REVIEW

Lung Cancer Incidence in the Arab League Countries: Risk Factors and Control

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Abstract

Although lung cancer incidence rates and mortalities are still low in the Arab world as compared to Europe or USA, they is gradually increasing in the region. Furthermore, there is great variation between different parts of the Arab world. For instance, the age-standardized rates (ASRs) for lung cancer incidence are about 15 fold higher in Tunisia than in Sudan for men, and about 10 fold higher in Bahrain than in Yemen for females. Percentage data for both sexes of lung cancer in the Arab world show that 15/22 (68.1%) of the Arab countries have lung cancer as one of the most frequent five types of cancer. Despite major advances in understanding and treating cancer, the 5-year relative survival rate in North Africa and the Middle East is only 8%. With the notable exception of Algeria, and to a lesser extent Tunisia, where squamous cell carcinomas are more common, the two main types show approximately the same proportions in males, while adenocarcinomas tend to predominate in females. The estimated numbers of new lung cancer cases in 2008 were 9,537 in ages below 65 for both sexes, and 7,059 cases for ages above 65. In 2020 there is expected to be 14,788 new lung cancer cases in the Arab countries for ages below 65, and 14,788 cases for ages above 65 in both males and females. Between 1990 and 1997, cigarette consumption increased 24% in the Middle East, one of only two regions of the world where cigarette sales increased during that period, so that continued rise in cancer rates can be expected. Improvement of tobacco control, registration and treatment are all necessary to decrease the burden of lung cancer in the Arab world.

Keywords: Lung cancer - Arab world - incidence data - mortality - histopathology - risk factors - treatment

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Background

Although the countries of the Arab world occupy two contiguous parts of two continents; namely the South Western Asia and Northern Africa, their populations are homogenous in terms of life style. The Arabs share language, history, culture, religions, habits and ethnicity. The Arab countries are non-industrial developing countries; nevertheless there are huge differences in the economic situation between one region and the other. The available data on cancer burden in the Arab world indicate that incidence rates are increasing due to many factors such as aging, westernization of life style and continued population growth, demonstrating evidence that the cancer problem will continue in the future.

Lung cancer is the most common cancer worldwide, accounting for 1.61 million new cases annually representing 12.7% of all new cancers. It is also the most common cause of death from cancer, with 1.38 million deaths (18.2% of the total). The majority of the cases now occur in the developing countries (55%). Lung cancer rates are particularly high in Central-Eastern and Southern Europe, Northern America and Eastern Asia. Very low incidence and mortality rates are still estimated in Middle and Western Africa with age standardized rate ASRs of 2.8 and 3.1 per 100,000, respectively. In females, incidence rates are generally lower, but, worldwide, lung cancer is now the fourth most frequent cancer of women (513,000 cases, 8.5% of all cancers) and the second most common cause of death from cancer (427,000 deaths, 12.8% of the total) (Ferlay et al., 2010, IARC). Although lung cancer incidence rates and mortalities are still low in the Arab world as compared to Europe or USA, it is gradually increasing in the region. In addition, there is huge variations between different parts of the Arab world. For instance, the age- (ASRs) of lung cancer incidence is about 15 fold times higher in Tunisia than in Sudan for men, and about 10 fold times higher in Bahrain than in Yemen for females. In general, when compared with the other main regions or continents in the world, the median overall incidence and mortality rates of lung cancer in the Arab world is one of the lowest in the world. The forthcoming prediction of estimated numbers of new lung cancer cases in the Arab world show a gradual increase every year. The overall upward trend, although slight, disguises considerable differences between the Arab

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countries. Population growth, aging, increased smoking prevalence particularly in youth and women, as well as increased exposures to environmental pollutants in the region may play a critical role. Although the frequency of different histological types of lung cancer has not been changed in the region; it shows a shift towards squamous cell carcinomas in males and adenocarcinomas in females. The trend has changed in the last two decades in USA and Eastern Europe reflecting changes in patterns of tobacco consumption, the latter is increasing in the Arab world. The comparison between the tobacco prevalence and lung cancer incidences in the Arab populations revealed an obvious risk in most of the Arab countries such as Bahrain, Tunisia, Algeria, Morocco and Libya for males, and Lebanon for both sexes. However, some Arab countries with high smoking prevalence had either low lung cancer incidence rates (Yemen, Sudan and Djibouti), or moderate incidence rates such as Egypt, Syria, and most of the Gulf Cooperation Council (GCC) countries except Bahrain. In contrast to the high incidence and mortality rates of lung cancer in African Americans over Caucasians in the USA, the African Arabs living in Mauritania, Somalia, Djibouti and Comros besides Yemen show the lowest incidence and mortality rates in the Arab countries. The underlying mechanisms for this trend in black Arabs warrant interest. In the recent few years most of the Arab countries showed an increasing attention for cancer care and control with increasing numbers of cancer registries and research societies. Therefore, there is a great need for networking all the cancer research data in the Arab region with involvement of distant populations in the region. This will be certainly of high advantage to the region and to the world (Jazieh et al., 2010).

Demographics

The Arab world is located south to the MediterraneanSea and Western Asia, West to the Arabian Gulf, North to the Pacific Ocean and the Arabian Sea, and East to the Atlantic Ocean. It is stretching from Tunisia, Syria and Iraq, in its most Northern Parts, Morocco and Mauritania in the West, Somalia and Yemen in the South, and the Arab Gulf Cooperation Council countries (GCC) in the East. The total population of the Arab world exceeds 330 million due to the last estimates in 2008, occupying a wide area of about 14 million km^2 which is about 10.3% of the whole world's area of land. Young and youth populations are more than 70% of the whole populations in the Arab countries (Figure 1).

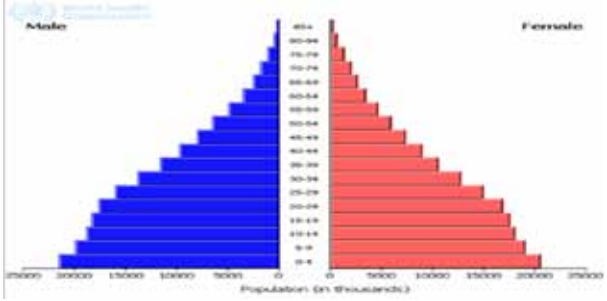

Figure 1. Estimated Midpoint (2008) Population pyramid for the Arab Nations by Gender

Until a few years ago, the information about the cancer epidemiological findings and literature were scant in the Arab world, however, recently there are growing serious efforts for data registry and networking in many parts of the region. Figure 2 shows cancer registries in the region. Over a period of a few years, cancer registries in North Africa (Morocco, Algeria, Tunisia, Libya, Egypt) but not Mauritania increased in number from one to nine (Zanetti et al., 2010). Currently they serve most of the total regional population. Recent publications in PubMed show that many of the national and regional populationbased- registries are effective in the region such as in Libya (Benghazi cancer registry, El Mistiri et al., 2007), Yemen (Aden cancer registry since 2003, Bawazir, 2006; BaSaleem et al., 2010), Morocco (Association Lalla Salmade Lutte Contre le Cancer, 2007), Gulf Center for Cancer Registration (GCCR) which includes Kuwait, Qatar, Oman, Bahrain, UAE and Saudi Arabia since 1998, Iraq (Basrah Cancer registry, Habib et al., 2007), Sudanese Khartoum and Madani cancer registries (Abu Idris et al., 2009), Lebanon: Lebanese Cancer Epidemiology Group since 1998 (LCEG) and others.

In this review, we discuss the lung cancer situationin general and in different areas of Arab world. As well, this report describes the risk factors of lung cancer in theregion particularly in relation with tobacco consumption. For the most part, understanding the various causes of lung cancer in the Arab world provides an opportunity for cancer control and possibly early detection in the region. Thus the incidence, mortality and other data are used in this article to offer insight into prognosis and efficacy of handling lung cancer. The data is estimated mainly from the statistics of IARC, Globocan 2008 (Ferlay et al., 2010), "Incidence of Cancer in Five Continents" IX (Curado et al., 2007), Middle East Cancer Consortium (MECC) (Freedman et al., 2007), and from available regional cancer registries in the region and publications from the PubMed.

Background Approach

This is one of our cumulative cancer incidence reports for the Arab countries. This report attempts to cover all lung cancer cases and epidemiological data in the Arab world in comparison to the neighboring regions and the world. The analysis depended mostly on the world's international data including crude incidence rates (CIR) and age standardized rates (ASRs) calculated using the mid-point estimates of Globocan 2008, IARC (Ferlay

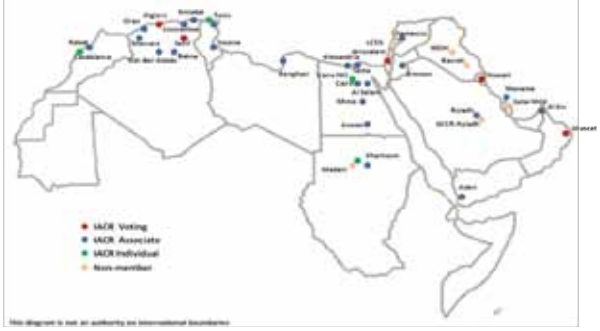

Figure 2. Cancer Registries in the Arab Countries

et al., 2010) and from the available published data in the PubMed, World Wide Web (internet), and personal communications with some cancer registries and specialists in the region. ASRs are a summary measure that a population would have if it had a standard age structure. We used the world standard population in countries with standardized incidence rate per 100,000 populations. ASR was used to compare cancer incidence between different countries. These rates are sensitive to changes in the number of reported cases due to underreporting and changes in the population structure. Therefore, there is a potential for some changes in cancer incidence rates in the Aarb countries that did not have recent population census available for this report or those depend on fewer sources for cancer case identification.

