

a =101	b=49
c =78	d =72

Methods of the odds ratio by Khoury and Weiss [27,28] for consanguineous marriages: (ad/bc) = 1.9. Relative risk (RR) = a/(c+d) / c(a+b)= 101/150: 78/150=0.67: 0.52=1.3. AF= AR= c(RR-1) : [1+c (RR-1)]. (c= frequency of consanguineous unions among SCA cases = 67.3%= 0.67). AF= 0.67x 0.3: [1+(0.67x 0.3)]=0.166 or 17%. The attributable risk of 0.166 means that about 17 % of SCA cases in Oman can be attributed to consanguineous marriage.

Genetic drift in small populations and isolation can explain the patchiness where some villages or some parts of the same tribe found to be either frequently affected or unaffected altogether. A third of tribes in Nizwa district had no affected members. A considerable condensation of 50% SCA patients found in less than 10% of local tribes. Small tribes and small sections of tribes (of 100-200 members) residing in isolation from main bulk of the tribe had the highest heterozygote frequencies reaching 40%, while larger tribes had comparatively low incidence. One way to study genetic drift is to estimate the effective population size (Kimura & Crow 1963, Emery, 1976). In estimating this it is probably better to avoid the present day populations since with the rapid improvements in public health the population has expanded by four fold in the last 40-50 years and there is now greater mobility which make the divisions between villages less significant. Fortunately Oman has good demographic and genealogical data collected on the tribal sizes in 1907 by Lorimer [6]. From this the size of even remote tribes are recorded together with the villages in which they lived. The effective population size "Ne" can be calculated from 4 Nm Nf

$$Ne = \frac{}{Nm + Nf} = 2Nm.$$

where Nm is the number of males and Nf is the number of females of reproductive years. Assuming that the numbers of females and males are equal (although polygamy and high maternal mortality might well alter this) and that with much lower life expectancy about half the population are children in the pre-reproductive stage of life, then the effective population size is roughly equal to the actual population in a tribe. From this it can be calculated that in a tribal village of 100 an initial HbS heterozygote frequency of 10% could vary between 1% and 19% in the next generation.

The frequency of Beta-thalassaemia was also analyzed independently and overall incidence found to be 1 in 2594 or 0.38 per 1000. One single major tribe or ethnic group contributed to 44% of all cases in Oman. The geographical distribution of BTM in Oman coincides with the distribution of this tribe (Figure 7).

