Lung Cancer Incidence Patterns in Four Countries of the Middle East Cancer Consortium (Cyprus, Jordan, Israel, Izmir (Turkey)) with Comparison to the United States Surveillance, Epidemiology and End Results (SEER) Program

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Abstract
Lung Cancer (LC) is the leading cause of cancer death worldwide. LC incidence data from four Cancer Registries of the Middle East Cancer Consortium (Cyprus, Israel, Izmir/Turkey and Jordan) are reported with the aim to examine the differences between these four countries and SEER. Cancer registry data on invasive lung cancer diagnoses for 2005-2010 were analyzed. Age-Standardized incidence Rates (ASR) and age distribution were calculated. The percentage of microscopically verified cases, the histological type and staging of the disease were also captured.

There is a greater than 4-fold difference in the total ASR for LC between Izmir/Turkey (51.6) and Jordan (11.6), whilst Cyprus (20.8), Israel Jewish (24.3) and Israel Arab (30.7) have intermediate ASRs. A much lower incidence was observed for women in the MECC countries compared to SEER (37.5), with Israeli Jews having the highest incidence (16.4). For men, both Turkey (98.0) and Israel Arab (54.3) have higher ASRs than SEER (52.5), whilst Jordan has the lowest (19.1). There is a larger proportion of adenocarcinoma in Cyprus and Israeli Jews, and of squamous cell cancer in Turkey. The proportion of patients with metastatic disease is between 52-60.8% for Cyprus, Israel, Izmir Turkey and SEER, but higher at 71.1% in Jordan. Despite the close geographic proximity there are significant differences in LC incidence rates, age distribution, histological types and staging in the four MECC countries that need to be taken into consideration in the design of cancer control and prevention activities in these countries.

Keywords: Population-based Cancer Registries, MECC, SEER, Lung cancer incidence, Histological types, Staging.

Abbreviations
MECC: Middle East Cancer Consortium; SEER: Surveillance, Epidemiology and End Results.

Introduction
The Middle East Cancer Consortium (MECC) is an intergovernmental organization, which was set up in 1996 by the governments of Cyprus, Egypt, Israel, Jordan, the Palestinian Authority and the United States of America (U.S.A.) through the National Cancer Institute (NCI) to help with cancer control activities in the Middle East [1]. The main goal of the MECC is...
to raise cancer awareness in the Middle East and, ultimately, to reduce the burden of cancer in the region. Its first main project was the establishment of population-based cancer registries in all six countries; of these registries, the Israel and Jordan registries were already operational at the time of the formation of MECC [2].

Subsequently in 2004, Turkey joined MECC and Izmir Cancer Registry which was operational since 1992, as the only population based cancer registry in Turkey, was involved in the MECC cancer registry project. Central to the MECC registry was the adoption of a standardized set of definitions, coding and quality control, hence the Manual of Standards for Cancer registration was established, so that reliable comparisons could be made [3].

MECC in conjunction with staff at the NCI, organized a number of training courses for each MECC Country Registry Staff, including training visits and workshops at the NCI. This was followed by a program to assess the levels of completeness and accuracy of the data at each registry, resulting in the establishment of mature population cancer registries in these Countries.

In this paper the data regarding Lung Cancer (LC) Incidence in four member countries, namely; Cyprus, Israel, Izmir/Turkey and Jordan, are being reported. The main aims are to identify and account for differences in LC incidence and as a result identify areas, that can be targeted for future cancer control activities and to generate ‘research hypotheses’ for further investigation by more in depth studies in the future.

Methods
Information about the participating population-based Cancer Registries is included below:

- **The Cyprus Cancer Registry (Cy CR)** is a population-based registry, which started functioning under the MECC structure in May 1998. Cy CR covers the population resident in the Government controlled area of Cyprus. The population resident in the area was 758,000 in 2013. Cy CR covers approximately 92-95% of all cancer cases of the Cyprus Government Controlled Area [4].

- **Jordan Cancer Registry (JCR)**: JCR is a population–based registry, which began as an operational reporting system in the Jordan ministry of health in collaboration with MECC in 1996. The JCR covers the entire kingdom, including all different population groups and nationalities, with a total population estimated to be nine (9) million. An assessment of the JCR of the rates of completeness and accuracy of data was undertaken in 1998 and an 88% completeness rate was found [2].

- **Izmir (Turkey) Cancer Registry**: Izmir is a province in the western region of Anatolia, at the western part of Turkey with 4.1 million inhabitants. Izmir Cancer Registry (ICR) is a provincial population based Registry established in 1993 and eventually has become the core of the Cancer Registry system of Turkey. The estimated completeness of the registration is higher than 97% [5].