The data included in this report were referenced according to the available references from the region. Some countries still do not have population-based national cancer registries, thus the data included are from Ferlay et al., (2010). A few other data such as histological findings of lung cancer in different Arab countries were calculated from CI5 Vol. IX, MECC (Freedman et al., 2007), and from some available reports from the PubMed. Thus not all Arab countries were included. Cases that are identified after the date of publication will be considered in the subsequent incidence reports. Moreover, some trivial discrepancy occurs sometimes between the data of Globocan 2008, IARC (Ferlay et al., 2010) and recent data published from some national or regional population-based cancer registries perhaps due to the differences in the time of data collection, however, we anticipate that the number of late reported cases in Ferlay et al., (2010) is proportionately related to the nearest accurate average data comparing to the number of sources. For better representation we sometimes mentioned both data from the two sources in this article.

Some Data Sources

National Population-based Cancer Registries:

- Gulf Center for Cancer Registration, Kuwait, Qatar, Oman, Bahrain, UAE and Saudi Arabia, 1999-2005.
- Oman: Cancer incidence in Oman 2008, MOH, Sultanate of Oman; www.moh.gov.om
- Saudi Arabia National Cancer Registry 2006.
- Jordan 2001, Jordan MECC (Freedman et al., 2007).
- Lebanon, Lebanese Cancer Epidemiology Group 1998 (LCEG) (Cancer Program-Tumor Registry, since 1998).

Regional Population-based Cancer Registries:

- Egypt: Gharbiah 2007, NCI 2008.
- Morocco: Association Lalla Salma de Lutte Contre le Cancer (2007).
- Yemen: Aden Cancer registry.
- Algeria: Algiers, Constantine, Oran, & Setif.
- Tunisia: Tunis, Sousse, Sfax.
- Libya, Benghazi cancer registry.
- Iraq: Basrah Cancer registry (Habib et al., 2007).

All others, Globocan (2008), IARC, Cancer mondial CIV volume (IX).

Comprehensive Comparison of International Lung Cancer Incidence

Figures 3 and 4 show the median ASRs of lung cancer globally by continent divisions and in accordance to more-developed or less-developed regions. In general, the overall median incidence and mortality ASRs are markedly higher in the developed regions (47.4, 39.4/100,000 population respectively) than in the developing regions (27.8, 24.6/100,000 population, respectively). The median incidence and mortality ASRs for lung cancer in the whole world is 34, 29.4/100,000 population for males and 13.5, 11/100,000 population for females, respectively. Globally, the incidence and mortality ASRs are highest in Europe, Northern America, Eastern and South-Eastern Asia and in Micronesia and Polynesia. In the developing regions, however, the highest incidence and mortality ASRs of lung cancer in men and women seems to be in Western Asia (30.7, 28.4/100 000 population, respectively) and the lowest incidence and mortality ASRs worldwide are in Eastern Africa (4.1, 4/ 100,000 population), Western Africa (3.1, 2.9/100,000 population) and in Middle Africa (2.8, 2.7/100,000 population) for males and females, respectively. Moreover, an almost similar trend is found in

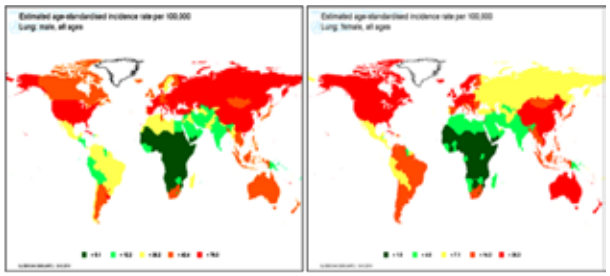

Figure 3. Estimated Age-standardized Incidence Rates for Lung Cancer per 100,000 Population World Wide, Males and Females

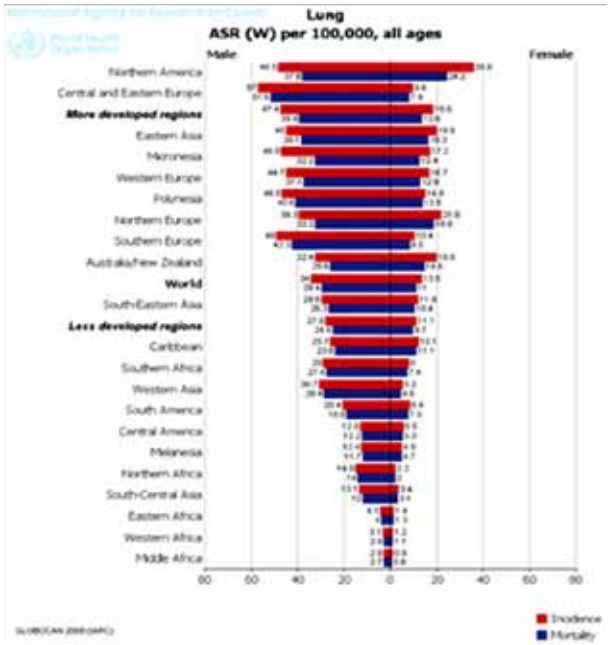

Figure 4. Worldwide Age-standardized Incidence and Mortality Rates of Lung Cancer per 100,000 Population, All Ages

females where the median incidence and mortality ASRs are higher in developed regions than in the developing regions of the world with marked lower rates in females than in the males. The median incidence and mortality ASRs for females are highest in Northern America (35.8, 24.2/100,000 population, respectively) and in Northern Europe (21.8, 18.8/100,000 population respectively) while the lowest median incidence and mortality ASRs in females were found in the same regions of Eastern, Western and middle Africa as in the males (see Figure 4).

Although it is the most frequent cancer in men worldwide, lung cancer is second to prostate cancer in incidence in more developed regions where ASRs are 62 for prostate cancer and 47.4 for lung cancer (Figure 5). Mortality rates are higher in lung cancer than prostate cancer (39.4 lung; 10.6 prostate). For less developed regions incidence and mortality ASRs for lung cancer are the highest among all types of cancer in males. In females, on the other hand, lung cancer incidence and mortality ASRs are the third type of cancer after breast and colorectal cancers in the more developed regions, and third after breast and cervical cancers in the less developed regions.

Overall Incidence and Mortality Rates of Lung Cancer in the Arab World

From data estimated in 2008 (Ferlay et al., 2010), there were 16,632 newly diagnosed lung cancer cases among the Arab league countries nationals. 13,826 cases (79.7%) of them were males and 2,806 (20.3%) were females. The majority of cases were reported in Arab countries in North Africa such as Egypt (20.6%), followed by Morocco (20.1%), Algeria (15.4%) and Tunisia (10%) for both males and females. Furthermore, there was a total of 15,421 deaths related to lung cancer in the Arab populations where (83.3%) of them were in males and (16.7%) were in females. The highest mortality rates due to lung cancer were again estimated in the Northern African Arab countries as compared to other regions of the Arab world. Egypt had 20.7% of the total deaths, followed by Morocco (20.4%), Algeria (15.4%) and then Tunisia (9.9%) (Table 1). The median incidence and mortality ASRs of lung cancer in all the Arab countries collectively showed that the rates in females were lower than those in the males. Incidence ASRs are 13.44/100,000 population for males and 2.91/100,000 population for females (male:female ratio is 4.62:1), while the overall median mortality ASRs in all the Arab countries are 12.59, 2.7/100,000 population for males and females, respectively (male:female ratio is 4.66:1) .

A Comparison between the Incidence and Mortality ASRs of Lung Cancer between the Arab World and Other Main Regions of the World

The median ASR incidence and mortality rates of lung cancer in both males and females in all the Arab countries collectively are one of the lowest in the world. The data are almost similar to the values estimated in the African continent as a whole (incidence ASRs are 12.45, 11.75/100,000 population respectively for males and mortalities are 13.5, 11/100,000 population for females (Figure 6). A huge difference occurs as the mean incidence and mortality ASRs data of the Arab world collectively are almost one fourth of the data estimated for Europe and Northern America and almost half of the estimated mean data for the entire world. The reason for these lower rates in Africa and the Arab world is still unknown. The

Table 1. Incidence and Mortality Rates of Lung Cancer in the Arab League Countries (Ferlay et al., 2010)

Population	Incicence								Mortality							
	Numbers		Crude Rate		ASR (W)		Cumulative Risk		Numbers		Crude Rate		ASR (W)		Cumulative Risk	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Tunisia	1538	117	30.1	2.3	33.5	2.3	4.30	0.29	1420	108	27.8	2.1	30.8	2.1	3.98	0.27
Bahrain	47	14	10.6	4.2	28.1	10.5	3.33	1.38	45	11	10.1	3.3	28.1	8.1	3.23	0.97
Lebanon	525	219	25.6	10.2	27.3	9.7	3.34	1.13	483	202	23.5	9.4	24.9	8.9	3.05	1.04
Libya	551	42	16.9	1.4	25.9	2.1	3.46	0.26	514	40	15.8	1.3	24.5	2.1	3.28	0.25
Morocco	3107	284	20.0	1.8	25.6	2.1	3.10	0.28	2892	265	18.6	1.6	24.0	2.0	2.91	0.27
Algeria	2226	328	12.8	1.9	19.4	2.5	2.49	0.32	2069	303	11.9	1.8	18.2	2.4	2.36	0.30
Jordan	277	59	8.8	2.0	16.5	3.3	2.06	0.40	254	53	8.1	1.8	15.3	3	1.91	0.36
Qatar	48	3	5.0	0.9	16.4	2.5	1.98	0.30	43	3	4.5	0.9	15.4	2.5	1.87	0.30
Iraq	986	329	6.5	2.2	14.7	3.6	1.70	0.40	925	310	6.1	2.1	14.1	3.4	1.62	0.38
Kuwait	92	19	5.3	1.6	13.2	3.9	1.57	0.40	60	23	3.4	2.0	10.4	4.8	0.99	0.49
Gaza and W. Bank	104	19	4.9	0.9	10.8	1.8	1.12	0.21	96	19	4.6	0.9	10.0	1.9	1.09	0.23
Syria	511	131	4.8	1.2	9.9	2.1	1.20	0.25	470	121	4.4	1.2	9.2	2.0	1.11	0.23
Egypt	2652	771	6.5	1.9	9.6	2.5	1.29	0.34	2467	717	6	1.8	9.1	2.3	1.21	0.33
Oman	72	14	4.6	1.2	9.5	2.3	1.16	0.25	67	14	4.3	1.2	0.1	2.3	1.10	0.25
UAE	74	23	2.4	1.6	9.0	4.6	1.13	0.62	67	21	2.2	1.4	8.6	4.4	1.09	0.60
Saudi Arabia	492	170	3.6	1.5	7.2	3.0	0.82	0.34	451	156	3.3	1.4	6.8	2.7	0.76	0.32
Mauritania	27	8	1.7	0.5	3.7	0.9	0.48	0.13	27	8	1.7	0.5	3.7	0.9	0.48	0.13
Comoros	5	0	1.5	0.0	3.6	0.0	0.46	0.00	5	0	1.5	0.0	3.6	0.0	0.48	0.00
Yemen	156	70	1.3	0.6	3.5	1.4	0.41	0.15	146	66	1.3	0.6	3.3	1.3	0.39	0.14
Somalia	60	33	1.4	0.7	2.9	1.4	0.39	0.16	57	31	1.3	0.7	2.9	1.3	0.37	0.15
Djibouti	6	1	1.4	0.2	2.9	0.4	0.35	0.04	6	1	1.4	0.2	2.9	0.4	0.35	0.04
Sudan	270	152	1.3	0.7	2.4	1.2	0.28	0.12	251	143	1.2	0.7	2.2	1.1	0.27	0.11