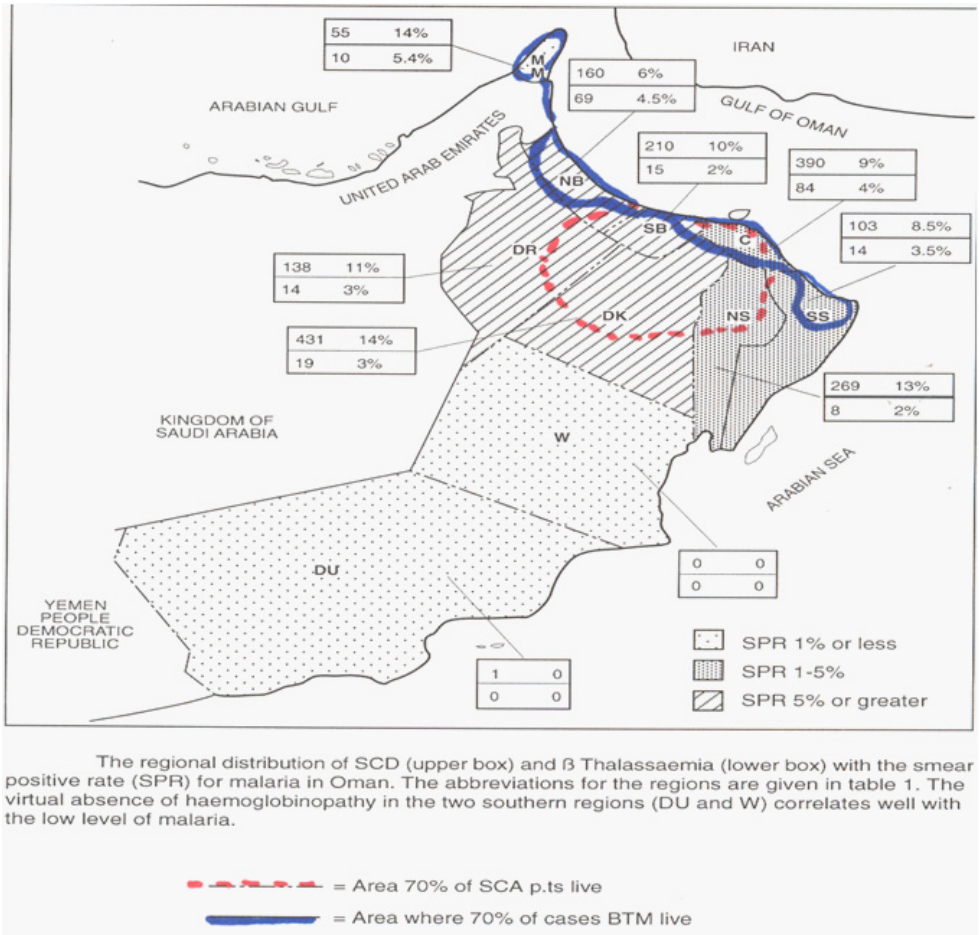


Figure 7: Regional distribution of SCA (upperbox) and BTM (lower box) with the smear positive rate (SPR) for malaria in Oman. First number in the box states the regional number of cases in 1995, second is the regional percent of heterozygotes.

70% of registered SCA cases reside in the area circled in red. 70% of BTM patients live in areas circled in blue.