- **The Israel National Cancer Registry (INCR)** is a population-based registry established in 1960. The registry covers the entire Israeli population, which numbers approximately 8 million (75% Jewish, 21% Arab, 4% other). Completeness of the registry for solid tumors has been estimated at 93% [6]. Israeli cancer incidence figures were calculated separately for the Jewish and Arab populations to allow comparison in the two ethnic groups.

- **US SEER**: The Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI) contains approximately 97% of all incident cancer cases from 18 Tumor registries in the US that cover 28% of the U.S. population for the time period of years 2005-2010 [7]. The SEER Program registries routinely collect data, as set up in the SEER Staging Manual [8].

Cancer registry data and population denominator data were provided by the four MECC cancer registries: Cyprus, Israel, Izmir/Turkey and Jordan. Data included all of invasive lung cancer diagnoses registered (ICD-Invasive C34.0 - C34.9) for both men and women between 2005 and 2010. Age-standardized incidence rates and age-specific LC incidence rates were calculated using the WHO reference population. The number and percentage of microscopically verified cases, as well as the histological type, and the trend for the 2005-2010 periods was also captured. To facilitate further understanding of the differences in LC Incidence in these MECC countries, the SEER Program data has also been reported to act as a benchmark and to allow comparison with the individual cancer registry data. Finally comparison could also be undertaken with the first publication of data from the MECC Cancer Registration Project, which contained information about cancer incidence from the registries in Cyprus, Egypt, Israel (Jews and Arabs), and Jordan for the period 1996-2001 [9].

Results
During the years 2005 to 2010 there were in total 27,307 lung cancer diagnoses in the four MECC registries; most of these cases come from Israel and Izmir/Turkey, which are the areas with the biggest populations (Table 1). The Age Standardized Rates (ASR) for Lung Cancer (LC), Izmir/Turkey has the highest incidence (51.6) followed by Israel Arab (30.7), Israel Jewish (24.3), Cyprus (20.8), and Jordan (11.6). All countries with the exception of Izmir/Turkey have ASRs between a quarter and two thirds of the SEER rates (44.0).

There are significant gender differences (Table 1). In women the population with the highest LC ASR is Israel Jewish (16.4) followed by Izmir/Turkey (11.4), Cyprus (9.5), Israel Arab (9.4) and Jordan (3.9); all countries with less than half of SEER (37.5). In men the population with the highest incidence is Izmir/Turkey (98.0) followed by Israeli Arab populations (54.3), both higher than SEER (52.5), followed by Cyprus (33.8), Israel Jewish (33.8).
Table 1: Total number of Lung and Bronchus Cancer Cases and Age Standardized rates (WHO World Standard Population) by sex, 2005-2010.

Table 2: Age Distribution of Lung and Bronchus Cancer Cases, by sex, 2005-2010.

and Jordan (19.1).

The age distribution of Lung and Bronchus Cancer Cases, by sex, for the period of 2005-2010 can be seen in table 2. There are similarities in the age distribution of LC cases between SEER, Cyprus and Israeli Jews; cases over 70 years old, in Cyprus and Israeli Jewish populations are respectively 45% and 51.8%, similar to the SEER rate (52.8%), whilst this is much lower for the Israeli Arab (34.6%), Izmir/Turkey (31.1%) and Jordan (25.7%) populations.

The number and percentage of Microscopically Verified Cases for the 2005-2010 periods can be seen in table 3. It ranges between 83-89% for Cyprus, Israel and Izmir/Turkey, similar to the SEER data, but is much higher, between 94-98% for Jordan.

The histological type of LC from the microscopically verified cases can be seen in table 4. There is a large proportion of adenocarcinoma in Cyprus (46.6% of total cases) and Israeli Jews (39.3%) similar to SEER (38.7%), whilst this is much lower in Israel Arab (31.6%), Jordan (28.4%) and Izmir/Turkey (23.1%). Conversely there is a high proportion of squamous cell cancer in Izmir/Turkey (28.2%), which is higher than the other MECC countries and SEER (ranging from 17.8% in Israeli Jews to 23.7% in Israeli Arabs). Small cell cancer rates range between 11.1% in Israeli Jews to 17.1% in Izmir/Turkey. When comparing histological type by gender, women have higher rates of adenocarcinoma compared to their male compatriots for all MECC countries and also SEER. The reverse holds true for squamous cancer, with the rates for men being higher than those for women.