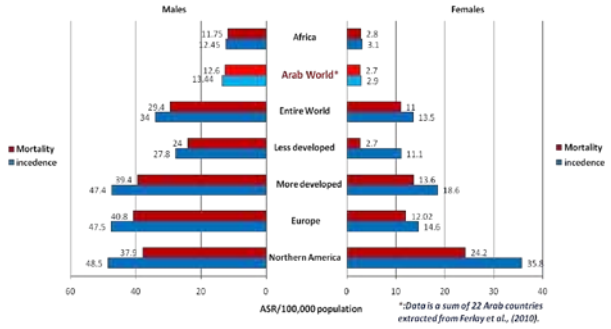

Figure 5. Age-standardised Incidence and Mortality Rates of Lung Cancer in the Arab World in Comparison with Different Parts of the World

Figure 6. Incidence ASRs/100,000 Population in the Arab World, both Sexes

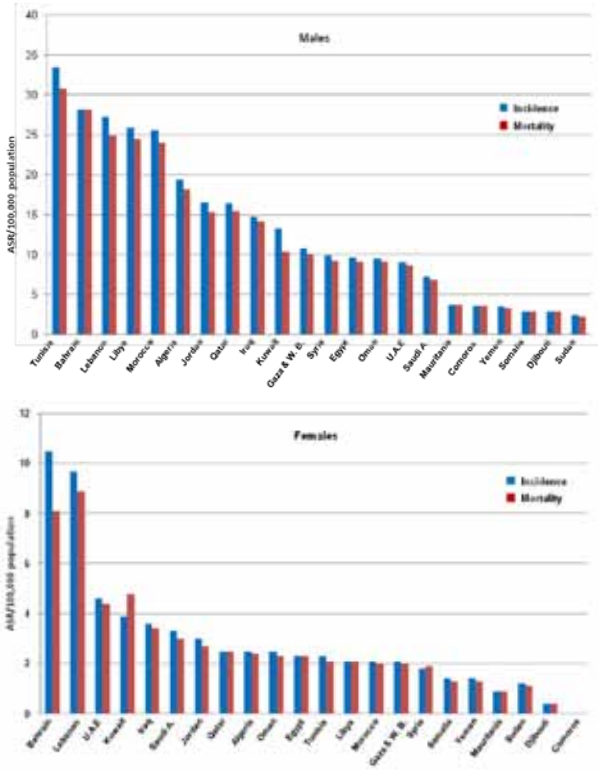

Figure 7. Incidence and Mortalities ASRs of Lung Cancer in All Arab Countries

problems facing cancer registry and information gathering in these two regions are probably one of the reasons in one side. Further genetic and environmental studies remain to be estimated.

African Americans are known to have higher incidence and poorer response to lung cancer treatment compared with Caucasians (Stellman et al., 2003). The risk of lung cancer in United States black men has been about 50% higher than in white men in the past 10-15 years. During 1975 to 1990, the age-adjusted lung cancer incidence in the United States black women was 10% to 20% higher than in white women. However, the underlying molecular mechanisms for the significant ethnic difference are still under investigation. A few studies examined the ethnic differences in the type and frequency of MET proto-oncogene (MET) mutation in lung cancer and correlated them with other frequently mutated genes such as epidermal growth factor receptor (EGFR), KRAS2, and TP53. East Asians, African-Americans, and Caucasians had different MET genotypes and haplotypes. MET mutations in the semaphorin domain affected ligand binding (Krishnaswamy et al., 2009) and could be activated by tobacco smoking. Smoking is responsible for 87% of African Americans lung cancer cases in America (CBCF Health Organization, 2004). Further studies are needed to estimate the risk factors for lung cancer in Africa and the Arab world in comparison with black Americans and other ethnic groups of the world.

Worldwide, the ratio of lung cancer in females is always lower than that in males. The highest incidence rate in the world is observed in Northern America (where lung cancer is now the second most frequent cancer in women), and the lowest is seen in Middle Africa (15th most frequent cancer). The highest incidence ASRs in the Arab countries was in Tunisia (33.5) followed by Bahrain (28.1), Lebanon (27.3), Libya (25.9), Morocco (25.6) then Algeria (19.4). The lowest incidence ASRs in males and females were found in Mauritania (3.7), followed by Comoros (3.6), then Yemen (3.5), Somalia (2.9), Djibouti (2.9), then Sudan (2.4). In females, Bahrain had the highest incidence ASRs (10.5) followed by Lebanon (9.7). The female incidence ASRs of lung cancer in the rest of the Arab countries were all below 5 (Figures 6 and 7).

Yemen which is very close to the Eastern African region also has very low incidence rates of lung cancer although Yemen is known to have a very high frequency of tobacco smoking (see below). Bawazir (2006) concluded that in 2003 the overall frequency of cancer reported in Aden cancer registry among males was cancer of the digestive system (13.8%), followed by buccal cavity, non-Hodgkin's (NH) lymphoma, Leukemia and cancer of liver (12.2%, 12.0%, 10.1%, and 7.1% respectively). In females breast cancer recognized 20.9% of the female reported cancer cases followed by digestive system cancers, female genital system, buccal cavity cancer and NH lymphomas (13.5%, 12.1%, 9.3% and 8.3%, respectively). Lung cancer had lower rates. The overall rate of cancer in Yemen was the lowest compared to other nearby countries either among males or females 26.8 /100.000 population and 29.8/100,000 population respectively. He concluded that the incidence of tobacco related cancer among population in Yemen is more peculiar to the community features with use of tobacco is high and associated with sessions of Kat chewing.

Chopra and Chopra (1977) concluded that among 392 cancers histologically diagnosed in Zanzibar during 1957-62 and 1964-67, skin and cervix cancers were the most common types in both Africans and Arabs. Skin

cancer was predominantly of the squamous cell type. The Zanzibar Arabs thus appear to be protected against basal cell carcinoma which in the Arab desert community has been diagnosed with about the same frequency as squamous-cell carcinoma. In the same manner, the Zanzibar Arab immigrants seem to have a reduced risk for stomach and oesophageal cancers, which are common in other Arab countries. This is probably because Arabs in Zanzibar have adopted the dietary habits and other customs of the Zanzibar Africans in whom cancer of the alimentary tract seems to be uncommon. On the other hand, unlike Zanzibar Africans, the Arabs have an increased risk for Hodgkin's disease similar to that of the Omani and Yemini Arab populations where most immigrants came from. Lung cancer incidence rates were very scant at the time of their survey.

Lung and colorectal cancer were the two leading causes of cancer-related deaths among Arab-American men and women (Darwish-Yassine and Wing, 2005). Lung cancer was the leading cause of death in Arab-American men, and breast cancer was the leading cause of death in Arab-American women while for both sexes lung & bronchus cancer was the most leading cause of cancer death in Arab-Americans between 1973 and 2002 in Michigan which is the home to the second-largest Arab-American population outside of the Middle East. New cancer cases and leading cause of cancer death was lung cancer for both men and women in the Arab Americans even when compared to Caucasians and other ethnicity groups in the area. The Michigan Special Cancer Behavioral Risk Factor Survey (SCBRFS) results indicated that Arab Americans with 50 years of age and older have one of the highest smoking prevalence rates compared to other population groups in the state of Michigan. Men are more likely to be smokers (Darwish-Yassine and Wing, 2005).

In the GCC countries, lung cancer was the seventh most common cancer in the GCC six states between 1998 and 2005 (Al-Kawari et al., 2009). 3,486 lung cancer cases (4.8% from all cancers) were reported from all GCC States at that period of time. The overall ASRs for all GCC States were 6.7 and 2.2 per 100,000 populations for males and females, respectively. Lung cancer incidence was significantly higher among men compared to women in all of the GCC States. It ranked third most common cancer in men next to Non Hodgkin's lymphoma and liver cancer. Bahrain had the highest incidence among men and women with ASRs of 31.4/100,000 for males and 12.2/100,000 for females. Qatar ranked second, followed by Kuwait, Oman, and UAE. KSA reported the lowest incidence among males and females (5.2 and 1.5 per 100,000 for males and females, respectively. The last published data of for lung cancer in Saudi Arabia Cancer registry, showed incidence ASRs were 6.1 for males and 2/100,000 for females in 2006. The data presented here from Ferlay et al., (2010) is 7.2 for males and 3 for females, indicating that a slight but gradual increase in the lung cancer incidence rates is occurring in Saudi Arabia. Al-Hamdan et al., (2006) postulated that its incidence has increased by 57% between 2001 and 2005. This observable fact deserves further investigation.

Freedman et al., (2007) showed that the Jordanians and Egyptians have the lowest rates of lung cancer rates in the Middle East Cancer Consortium (MECC) populations. In Lebanon, however, Shamsuddin and Musallam (2010) concluded that national trends in lung cancer incidence and mortality reflect maturity of the smoking epidemic in men but the trend in women is still gradually increasing. Lung cancer was approximately 40% in Jordan around the same period. In Egypt, according to the Gharbiah Cancer registry data between 2000-2002 published in (2007), lung cancer is the fourth most common cancer in men and ninth in women. It represents 7.4% of all male and 2.7% of female malignancies. The Egyptian National Cancer Institute data shows that the frequency of lung cancer was not much different between 2001 and 2006 (NCI, Cairo, 2006).