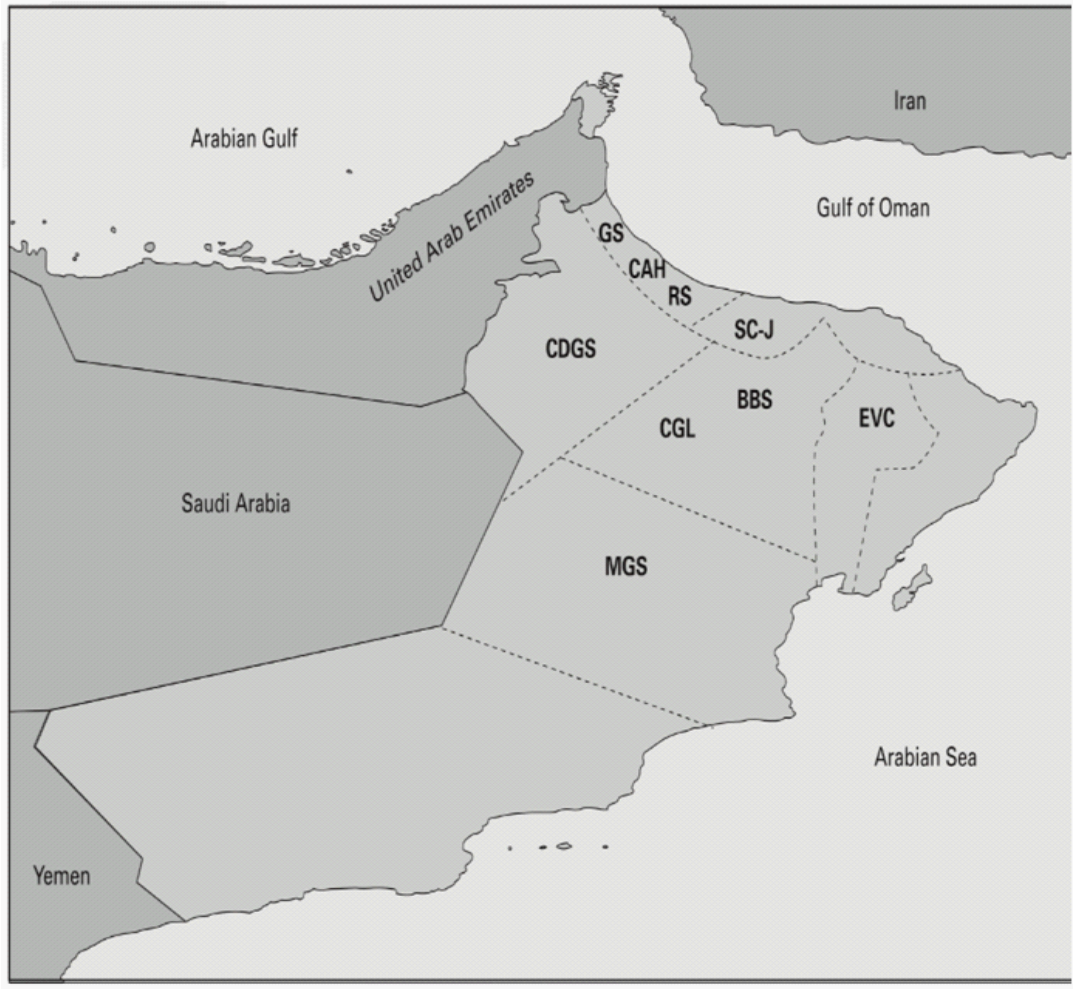
Genetic Disorders

An attempt to measure birth prevalence of recessive disorders frequently ascertained in pediatric practice from Hospital based data 1993-2002 [29] presented in Table 5.

Table 5: Commonly ascertained Autosomal recessive diseases in the Sultanate of Oman among 420.000 livebirth (1993-2002).

Autosomal Recessive Diseases	No of patients born 1993-2002	Observed incidence
Spinal Muscular Atrophy (Wernig-Hoffman disease)	56	1 in 10.000 birth
Congenital Adrenal Hyperplasia	55	1 in 10.000 birth
Polycystic kidneys	34	1 in 12.000 birth
Cystic Fibrosis	32	1 in 15.000 birth
Primary Microcephaly	31	1 in 15.000 birth
Renal Tubular Acidosis	28	1 in 20.000 birth
Congenital Nephrotic Syndrome (Finish type)	25	1 in 20.000 birth
Nesidoblastosis	24	1 in 20.000 birth
Apple-peel bowel syndrome	21	1 in 20.000 birth
Zellweger Syndrome	19	1 in 20.000 birth
Metachromatic Leukodystrophy	18	1 in 25.000 birth
Congenital GeneralisedLipodystrophy	18	1 in 25.000 birth
Ellis-Van Creveld Syndrome	18	1 in 25.000 birth
Scwartz-Jampel Syndrome	15	1 in 30.000 birth
Bardet-Biedl Syndrome	14	1 in 30.000 birth
Robinow syndrome	12	1 in 35.000 birth
Oculocutaneous Albinism	14	1 in 30.000 birth
EpidermolysisBullosa	15	1 in 30.000 birth
Galactosialidosis	9	1 in 50.000 birth
Cerebro-Oculo-Musculo-SceletalSyndrome	9	1 in 50.000 birth
Meckel-Gruber Syndrome	9	1 in 50.000 birth
Carbohydrate Deficient Glycoprotein Syndrome	8	1 in 50.000 birth
Mucopolysacharidoses	8	1 in 50.000 birth

Note: Hospital based data collection indicated high frequencies of rare disorders (Rajab et al., 2005 Community Genet (8): 27-30).



Individual genetic disorders can be often linked to tribal origin and geographical areas of tribal territories (Figure 8).

RS = Robinow Syndrome

CAH = Congenital Adrenal Hyperplasia

CGL = Congenital GeneralisedLipodystrophy

CDGS = Carbohydrate-Deficient Glycoprotein Syndrome

MGS = Meckel-Gruber Syndrome

EVC = Ellis Van Creveld Syndrome

SC-J = Schwartz Jampel Syndrome

GS = Galactosialidosis

BBS = Bardet-Biedl Syndrome

Figure 8: Geographical Areas of Oman Representing High Density of (90% of cases) Autosomal Recessive Conditions.

Rajab et al., 2005 Community Genet (8): 27-30. Copyright permission from S. Karger AG, Basel 28.05.2005.

Mutation data

A Mutation Repository of omani nationals was compiled in order to maximize both scientific and clinical utility of currently available data [18]. It includes 300 mutations causing more than 150 rare genetic disorders. The repository is yet to prove real load of recessive mutations in Oman and may reflect the interest of individual physicians and the accessibility of research facilities. Hemoglobin disorders constituted the largest number of mutations in Repository followed by conditions with intellectual disability and inborn errors of metabolism. Many of the mutations reported are unique to the Omani population, suggesting a founder effect.