Stage at presentation has been reported according to criteria established by MECC and the 2000 SEER Summary Staging Manual, and subsequently these stages have been grouped together into three categories: localized disease, regional or locally advanced disease and distant or metastatic disease. Unfortunately
<table>
<thead>
<tr>
<th>Country</th>
<th>Number of MV cases</th>
<th>% MV</th>
<th>Cyprus</th>
<th>Israel</th>
<th>Israel-Arab</th>
<th>Izmir-Turkey</th>
<th>Jordan</th>
<th>SEER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Men Women</td>
<td></td>
<td>Total Men Women</td>
<td>Total Men Women</td>
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<td>Total Men Women</td>
<td>Total Men Women</td>
</tr>
<tr>
<td></td>
<td>1179 901 278</td>
<td>85.2</td>
<td>10450 5679 3302</td>
<td>1311 998 181</td>
<td>10532 9364 1168</td>
<td>1825 1510 315</td>
<td>272330 145656 126674</td>
<td></td>
</tr>
<tr>
<td></td>
<td>86.0 86.7 84.6</td>
<td></td>
<td>89.9 90.7 85.8</td>
<td>85.7 86.4 80.6</td>
<td>97.6 97.5 98.1</td>
<td>88.4 89.0 87.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Number and Percentage of Microscopically Verified (MV) Cases, 2005-2010.

<table>
<thead>
<tr>
<th>Country</th>
<th>Total Men Women</th>
<th>Total Men Women</th>
<th>Total Men Women</th>
<th>Total Men Women</th>
<th>Total Men Women</th>
<th>Total Men Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Squamous</td>
<td>Adenocarcinoma</td>
<td>Small cell</td>
<td>Large cell</td>
<td>All others</td>
<td>Total</td>
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<tr>
<td></td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
</tr>
<tr>
<td></td>
<td>236 20.0%</td>
<td>549 46.6%</td>
<td>189 16.0%</td>
<td>24 2.0%</td>
<td>181 15.4%</td>
<td>1179 100%</td>
</tr>
<tr>
<td></td>
<td>200 22.2%</td>
<td>390 43.3%</td>
<td>162 18.0%</td>
<td>19 2.1%</td>
<td>130 14.4%</td>
<td>901 100%</td>
</tr>
<tr>
<td></td>
<td>36 12.9%</td>
<td>159 57.2%</td>
<td>27 9.7%</td>
<td>5 1.8%</td>
<td>51 18.3%</td>
<td>278 100%</td>
</tr>
<tr>
<td></td>
<td>1603 17.9%</td>
<td>3525 39.3%</td>
<td>997 11.1%</td>
<td>635 7.1%</td>
<td>577 18.3%</td>
<td>278 100%</td>
</tr>
<tr>
<td></td>
<td>1236 21.8%</td>
<td>1956 34.4%</td>
<td>708 12.5%</td>
<td>404 7.1%</td>
<td>280 11.1%</td>
<td>278 100%</td>
</tr>
<tr>
<td></td>
<td>367 11.1%</td>
<td>1569 47.5%</td>
<td>289 8.8%</td>
<td>231 7.0%</td>
<td>998 100%</td>
<td>278 100%</td>
</tr>
<tr>
<td></td>
<td>280 23.8%</td>
<td>373 31.6%</td>
<td>165 14.0%</td>
<td>80 6.8%</td>
<td>1179 100%</td>
<td>181 100%</td>
</tr>
<tr>
<td></td>
<td>260 26.1%</td>
<td>291 29.2%</td>
<td>151 15.1%</td>
<td>68 6.8%</td>
<td>998 100%</td>
<td>181 100%</td>
</tr>
<tr>
<td></td>
<td>20 11.3%</td>
<td>82 45.3%</td>
<td>14 7.7%</td>
<td>12 6.6%</td>
<td>181 100%</td>
<td></td>
</tr>
</tbody>
</table>

Table 4: From Microscopically Verified Cases: Number and Percentage, of Lung and Bronchus cases by Histological Type, 2005-2010.

Discussion
There is a marked variation in LC incidence in the four member countries of MECC, with greater than a 4-fold difference in the total ASR for LC between the country with the highest incidence, Turkey/Izmir and Jordan, the country with the lowest incidence. When comparing to SEER, all countries with the exception of Turkey have ASRs between a quarter and two thirds of the SEER rates, whilst Turkey’s ASR for LC is in fact higher than SEER’s. Furthermore there are even larger differences when analyzing LC ASR according to gender, with LC ASR for women being less than half of SEER in all countries, and as low as one tenth of the
SEER ASR in Jordan, which is the MECC country with the lowest incidence. In contrast in men for both Turkey and Israeli Arabs, there is a higher LC ASR compared to SEER.

There is evidence of an exaggerated gender gap in LC incidence especially relevant in Turkey, the Israel Arab and Jordan population. This can be seen by comparing the ratio of LC ASR of men versus women in MECC countries, with a greater than 8 fold difference in Turkey, 5-fold difference in Israeli-Arab, 4-fold difference in Jordan, 3-fold difference in Cyprus and 2-fold difference in Israeli Jewish populations, which can be compared to the 1.4 fold difference in the SEER data between men and women (Table 1).