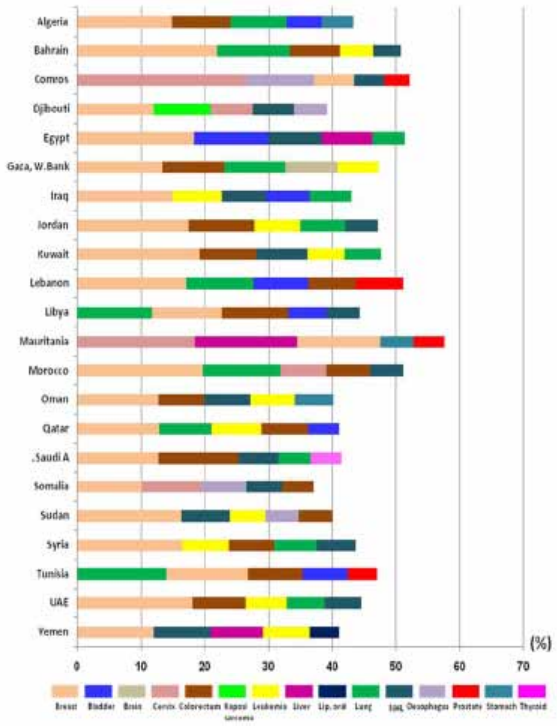

Figure 8. Percentage Data for the Five Most Prevalent Cancers in the Arab Countries, both Sexes

Lung Cancer Ranking in the Arab World

Figure 8 shows the percentage data of most common five types of cancers in both males and females in the Arab world. The data shows that 16/22 (72.7%) of the Arab countries have the lung cancer as one of the most common five types of cancer. More than half 12/22 (54.5%) of the Arab countries have the lung cancer incidence ASRs as the most common cancer type. In females, where breast cancer was the most common (100%) in all Arab countries, while the incidence ASRs of lung cancer rates were relatively low in terms of the most common five types of cancer in females in the region. Only two countries; Bahrain and Lebanon have lung cancer as one the most common five types of cancer (9%). The rank of the lung cancer was different among the Arab countries indicating that the life style, smoking rates, occupational exposure may represent the main risk factors for lung cancer initiation in males as compared to females. Percentage data for both sexes of

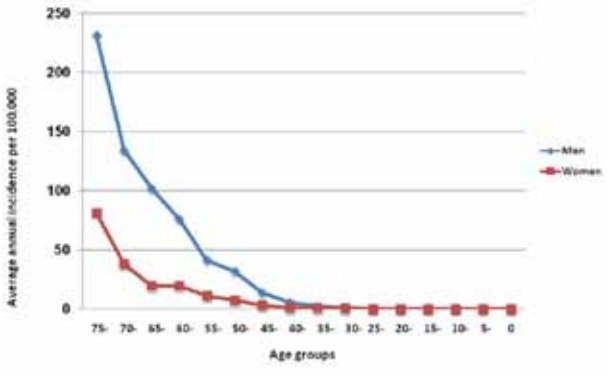

Figure 9. Average Annual Incidence ASRS of Lung Cancer in Arab Countries per 100,000 by Age Group (Data Extrapolated from CIV [Curado et al., 2007])

lung cancer in the Arab world Figure 8 show that 15/22 (68.1%) of the Arab countries have the lung cancer as one of the most frequent five types of cancer in the region. Bahrain and Lebanon had its percentages as the second, while Libya and Tunisia had it as the most frequent type of cancer among all cancers. Breast cancer was the most prevalent type of cancer in both sexes among all types of cancers.

Survival Rates and Age Distribution of Lung Cancer in the Arab World

Lung cancer remains a highly lethal disease. Survival at 5 years measured by the SEER program in the United States is 15%, the best recorded at the population level (Parkin et al., 1999). The average survival in Europe is 10%, not much better than the 8.9% observed in developing countries. According to the World Health Organization, three people die every minute worldwide from lung cancer. The 1-year survival rate for lung cancer has increased from 34% in 1975 to 42% in 1998. Despite major advances in understanding and treating cancer, the 5-year relative survival rate in North Africa and the Middle East is only 8%, a rate that has improved only slightly over the last 30 Years (Parkin et al., 2005). The average annual incidence ASRs of lung cancer in the Arab countries per 100,000 by age group extrapolated from CIV (Curado et al., 2007) shows that lung cancer in the Arab region increases by aging particularly after age 40 for males and 45 for females and then the incidence sharply increases particularly in males more than in females (Figure 9). The probability of developing lung cancer remains low in both sexes until age 39 years (annual incidence per 100,000 is approximately 2.2, 1 for males and females respectively). It then starts to increase among men compared with women, reaching a maximum in those older than 75 years (annual incidence per 100,000 is approximately 231.5, 81.4 among men and women, respectively).

Histology of Lung Cancer

Carcinoma of the lung is divided into four main types: squamous cell carcinoma, adenocarcinoma, small-cell carcinoma and large cell carcinoma (Chung, 1994). Adenocarcinoma has always been more common in women than in men, in both smokers and non-smokers worldwide (Travis et al., 2004). Adenocarcinomas of lung cancer are more frequent in non-smoking patients, and they are lower in frequency in Europe than in Asia or North America (Dosemeci et al., 1997). At present, nearly all widely recognized lung cancer classification scheme is the 4th revision of the Histological Typing of Lung and Pleural Tumors, published in 2004 as a cooperative effort by the World Health Organization and the International Association for the Study of Lung Cancer (Travis et al., 2004). It recognizes numerous distinct histopathological units of small cell lung carcinoma (SCLC) and non-small cell lung carcinoma(NSCLC), categorized by the size and appearance of the malignant cells, as the main types of lung cancer. The treatment is different; NSCLC is sometimes treated with surgery, while SCLC usually responds better to chemotherapy and radiation (Vaporciyan et al., 2000). The majority of lung cancers are carcinomas—malignancies that arise from epithelial cells, with NSCLCs accounting for around 80%..

The NSCLCs are grouped together because their prognosis and management are similar. There are three main sub-types: squamous cell lung carcinoma, adenocarcinoma, and large cell lung carcinoma. Most cases of adenocarcinoma are associated with smoking; however, among people who have never smoked ("never-smokers"), adenocarcinoma is the most common form of lung cancer (Subramanian and Govindan, 2007). A subtype of adenocarcinoma, the bronchioloalveolar carcinoma, is more common in female never-smokers, and may have different responses to treatment (Raz et al., 2006). SCLC is less common. It was formerly referred to as "oat cell" carcinoma. Most cases arise in the larger airways (primary and secondary bronchi) and grow rapidly, becoming quite large. This type of lung cancer is strongly associated with smoking (Collins et al., 2007).

Available data of the Arab world enrolled in CIV, and from publications from some cancer registries in the Arab world are shown in Table 2. With the notable exception of Algeria, and to a lesser extent Tunisia, the two main types show approximately the same proportions in males,while

Table 2. Lung Cancer Histopathology: Squamous Cell Carcinoma (SCC): Adenocarcinoma (AC) Ratios of some Arab Countries

	Male			Female		
	SCC	AC	Ratio	SCC	AC	Ratio
Algeria*	63.0	6.4	9.8:1	43.8	28.1	1.6:1
Egypt*	22.4	24.2	0.9:1	9.1	50.0	0.2:1
Tunisia*	46.6	18.5	2.5:1	23.5	29.4	0.8:1
GCC**	24.7	15.8	1.6:1	19.6	29.0	0.7:1
Palestine*	28.0	26.6	1.1:1	7.4	50.0	0.1:1
Israeli Arabs#	31.4	28.5	1.1:1	11.3	49.3	0.2:1
Jordan#	33.9	24.7	1.4:1	17.7	43.4	0.4:1
Libya***	32.0				23.0	
Morocco***	38.0				40.0	
Iraq****	37.6				13.0	

*Curado et al., 2007; **GCC, sum of the ratio by histological type in 6 Arab countries (Kuwait, Qatar, Bahrain, UAE, Oman and Saudi Arabia) (Al-Kawari et al., 2009); ***Benghazi cancer registry, (2004) #MECC (Freedman et al., 2007); ***: http://www.emro.who.int/ncd/pdf, ****Al Hasnawi et al., (2009)

adenocarcinomas tend to predominate in females. The study of Benghazi Cancer registry of Eastern Libya 2004 (Benghazi Cancer Registry, 2004), showed that the overall ratio for squamous cell carcinomas in both men and women were (32%) higher than adenocarcinomas which accounted for (23%) of all patients with lung cancer. In Morocco (Association Lalla Salma de Lutte Contre le Cancer, 2004), the predominant type of lung cancer was squamous cell carcinoma in men (38%) and adenocarcinoma (40%) in women. The incidence rates observed in Morocco approximated those of Algeria (Setif) and were very low compared to those of western countries and even of Tunisia. In Tunisia, however, the adenocarcinoma incidence was relatively low in 1990 when compared to western countries, but this has been shown to increase to become more common than the squamous cell carcinoma type (B'chir et al., 2007).

In the Arab Gulf Cooperation Council countries (GCC), squamous cell carcinoma was the most frequent cancer in males accounted to 24.7% followed by adenocarcinoma, whereas adenocarcinoma was the most frequent histological type in females accounted to 29% followed by squamous cell carcinoma between 1998 and 2005. The proportion is higher than in European women (Al-Kawari et al., 2009). Al-Hamdan et al., (2006) showed that only Qatar had the highest percentage of lung cancer adenocarcinoma in males than in females in the years between1998-2001, but the ratio in females having adenocarcinomas was higher in all other the GCC countries. The same data was confirmed by Ibrahim et al., (2010) who postulated that lung cancer adenocarcinomas predominated in both male Qatari natives and expatriates; although the study showed that a great majority of the patients (82.5%) were current or ex-smokers at the time of diagnosis. The ratio of lung cancer in Qatar was 8 in males:1 in females which is one of the highest ratios in the world. Adenocarcinomas of the lung in Qatar accounted for about 44% of all lung cancer subtypes while squamous cell carcinomas accounted for 26%. Thus, there is preponderance of adenocarcinoma among lung cancer types in Qatar and squamous cell carcinoma in other neighboring GCC and the Arab counties, besides the reasons of the overall high incidence of lung cancer in Bahrini nationals warrant to be addressed in the future studies and to be compared with the other neighboring Arab countries. On the other hand, Al Hasnawi et al., (2009), reported that the four commonest histopathological types of lung cancer in Iraqi patients were squamous cell carcinoma accounting for 37.6% of the cases, adenocarcinoma (13%), small cell carcinoma (8.3%) and large cell carcinoma accounting for 7 % of the cases.