The considerable proportion of novel disease genes as well as novel genetic variants was expected due to the presence of inbred and geographically isolated communities, the practice of consanguineous marriages, all of which have tended to skew the allelic spectrum toward rare and private variants. In addition to this, the list of genetic variants also reveals known mutations that were previously reported in certain non-Omani populations, thereby reflecting the historic genetic admixture that occurred in Oman.

Birth defects and genetic conditions, community prevalence 2010-2012

A recently completed population-based study [11] confirmed that autosomal recessive disorders are by far the commonest of the genetic disorders and remain the major contributor to childhood mortality, morbidity and handicap in Oman.

Study demonstrated that large proportion of genetic disorders remain confined to clinical observations with no attempts to delineate their molecular pathologies.

MULTIFACTORIAL DISORDERS

Congenital Malformations Statistics

The types of malformations studied presented in Figure 9. These were 1995-2000 patients inevitably required specialist pediatric surgery, were referred to the only Pediatric Surgery Unit which covers the whole population in Oman and, therefore were more completely ascertained.

A considerable geographical variation in the incidence and distribution of various congenital malformations in the different regions of Oman was noted.

No specific environmental factor has been found to explain the high frequency, but the high rate of consanguinity in this population may play a part. The frequency of first cousin marriages in these cohorts (Figure 9) was roughly twice that of the background population.

Condition	Birth prevalence per 1,000 live births	Reference
Neural tube defects	1.25	Rajab et al. (1998), PMID: 9819495
Facial clefts	1.5	Rajab and Thomas (2001) ISSN: 0930343X CODE: EJPSE in SCOPUS
Hirschsprung's disease	0.3	Rajab et al. (1997) PMID: 9165461
Congenital heart disease	7.1	Subramanyan et al. (2000) PMID: 11219172
Posterior urethral valves	1 in 2,000 males	Rajab et al. (1996) PMID: 8705230

Figure 9: Published figures of birth defects from Oman.

The concentration of patients with certain malformations in some omani tribes suggests the possibility of genetic predisposition. Segregation analysis of the data here did not support autosomal recessive inheritance. An increased frequency of congenital anomalied in the Omani population can be explained by increased polygenic predisposition due to the concentration of predisposing genes.

NON COMMUNICABLE DISEASES

Hypertension and Cardiovascular disorders

In Oman, Cardiovascular diseases **(CVDs)** are the leading cause of death around 30% of all Ministry of Health hospital deaths [30]. Hypertensive heart diseases are the main form of all CVDs in Oman (accounting for 71%) whilst ischaemic heart disease is the foremost cause of CVDs death globally.

Abd El-Aty MA et al. [31] analysed the data from Oman World Health Survey **(OWHS)**, 2008 and estimated prevalence of hypertension in Oman as 41.5%.

Work by Panduranga et al. [32] described the demographics and clinical characteristics of 988 patients in Oman with Acute Heart Failure **(AHF)** as part of the Gulf aCute heArt failuRe rEgistry **(CARE)** project. Ischemic Heart Disease **(IHD)**, hypertensive heart disease, and idiopathic cardiomyopathy were the most common etiologies of AHF in Oman. The mean age of our patients was 63±12 years. The primary comorbid conditions were hypertension (72%), coronary artery disease (55%), and diabetes mellitus (53%).