Although tobacco smoking induces all major histological types of lung cancer, the strongest associations are with squamous cell and small cell carcinoma: the ratio for adenocarcinoma are four- to five fold lower than for other histological types (Thun et al., 1997).The frequency of different histological types of lung cancer has changed over the last two decades in the USA and Europe, so that squamous cell carcinoma has become less common and adenocarcinoma more frequent (Travis et al., 1995). Kuper et al., (2002) estimated that relative risk for lung cancer for ever smokers is 15 for small cell and squamous cell carcinoma, and 3-5 for adenocarcinoma. The attributable risk was 85% in men and 46% in women. The dose response shows, possibly stronger effect with higher smoking intensity and longer duration. And on cessation, a sharp decline in risk occurs, particularly for young people. Fontham et al., (1994) showed that all smoking tobacco products and passive smoking linked to lung adenocarcinoma of duration but some excess risk remains cancer, but not smokeless tobacco. Thus in conclusion, the shifts in histological tumor type distribution, through an increase in adenocarcinoma, reported in the last two decades in the United States, UK and several other developed countries were not observed in most of the Arab patients with lung cancer except for Qatari and Tunisian patients.

10-Year Prediction of Lung Cancer Incidence Rates in the Arab World

The estimated numbers of lung cancer cases worldwide has increased by 51% since 1985 (+44% in men and +76% in women). In men, this increase is due solely to population growth and aging; there has actually been a small (-3.3%) decrease in the actual age-standardized incidence (risk). However, the ASRs have increased by 22% in women (Parkin et al., 2005). This overall increasing trend masquerades substantial variation among countries. In men, several populations have now passed the peak of the lung cancer epidemic, and incidence rates are now declining (such as in the United States (Jemal et al., 2001) and the countries of Northern and Western Europe (Bray et al., 2004). In contrast, incidence and mortality are increasing rapidly in Southern and Eastern European countries (Tyczynski et al., 2004). In women, the epidemic is less advanced; most Western countries are still showing a rising trend in incidence and mortality, although in some this is recent and affecting only recent generations (Spain),

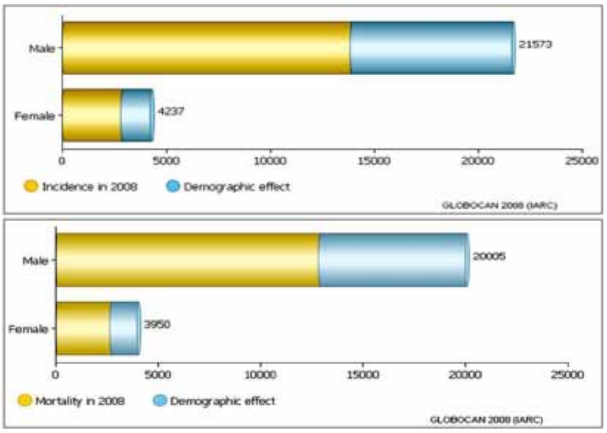

Figure 10. A 10-Year Prediction of Lung Cancer Incidence and Mortality Rates in 22 Arab Countries after Ten Years (2020) Estimated from a population forecast of age-speific incidence and mortality rates and corresponding populations. (extracted from the United Nations World Population prospects, the 2008 revision) (Ferlay et al., 2010). *Demographic effects: are forecasted new number due to corresponding population in 2020)

Table 3. A 10-Year Prediction of Lung Cancer Incidence and Mortality Rates in 22 Arab Countries After Ten Years (2020)

Year	Estimated number of new lung cancers (all ages)	Male	Female	Both sexes
2008		13826	2806	16632
	ages < 65	7985	1588	9537
	ages >= 65	5841	1218	7059
2020		21573	4237	25810
	ages < 65	12393	2395	14788
	ages >= 65	9180	1842	11022
	Demographic change	7747	1431	9178
	ages < 65	4408	807	5215
	ages >= 65	3339	624	3963
Year	Estimated number of cancer deaths (all ages)	Male	Female	Both sexes
2008		12815	2615	15430
	ages < 65	6902	1400	8302
	ages >= 65	5913	1215	7128
2020		20005	3950	23955
	ages < 65	10745	2118	12863
	ages >= 65	9260	1822	11092
	Demographic change	7190	1335	8525
	ages < 65	3843	718	4561
	ages >= 65	3347	617	3964

GLOBOCAN 2008 (IARC)

while for others (United Kingdom), it seems that the peak of risk may now have been reached (Jemal et al., 2004).

In the Arab world, however, although the lung cancer rates are between moderate to low incidences and mortalities, the rates are confirmed to be increasing gradually every year (Shafey, 2007). The Population forecasts extracted from the United Nations, World Population prospects, the 2008 revision (Ferlay et al., 2010), showed that computed numbers using age-specific rates and corresponding populations for 10 age-groups are increasing (see Figure 10). The estimated numbers of new lung cancer cases in 2008 were 9537 in ages below 65 for both sexes, and 7059 cases for ages above 65. In 2020 it is expected to have 14,788 new lung cancer cases in the Arab countries for ages below 65, and 14,788 cases for ages above 65 in both males and females. Also cancer deaths will increase to 12,863 cases in 2020 for ages below 65 and into 11,092 cases for ages above 65 in both sexes in all the Arab countries collectively (Table 3).

Risk Factors for Lung Cancer

The most universal cause of lung cancer is long-term revelation to tobacco smoke (Peto et al., 2006). The rate of lung cancer in nonsmokers, who report for as many as 15% of cases (Thun et al., 2008), is often attributed to amalgamation of genetic factors (Gorlova et al., 2007), radon gas (Catelinois et al., 2006), asbestos (O'Reilly et al., 2007), and air pollution including secondhand smoke (Kabir et al., 2007). All above, and other factors causing chronic bronchitis and inflammation and/or suppression of immunity may lead eventually to lung cancer.

Tobacco smoke

Lung cancer was a rare disease until the beginning of the twentieth century, but since then it has become the most common malignancy worldwide, in terms of both incidence and mortality (Parkin et al., 1999). The geographical and temporal patterns of lung cancer incidence are largely determined by tobacco consumption patterns that took place two or more decades earlier. Populations with a high incidence of lung cancer are therefore those where tobacco consumption has been high during the last decades (e.g. USA, Canada and UK) and lung cancer incidence is low in countries where tobacco consumption has recently declined (e.g. Sweden) or consumption has only increased lately (e.g. China, India, Africa). As men took up tobacco use earlier than women, the increase in lung cancer incidence in men generally precedes that in women by several decades.

Smoking causes more than 80-85 per cent of lung cancer cases. In women, smoking is the source of 45 per cent of all lung cancer worldwide, and more than 70 per cent in North America and Northern Europe (Doll et al., 2005). In both males and females, the frequency of lung cancer is low before age 40, and increases up to age 70 or 75. The rise in female smoking prevalence is a major public health concern. In the US, more women die from smoking-induced lung cancer than from breast cancer. Across the developed world, almost 90% of lung cancer deaths are caused by smoking (Peto et al., 2006). In the United States, smoking is estimated to account for 87% of lung cancer cases (90% in men and 85% in women) (Samet et al., 1998). Among male smokers, the lifetime risk of developing lung cancer is 17.2% while among female smokers, the risk is 11.6%. This risk is significantly lower in nonsmokers: 1.3% in men and 1.4% in women and in some Nordic countries, including Iceland and Denmark, female lung cancer deaths have begun to increase over male tobacco sufferers (Villeneuve and Mao, 1994). In several European countries up to 50 per cent of young women are currently regular smokers; this will cause a disease burden that radically will reduce the women's health in the next decades (Parkin et al., 2005). The relative risk of deaths due to lung cancer is about 20 times higher in smokers rather than nonsmokers. The risk depends on the number of cigarettes smoked per day and the smoking duration. If smoking has started at younger age, the relative risk of dying from lung cancer increases (Wiencke et al., 1999).

Women who smoke (former smokers and current smokers) and take hormone therapy are at a much higher risk of dying of lung cancer. In a study by Chlebowski et al., (2009), the women taking hormones were about 60% more likely to die of lung cancer than the women taking a placebo. Not unexpectedly, the risk was highest for current smokers, followed by past smokers, and lowest for never smokers. Among the women who smoked (former or current smokers), 3.4% of those taking hormone therapy died of lung cancer compared to 2.3% for women taking the placebo. The time a person smokes (as well as rate of smoking) increases the person's chance of developing lung cancer. If a person stops smoking, this chance steadily decreases as damage to the lungs is repaired and contaminant particles are gradually removed (US Department of Health and Human Services, 1990). 10-

15% of lung cancer patients have never smoked (Thun et al., 2006). In the United States, between 20,000 and 30,000 never-smokers are diagnosed with lung cancer each year. Because of the five-year survival rate, each year in the U.S. more never-smokers die of lung cancer than do patients of leukemia, ovarian cancer, or AIDS (Sun et al., 2007). In addition, there is evidence that lung cancer in never-smokers has a better prognosis than in smokers, and that patients who smoke at the time of diagnosis have shorter survival times than those who have quit (Nordquist et al., 2004). Smoking cessation at any age was proved to reduce lung cancer risk over an extended period of time (15-20 years), but it remains higher than never smoker's risk (Peto et al., 2006).

Second-hand (passive) smoking-the inhalation of smoke from another's smoking-is a cause of lung cancer in nonsmokers. Sidestream smoke has a higher concentration of carcinogenic compounds than main stream smoke (Jenkins et al., 2000). A passive smoker can be classified as someone living or working with a smoker. Studies from the U.S., Europe, the UK, and Australia have consistently shown a significant increase in relative risk among those exposed to passive smoke. Recent investigation of side flow smoke suggests that it is more hazardous than direct smoke inhalation (Schick and Glantz, 2005). Second-hand smoking increases the lung cancer risk by 27-80% and about 25% of lung cancer in nonsmokers is attributed to second-hand smoking, which constitutes about 5% of all lung cancer cases. For instance, the risk of nonsmoker spouse increases by 20-30% if the spouse is a smoker (Wen et al., 2006).

Between 1990 and 1997, cigarette consumption increased 24% in the Middle East. The Middle East and Asia are the only two regions of the world where cigarette sales increased during that period. This trend reflected the high male smoking prevalence in the Arab world and the uptake of smoking by a growing number of women (WHO: Tobacco or Health, 1997). Male smoking prevalence in the Arab world remains significantly higher than female smoking prevalence (Mackay and Eriksen, 2002). Many Arab countries (Yemen, Lebanon, Jordan, morocco, Qatar, Egypt, Tunisia, Syria, and Iraq) have very high adult male smoking prevalence rates. Yemen, Tunisia and Djibouti have some of the highest male smoking prevalence rates in the world, close to 60% (Table 4). Smoking prevalence among women in Arab countries is generally low, under 10%, with only three exceptions: Egypt, Lebanon and Yemen. A larger percentage of women in Lebanon and Yemen smoke tobacco than women in the United States (The Tobacco Atlas: WHO, Mackay J and Eriksen, 2002). Worryingly, there are more than 12 Arab countries where at least 10% of girls at age 13-15 smoke. This seems to indicate a dangerous trend toward more widespread female smoking in the Arab World (Shafey, 2007). In Lebanon, Smoking prevalence rates among men were in the range of 50% to 60%. In women, smoking prevalence increased from 28% in the 1960s to 35% in 1992 (Shamsuddin and Musallam, 2010). A the 2005 Global Youth Tobacco Survey in Lebanon which surveyed 3,314 Lebanese school children aged 13-15 years, stated that the rate of use for any tobacco product was 60.1%; for cigarettes the rate was 10% and for other tobacco products it was 59% (Saade et al., 2008). In the Arab world, the Shishah (also known as the water pipe, Hookah, nargileh, arghileh or hubble-bubble) poses a special tobacco problem besides cigarette smoking. Approximately 80% of students lived in homes where others smoked.

Generally there is not sufficient data for quitting rates among tobacco smokers in most of the Arab countries. Comparing the data of the incidence ASRs of lung

Table 4. Adult and Youth Smoking Prevalence, Cigarettes Smoked, and Quit Rates in the Arab countries (Source: Mackay J and Eriksen M. The Tobacco Atlas. Geneva (Switzerland): World Health Organization; 2002)

Country	Population	Adult Smoking Prevalence			Youth Smoking Prevalence			Cigarettes Smoked	Quitting
	(in thousands)	Total	Male	Female	Total	Male	Female	Annually (per person)	Rates*
Algeria	30,291	25.2%	43.8%	6.6%	-	-	-	98	-
Bahrain	640	14.6%	23.5%	5.7%	-	-	-	2,179	-
Comoros	600	-	-	-	-	-	-	-	-
Djibouti	632	31.1%	57.5%	4.7%	-	-	-	-	-
Egypt	67,884	18.3%	35%	18%	-	-	-	1.275	50.0%
Iraq	22,946	22.5%	40.0%	5.0%	-	-	-	1,430	-
Israel**	6.040	28.5%	33.0%	24.0%	-	-	-	2,162	10.0%
Jordan	4.913	29.0%	48.0%	10.0%	20.6%	27.0%	13.4%	1.832	-
Kuwait	1.914	15.6%	29.6%	1.5%	-	-	-	3,062	9%
Lebanon	3,496	40.5%	46.0%	35.0%	-	-	-	-	-
Libya	5,290	4.0%	-	-	-	-	-	1,482	-
Mauritania	2,665	-	-	-	-	-	-	317	-
Morocco	29,878	18.1%	34.5%	1.6%	-	-	-	800	-
Oman	2,538	8.5%	15.5%	1.5%	-	-	-	-	-
Qatar	565	18.8%	37.0%	0.5%	-	-	-	-	-
Saudi Arabia	20,346	11.5%	22.0%	1.0%	-	-	-	810	9%
Somalia	8,778	-	-	-	-	-	-	-	-
Sudan	31,095	12.9%	24.4%	1.4%	-	-	-	77	1%
Syria	16,189	30.3%	50.6%	9.92%	-	-	-	1,283	-
Tunisia	9,459	34.8%	61.9%	7.7%	-	-	-	1,341	-
U AE	2,606	9.0%	18.3%	<1.0%	-	-	-	-	-
Yemen	18,349	44.5%	60.0%	29.0%	-	-	-	-	-

*percentage of people who quit smoking by 2002; ** Including Jews and other ethnic groups, mainly Arabs

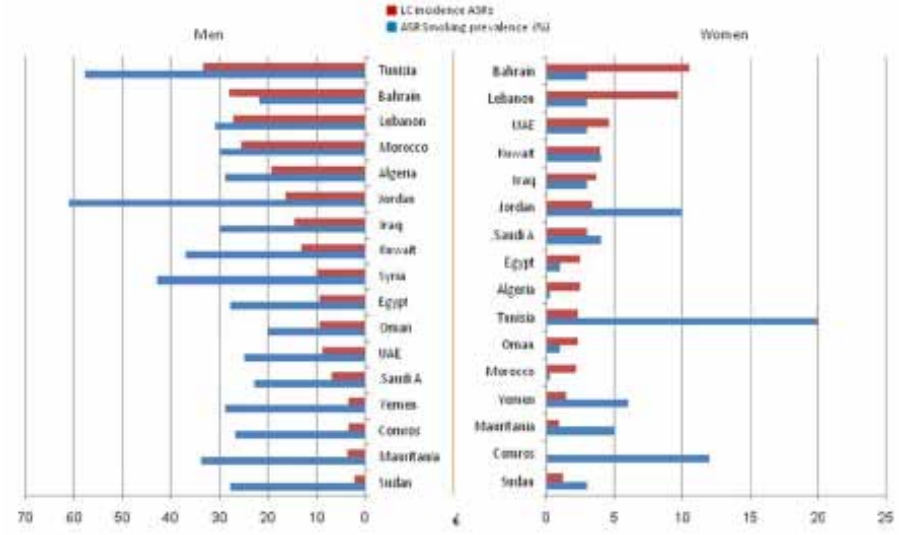

Figure 11. Age-standardized Prevalence of Smoking(%) and ASRs of Lung Cancer Incidence in Most Arab Countries

cancer with the age-standardized prevalence estimates for smoking in the Arab countries (WHO report on the global tobacco epidemic, 2009), shows that most of Arab countries have a high rate of age-standardized (AS) smoking prevalence particularly in males. The highest rates close to 60% in Jordan and Tunisia, around 40% in Syria and Kuwait, around 30% in Lebanon, Morocco, Algeria, Iraq, Egypt, UAE, Saudi Arabia, Yemen, Comros and Sudan while the rate in Oman is 20%. On the other hand, the highest AS smoking prevalence in women was in Tunisia (20%) followed by Comros (12.5%) and Jordan (10%). The other countries had AS-prevalence rates below 10%, where some other Arab countries have very low rates (below 1%) such as Algeria and Morocco (mentioned earlier). The trend for incidence ASRs of lung cancer shows obvious correlation with the smoking frequency in most of the Arab countries, however, in countries such as UAE, Saudi Arabia, Yemen, Comros, Mauritania and Sudan, the incidence of lung cancer is relatively low although high prevalence of tobacco smoke. In women, the high lung cancer incidence rates are seen in some countries with high smoking prevalence, however, in other countries, for example Comros, Mauritania, and Yemen, the lung cancer incidence rates were low although relatively higher smoking prevalence (see Figure 11).

The prevalence of smoking in the GCC countries, obtained from surveys conducted in the mid-1990s (UAE, Bahrain and Oman in 1995; Saudi Arabia and Kuwait in 1996; Qatar in 1998) are published elsewhere (quoted from Al-Hamdan et al., 2006). However the incidence of lung cancer could not be directly attributed to the smoking prevalence from these surveys. The higher prevalence and longer history of smoking among Bahrinians (both men and women) than other GCC nationalities was reflected in the higher incidence of lung cancer and the higher proportion of lung cancer attributable to tobacco smoking compared with other GCC countries (UAE: 28%, 0%; Bahrain: 84%, 65%; Saudi Arabia: 5%, 0%; Oman 40%, 0%; Qatar 69%, 26% and Kuwait: 61%, 2% of percentages of lung cancer cases attributable to tobacco smoking in males and females respectively (Al-Hamdan et al., 2006). In a recent study in Qatar (Ibrahim et al., 2010) a great majority of the lung cancer patients (82.5%) were current or ex-smokers at the time of diagnosis. This is not surprising in view of the etiological role of smoking in lung cancer and in a country with a smoking prevalence of 37%.

In Sudan, although the risk of lung cancer incidence and mortalities is very low, the smoking prevalence is quite high reaching (24.4%) and the AS-smoking prevalence is 28% (Table 9 and Figure 14). Murphy et al., 1994, analyzed the high risk of lung cancer carcinogens in toombak, a type of snuff used in the Sudan. They found high levels of the tobacco-specific carcinogen NNK received by individuals who use this type of tobacco. Two metabolites of NNK which are very strong lung carcinogens namely, 4-(methylnitrosamino)-1 -(3-pyridyl)-1-butanol (NNAL) and its O-glucuronide, NNAL-Gluc were found in the urine of individuals. In the same study, there was a very high risk of wide range of adduct levels which were observed suggested that despite similar levels of NNK exposure, there are significant differences in the ability of individuals in this population to activate NNK, as well as potential differences in their cancer risk. The tobacco borne carcinogens are known to cause 15 different types of cancer, and not only lung cancer (WHO: Tobacco or Health, 2006). Thus the investigation of the relationship of tobacco smoking with other types of cancer is necessary in Sudan and other countries of relatively low lung cancer incidence in the Arab world. Lung cancer incidence (by country) has an inverse correlation with sunlight and UVB exposure. One possible explanation for lower lung cancer incidence in some countries was found to be the preventive effect of vitamin D (which is produced in the skin on exposure to sunlight). Mohr et al., (2008) showed that Lower levels of UVB irradiance were independently associated with higher incidence rates of lung cancer in 111 countries. Also, the high consumption of vegetables and fruits besides enough physical activities and low alcohol consumption could also play pivotal roles in lower incidence of lung cancer in some parts of the Arab world (Bahader and Jazieh, 2008). In fact the reasons for lower cancer rates in most of the Arab countries particularly in these countries lying in Central and Eastern Africa and

Yemen and in women deserve further investigation.