Diabetes

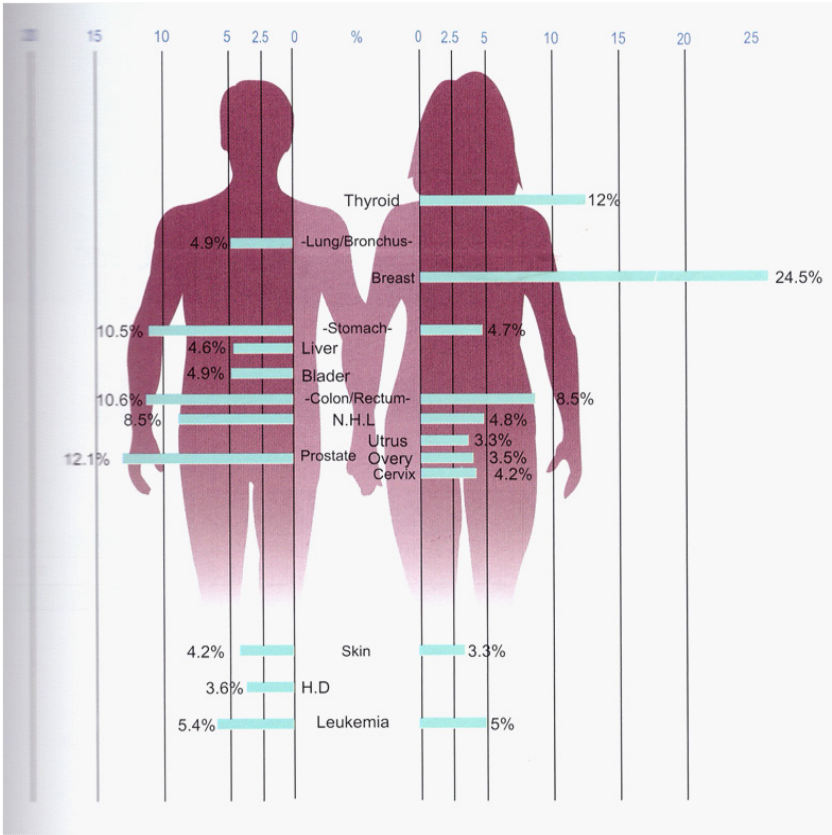
Diabetes and obesity are leading risks posed by the chronic diseases. The burden of diabetes has increased sharply in Oman over the last decade, rising from 8.3% in 1991 to 11.6% in 2000 among adults aged 20 years and older [33].

Al-Lawati [34] describes the epidemiology of diabetes mellitus over the past two decades in Oman, particularly in terms of its prevalence and incidence. Three national and three regional surveys conducted between 1991 and 2010 were analysed to obtain the age-adjusted prevalence and undiagnosed proportion of Type 2 Diabetes Mellitus **(T2DM)** among Omani subjects aged ≥20 years. Diabetes mellitus registers and published studies were used to determine incidence rates of both Type 1 Diabetes Mellitus **(T1DM)** and T2DM in Oman. Linear regression was used to determine trends and projections for diabetes in 2050. The age-adjusted prevalence of T2DM in Oman varied from 10.4% to 21.1%, while the highest prevalence of impaired fasting glucose was found in males (35.1%). In comparison to men, higher incidence rates of T2DM were found in women (2.7 cases compared to 2.3 cases per 1,000 person-years, respectively).

Cancer

The profile of the cancer incidence in Oman for a nine-year period from 1998-2006 presented based on population-based National Cancer Registry [35]. There were a total of 8,005 (4,224 males and 3,781 females) cases reported and registered in the registry from January 1998 till December 2006 with a male female ratio of 1.1:1. The crude incidence rate was 49.4 per 100,000 males and 45.7 per 100,000 females. The corresponding age-standardized rates were 91.4 and 80.4 per 100,000 in males and females respectively.

Stomach cancer, non-Hodgkin lymphoma and leukemia are three commonest cancers in males and breast, thyroid and cervical cancers are the most common in females in the nine-year period (Figure 10). The figures of the incidence of cancer in Oman are lower than in some Gulf countries and many developed countries.



Legend 10: Percentage Distribution of cancers in Oman in males and females. Ministry of Health Sultanate of Oman report 2012 <<www.moh.gov.om>>.

Psychiatric Disorders

A cross-sectional study was conducted on 2005 participants of 25-50 age group attending 27 different PHCs in Muscat Governorate during 2011 [36] showed the prevalence of depression was 8.1% which is in the lower range compared to rate reported from elsewhere.

The adjusted odds ratios generated by logistic regression models indicated that depression was significantly associated with age greater than 50 years old, female gender, married, graduated or attended higher education and having chronic illness such as diabetes mellitus, hypertension, asthma, heart, thyroid, and renal diseases.

In elderly population of Oman the rate of depression was estimated as 16.9% based on comprehensive health assessment conducted in Al Dakhliya governorate 2008-2010 [37]. The information gathered from family pedigrees reflected high incidence of psychiatric disorders in some isolated families (unpublished data).

Aging, rapid unplanned urbanization, and unhealthy lifestyles are risk factors for Non Communicable Diseases **(NCDs)** worldwide. In Oman, NCDs account for approximately 68% of

total deaths. Of these, **(CVDs)** account for 33%, diabetes and cancer account for10% each, and chronic respiratory diseases account for 2% [30].

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