One of the important causes of lung cancer in the Arab world particularly in the Maghreb Arab countries (Morocco, Algeria, Tunisia and Libya) besides Egypt and Lebanon and perhaps others is the use of Marijuana (also termed Bango) and Hashish (cannabis). (Berthiller et al., 2008) conducted three hospital based case-control studies in Tunisia, Morocco, and Algeria, three areas of high prevalence of cannabis consumption and production. They presented the pooled analysis of these three studies restricted to men with a total of 430 cases and 778 controls suggesting that cannabis smoking may be a risk factor for lung cancer in Morocco, Algeria and Tunisia. Residual confounding by tobacco smoking or other potential confounders may explain part of the increased risk in the three countries. In an earlier study (Sasco et al., 2002), evaluating etiologic risk factors for lung cancer in Casablanca, Morocco, a combined use of hashish/kiff and snuff had an odds ratio (OR) of 6.67 (1.65-26.90), whereas the OR for hashish/kiff (without snuff) was 1.93 (0.57-6.58). History of chronic bronchitis had an OR of 4.16 (1.76-9.85). Other slightly increased risks of lung cancer were found for exposure to passive smoking (1.36; 0.71-2.62), occupational exposures (1.75; 0.84-3.63), use of candles for lighting (1.44; 0.42-5.01), and poor ventilation of the kitchen (1.22; 0.57-2.58). Although a study in USA (Hashibe et al., 2006), showed the association of lung and upper aero-digestive tract cancers with marijuana may be below practically detectable limits, the high increase in the use of Hashish and Marijuana (Bango) in certain countries in the Arab world particularly in Egypt and the Maghreb countries, and its relation to lung cancer warrants further attention.

Radon gas

Radon exposure is the second major cause of lung cancer in the general population, after smoking (Catelinois et al., 2006) with the risk increasing by 8% to 16% for every 100 Bq/m^3 increase in radon concentration (Schmid et al., 2010). The exposure to the radon gas was established to be responsible for about 9% of lung cancer in western countries. It is known to have a synergistic effect with tobacco smoking as the latter increases the risk in smoking miners by 10 times over the nonsmoker miners (Darby et al., 2005). Radon is a colorless and odorless gas generated by the breakdown of radioactive radium, which in turn is the decay product of uranium, found in the Earth's crust. The radiation decay products ionize genetic material, causing mutations that sometimes turn cancerous. The United States Environmental Protection Agency (EPA) estimates that one in 15 homes in the U.S. has radon levels above the recommended guideline of 4 picocuries per liter (pCi/L) (148 Bq/m^3) (EPA, 2006). The connection with radon gas was first recognized among miners in the Ore Mountains near Schneeberg, Saxony. Miners developed a disproportionate amount of lung disease, eventually recognized as lung cancer in the 1870s. An estimated 75% of former miners died from lung cancer (US Department of Health Education and Welfare, 1964). To our knowledge, there is no history of exposure to Radon gas in the Arabian region.

Asbestos

Asbestos can cause a variety of lung diseases, including lung cancer. Asbestos exposure has been suggested to be strongly associated with the causation of lung cancer, malignant pleural mesothelioma (MPM) (which is different from lung cancer), and pulmonary fibrosis. The silicate type of asbestos fiber is an important carcinogen. Asbestos exposure increases the risk of developing respiratory tract cancer by as much as 5 times. Tobacco smoke and asbestos exposure act synergistically, and the risk of developing lung cancer for persons who currently smoke tobacco and have a history of asbestos exposure approaches 80-90 times that of control populations (O'Reilly et al., 2007). In the UK, asbestos accounts for 2-3% of male lung cancer deaths (Darnton et al., 2006), Over the past several years, the presence of fibrous asbestos particulates has been observed in a number of municipal water supplies throughout the USA, Canada, and several other regions all over the world. In Egypt, out of all cancer cases, mesothelioma represents 0..5%, and is mainly caused by exposure to asbestos and is currently a problem in Egypt and the incidence is rising (the Egyptian Society of Chest diseases and Tuberculosis, 2006). Asbestos manufacturing began in Egypt more than 50 years ago. By 2004, there were 14 asbestos factories employing thousands of workers with working conditions allowed occupational exposure to various asbestos types on a daily basis. From 2000-2004, 832 cases of mesothelioma were diagnosed at NCI, and Abbassia Chest Hospital, Cairo. Median age was 53 (19-90) years. Females represented 39.2% and young adults = 40 years represented 19.1%. Residential exposure was evidenced in 64.7% of cases. The NCI hospital based-registry showed an increase in the relative frequency of malignant pleural mesothelioma (MPM) from 0.47% in 2001, to 1.4% in 2004 (Gaafar, 2007; Madkour et al., 2009). Since 2006 asbestos industry has been prohibited in Egypt. Another survey in 2006 has detected that old water pipes in Alexandria are made of asbestos-cement (A/C) with drinking water contaminated with traces of asbestos (Hosny and Akel, 2006). In Lebanon Kattan et al., (2001) estimated the incidence of pleural mesothelioma and its relationship with the occupational and environmental exposure to asbestos in Chekka region between 1991 and 2000. In Jordan, Bani-Hani and Gharaibeh (2005) showed only two cases out of seven of MPM were with history of asbestos exposure. In Tunisia also a few cases of occupational exposure occurred in two patients had pleural mesothelioma due to an exposition to asbestos in the field of navy constructions and building (M'barek et al., 2006).

Viruses

Viruses are known to cause lung cancer in animals (Leroux et al., 2007), and recent evidence suggests similar potential in humans. Implicated viruses include human papillomavirus, JC virus, simian virus 40 (SV40), BK virus, and cytomegalovirus (Giuliani et al., 2007). These viruses may affect the cell cycle and inhibit apoptosis, allowing uncontrolled cell division. Moreover, a recent report (Pakkala and Ramalingam, 2010) showed that

lung cancer is the leading cause of mortality among the non-acquired immunodeficiency syndrome defining malignancies. Within the HIV population, the incidence of lung cancer is estimated to be approximately 2 to 4 times that of the general population. Often these patients present with advanced disease (stage III or IV) at a younger age and have an inferior overall survival, when compared with non-HIV patients. Development of lung cancer in patients with HIV has been linked to various factors including immunosuppression, CD4 count, viral load, and smoking. No data available about viral infection and lung cancer in the Arabian region.

Particulate matter

Studies of the American Cancer Society cohort directly link the exposure to particulate matter with lung cancer. For example, if the concentration of particles in the air increases by only 1%, the risk of developing a lung cancer increases by 14% (Krewski et al., 2005). Further, it has been established that particle size matters, as ultrafine particles penetrate further into the lungs (Valavanidis et al., 2008).

Other environmental agents

Air pollution particularly exposure to nitrogen oxides and polyaromatic hydrocarbons (PAHC) from engines and traffic vehicles' exhaust is known to increase the risk of lung cancer (Nafstad et al., 2004). Also exposure to kitchen fumes or metals such as arsenic, beryllium, nickel, copper, chromium, and cadmium has all been implicated in causing lung cancer (Sorahan, 2009). Dietary high fiber fruits and vegetables have been suggested as protective from lung cancer. Although diets rich in fruits and vegetables appear to be associated with lower rates of lung cancer, trials of supplemental beta-carotene, alone or in combination with vitamin E or retinyl palmitate, in persons at high risk for lung cancer found that this supplementation increased the incidence of lung cancers (Wright et al., 2008). On the other hand, sedentary life, alcohol and various dietary factors are known to be associated with the increase in incidence of lung cancer (Byers, 2008).

Genetic Abnormalities in Lung Cancer

It is known that a family history of lung cancer increases the possibility of lung cancer risk in some patients (Stein and Flanagan, 2010). A minority of lung cancers develop in those who have never smoked. These lung cancers are genetically distinct from smoking-related non-small cell lung cancer and may have therapeutic implications. Similar to many other cancers, lung cancer is initiated by activation of oncogenes or inactivation of tumor suppressor genes. Oncogenes are genes that are believed to make people more susceptible to cancer. Proto-oncogenes are believed to turn into oncogenes when exposed to particular carcinogens (Herbst et al., 2008). Mutations in the *K-ras* proto-oncogene are responsible for 10-30% of lung adenocarcinomas (Aviel-Ronen et al., 2006). *Her2/neu* is affected less frequently (Engels et al., 2007). The observed genetic differences include a lower frequency of *K-ras* and a higher frequency of mutations in epidermal growth factor receptor (EGFR) and likely are responsible for the higher efficacy of EGFR inhibitors in the patient population. EGFR regulates cell proliferation, apoptosis, angiogenesis, and tumor invasion. Mutations and amplification of EGFR are common in non-small cell lung cancer and provide the basis for treatment with EGFR-inhibitors (Thun et al., 2008).

Moreover, a diverse range of genetic abnormalities are seen in lung cancer cells. Some may be markers of disease progression; others may have a direct role in lung cancer etiology in the context of gene-environment interactions. TP53 mutations are among the most frequent abnormalities occurring in 80-100% of SCLC and 50-80% of NSCLC (Lee et al., 2010). Mutations of *RB1* are also seen in most SCLCs (80-90%), while they are less frequent in NSCLC (20-30%). Abnormalities of *CDKN2A* (*P16 INK4A*) are inversely correlated with *RB1* mutation; these are seen in about 60% of NSCLC, while less than 1 in 10 SCLC have *CDKN2A* abnormalities (Blons et al., 2008). Bastide et al., (2009) indicated that *Ink4a/Cdk4/Rb1* pathway deregulation, more than Arf/Mdm2/Tp53 pathway, has a major role in the development of radon-induced lung tumors through p16(Ink4a) deregulation. Another frequent mutation is in *FHIT* which is abnormally spliced in about 75% of both SCLC and NSCLC. It has been suggested that the gene is a target of tobacco carcinogens and asbestos (Jayachandran et al., 2007). Up-regulation of the RNA component of telomerase is seen in most lung cancers (98% of SCLC). This may provide a target for future therapies (Chiang et al., 2010).

Genetic polymorphisms are also common in different lung cancer patients. A recent study suggested that the MDM2 309G allele is a low- penetrant risk factor for developing lung cancer in Asians. Common chromosomal abnormalities in lung cancer include del(3p) and del(9p) (Du et al., 2010). Chromosomal damage can lead to loss of heterozygosity. This can cause inactivation of tumor suppressor genes. Damage to chromosomes 3p, 5q, 13q, and 17p are particularly common in SCLC. The *p53* tumor suppressor gene, located on chromosome 17p, is affected in 60-75% of cases (Devereux et al., 1996). Other genes that are often mutated or amplified have been implicated in lung cancer including *c-MET, NKX2-1, LKB1, PIK3CA, MYCN, TP73, MADH2, MADH4, PPP2R1B*, and *PTEN BRAF* (Herbst et al., 2008).

Molecular Attribution of Tobacco Smoke in Lung Cancer Etiology

Unlike many other malignancies, whose causes are largely unidentified, the cause of different types of lung cancer is tobacco smoking in as many as 90% of patients (Biesalski et al., 1998). Tobacco smoke contains more than 300 harmful substances with at least 60 known potent carcinogens including radioisotopes from the radon decay sequence, nitrosamine, and benzopyrene (Hecht, 2003). Additionally, nicotine appears to depress the immune response to malignant growths in exposed tissue (Sopori 2002). This exposure causes cumulative changes to the DNA in the tissue lining the bronchi of the lungs (the bronchial epithelium). As more tissue becomes

damaged, eventually a cancer develops (Vaporciyan et al., 2000). Polyaromatic hydrocarbons and the nitrosamine-4-(methylnitrosamino)-1 -(3-pyridyl)-1 -butanone (NNK) are known to cause DNA damage by forming DNA adducts in animal models (Fujimoto et al., 2010). Benzo-(a)-pyrene also appears to induce molecular signaling such as AKT pathway as well as inducing mutations in p53 and other tumor suppressor genes (Jiao et al., 2008). Recently, advanced molecular techniques have identified amplification of oncogenes and inactivation of tumor suppressor genes in NSCLCs. The most important abnormalities detected are mutations involving the ras family (*H-ras*, *K-ras*, and *N-ras*) encoding proteins on the inner surfaces of cell membranes with GTPase activity involved in signal transduction (Loboda et al., 2010).

Studies performed on mice suggest the involvement of ras mutations in the molecular pathogenesis of NSCLC (Yao et al., 2005). Studies in humans suggest that ras activation contributes to tumor progression in persons with lung cancer. The *ras* gene mutations occur almost exclusively in adenocarcinoma and are found in 30% of such cases. These mutations were not identified in adenocarcinomas that developed in persons who do not smoke. The *K-ras* mutation appears to be an independent prognostic factor. Studies are ongoing to develop management plans according to the presence or absence of *ras* gene mutations (Aviel-Ronen et al., 2006). Other molecular abnormalities found in NSCLC include mutations in *c-myc* and *c-raf* among oncogenes and retinoblastoma (*Rb*) and p53 among tumor suppressor genes (Harris and McCormick, 2010).

Common polymorphisms of certain genes may help explain why some smokers (and passive smokers) are more susceptible to lung cancer than others. In particular, the GSTM1 null allele is associated with increased risk of lung cancer, especially in women (Gervasini et al., 2010). Several genetic polymorphisms are associated with lung cancer. These include polymorphisms in genes coding for interleukin-1 (Engels et al., 2007), cytochrome P450 (Wenzlaff et al., 2005), apoptosis promoters such as caspase-8 (Son et al., 2006), and DNA repair molecules such as XRCC1 (Yin et al., 2007). People with these polymorphisms are more likely to develop lung cancer after exposure to carcinogens such as the chemical carcinogens found in tobacco smoke. On the other hand, although tobacco smoking is the major cause of lung cancer, it is now believed that there may be differences in susceptibility to carcinogenic effects of tobacco smoke among males and females. This may be due to differences in DNA repair mechanisms (Yin et al., 2009). Although still considered controversial, it is known that women are more likely to develop adenocarcinomas, and stage for stage women live longer than men. In addition, differences in response to certain biologic therapies (ie, EGF inhibitors) and anti-angiogenic agents have been observed between sexes (Dempke et al., 2010).

Gene Targeted Therapy for Lung Cancer

Recently, different molecular targeted therapies are used for the treatment of advanced stages of lung cancer. One of these drugs, Gefitinib (Iressa) targets the tyrosine kinase domain of EGFR, which is highly up-regulated in most numbers of NSCLC. However, treatment with Gefitinib was not shown to increase survival rates of most lung cancer patients, however, it gives better results with females, Asians, nonsmokers, and patients with bronchioloalveolar carcinoma (Bencardino et al., 2007). Another tyrosine kinase inhibitor, Erlotinib (Tarceva), was found to increase survival rates in lung cancer patients (Feld et al., 2006), and gives better results, similar to gefitinib, with females, Asians, nonsmokers, and those with bronchioloalveolar carcinoma, specifically those with specific mutations in EGFR (Bencardino et al., 2007). This drug is approved by the FDA for second-line treatment of NSCLC. Bevacizumab, an angiogenesis inhibitor, (in amalgamation with paclitaxel and carboplatin), was shown to improves the survival rates of patients with highly developed non-small cell lung carcinoma (Sandler et al., 2006). However, this drug was shown to have adverse side effects such as increasing the risk of lung bleeding in patients with squamous cell carcinoma. Ongoing research is for a big deal of cytotoxic drugs, pharmacogenetics, and targeted drug design is highly promising (Blackhall and Shepherd, 2007), while a number of objective drugs are at the untimely stages of clinical research, such as cyclo-oxygenase-2 inhibitors, the apoptosis promoter exisulind, proteasome inhibitors, bexarotene, and vaccines (Albright and Garst, 2007). Prospective areas of research comprise ras proto-oncogene inhibition, phosphoinositide 3-kinase inhibition, histone deacetylase inhibition, and tumor suppressor gene substitution (Sun et al., 2007).

Future Perspectives for Lung Cancer Prevention and Treatment

Though the majority of the registries in the Arab countries have not been updated long enough to give information on time-trends, data has been available for a long time in some countries such as Egypt, Jordan, Algeria, Oman, Bahrain, Qatar, Saudi Arabia, Kuwait, UAE and Lebanon. Thus, the indication of lung cancer burden in the countries presented here represents a somehow above average examination of the sufficient data that is available concerning the distribution of the disease in the region.

In spite of the limitations of the present study, convincing values and data are clearly evident. The burden of lung cancer in the Arab countries varies according to community. The median overall incidence and mortality rates of lung cancer in the Arab world are relatively low as compared to different continents and main regions of the world. The scope of dissimilarity when countries are compared may be due racial-ethnic groups, or by a community exposed to certain risk factorsas well as hidden differences in genetic susceptibilities of women and certain ethnic group such as black Arabs. The highly established risk factor for lung cancer in the region is tobacco smoking that functions as main cause of the disease, for which some biological mechanisms are being progressively clarified. For example, the squamous cell carcinomas type of lung cancer still overcomes the adenocarcinoma types in most of the Arab countries

clarifying that the risk, in contrast to certain Western countries where the incidence of squamous cell types are declining due to a decrease in tobacco consumption in the last two decades, is not declining in the Arab countries.

Also, comparative data of time trends of lung cancer in different Arab countries and future calculated predictions indicate that the burden of the disease will loom in the future. Combining tobacco smoking with some occupational or environmental pollutants such as the Asbestos problem in Egypt and-besides drug intake of Marijuana (Bango) and Hashish (Cannabis) in certain countries such as Egypt, Morocco, Algeria, Tunisia and Lebanon are probably one of the key roles for lung cancer initiation in certain communities in the region. This warrants further investigation. No conclusive or sufficient data on the reflection of chronic bronchitis and lung inflammation due to air tract diseases combined with tobacco smoking and expected risk of lung cancer in the region. Arab countries such as Bahrain, Lebanon and Tunisia, have significantly higher ratios of lung cancer incidence and mortalities in both males and females linked to high prevalence of tobacco smoking.

However, higher prevalence of tobacco smoking could not be predicted as a factor affecting low incidence of lung cancer in some other Arab countries with high smoking prevalence (or age-standardized prevalence) rates such as Yemen, Mauritania, Comros, Djibouti and Sudan. These countries have lower incidence rates of lung cancer, perhaps one of the lowest in the world, indicating that other environmental risk factors are more comprehensive for lung cancer interference in certain Arab communities. No studies on the genetic polymorphism in Arab people particularly black Arabs for certain genes responsible for metabolizing tobacco smoke such as GST, CYP1A1, CYP1A2 and others linked with lung cancer. For the most important part, understanding the causes of lung cancer in the Arab world provides a prospect for cancer prevention or premature detection in the region. The changeover from the documentation of the disease to a starting point of action against lung cancer may also be pursued in relation to treatment. Thus incidence, mortality and other research data of genetic polymorphisms and risk factors offer insight into the prognosis and efficacious treatment of lung cancer.

Prominently, stricter ban laws for all forms of tobacco in the Arab league countries for both adults and youth is urgently needed to prevent increased annual incidences of lung cancer. Moreover, a great need for networking all research and epidemiology data between the Arab countries is imperative. More research on the variable genetic polymorphisms of the Arabs and the susceptibilities of certain genes to certain environmental risk factors and pollutants in relation to lung cancer warrants immense interest.

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