International variations in LC incidence are commonly thought to reflect differences in the stage and extent of the tobacco epidemic [10,11]. Hence the assumption is that compared to the US, where the tobacco epidemic started earlier and peaked around the middle of the last century, in the countries of the Middle East, the tobacco epidemic has been established more recently, and therefore LC incidence has not peaked as yet. This is especially true for women, with a much lower LC incidence in the Middle East countries compared to the US, probably due to both social and religious reasons prohibiting women from taking up smoking. In men there is a mixed picture, with Turkey and Israeli Arabs having a higher incidence than SEER, hence reflecting higher smoking prevalence in the past in these two populations compared to the US and the fact that both smoking prevalence and LC ASR has been declining in the recent past in the US, whilst Jordan has less than 40% of the SEER LC ASR.

This marked difference in LC incidence in Jordan compared to both SEER and the other MECC countries (especially the 5-fold difference in men/3 fold difference in women compared to Turkey) suggests large differences in smoking habits / tobacco consumption between Jordan and the other countries in question. Furthermore given that LC occurrence closely reflects patterns of smoking, but rates of LC occurrence lag smoking rates by about 20 years, smoking prevalence rates in the countries in question in the 1980’s need to be sourced and to be compared with LC incidence rates presented in this study [12]. Various surveys documenting the smoking prevalence in these countries, however do not show such large differences in smoking prevalence in Jordan compared to the other MECC countries, with the limitation that the data from Jordan stem from the 1990s and not the 1980s [13-19].

Furthermore a study that summarized nationally represented sources regarding tobacco use from 187 countries, providing estimates of smoking prevalence between 1980 and 2012, shows similar smoking prevalence in Jordan (in fact higher) in 1980 in men compared to the other MECC countries and SEER (Data summarized in table 6) [20]. Hence there is a paradox of a much lower LC ASR in men for Jordan (and to a lesser degree in Cyprus) compared to SEER, despite a higher / similar smoking prevalence. Equally for women whilst Israel and Cyprus have similar smoking prevalence rates to the US population, both countries have much lower LC ASR than SEER, whilst Jordan with about one third of the USA smoking prevalence has one tenth of the incidence (Table 6).

Other factors that may play a role in lung carcinogenesis include asbestos exposure, radon exposure, environmental pollution and occupational exposure [21,22]. In Turkey there is evidence to support the presence of both asbestos and arsenic as potential carcinogens causing Lung Cancer, and potentially accounting at least partly for the increased LC incidence seen compared to the other MECC countries /SEER [23,24]. It is also possible that in both Cyprus and Jordan due to lack of heavy polluting industries and less traffic, there is less exposure to other environmental carcinogens than in the US/Israel and Turkey. In the past a similar paradox of low incidence of LC despite a high smoking prevalence was reported for Israeli Arabs, which subsequently was shown to change, with a marked increase in LC among Israeli Arabs, with the authors postulating a gradual loss of some apparent protection in this population, with changes in lifestyle, particularly in dietary habits thought to be involved [25]. There is consistent evidence for protective effects of the Mediterranean diet decreasing the risk of Lung Cancer among heavy smokers, and more generally that high intake of fruit and vegetables is associated with a decreased risk of lung cancer in both smokers and also non-smokers [26-29]. More recently the protective role of cruciferous vegetables in decreasing lung cancer risk has also been shown [30,31]. Finally a potential role of green vegetables protecting against gene promoter methylation in the aero digestive tract of smokers has been proposed as the mechanism by which they protect against the development of lung cancer [32].

Alternative explanations for the low LC incidence in Jordan and to a lesser extent in Cyprus would require large deficiencies on behalf of the Cancer Registries to report all LC cases. A program to assess the level of completeness and accuracy of the data at each registry showed however an overall completeness of 78% for Jordan and 92-95% for Cyprus, hence making it unlikely that failure of the Cancer Registries to capture cases would fully explain the paradox of the low LC incidence in these countries [6,4]. There is however some indirect evidence from the percentage of Microscopically Verified Cases which ranges between 85-89% for Cyprus, Israel and Turkey, similar to the SEER data, but is much higher, at 98% for Jordan, that in the Jordan Cancer Registry patients with a clinical/radiological diagnosis of LC (without histological/cytological proof), may not be recorded, hence LC incidence may be under-

<table>
<thead>
<tr>
<th>Country</th>
<th>Males</th>
<th>Females</th>
<th>Smoking prevalence ratio M/F</th>
<th>Rate LC ASR M/F (table 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyprus</td>
<td>47.9 (42.6,53.5)</td>
<td>23.0 (18.1,28.6)</td>
<td>2.08</td>
<td>3.6</td>
</tr>
<tr>
<td>Israel</td>
<td>39.0 (34.6,43.5)</td>
<td>27.3 (22.4,32.6)</td>
<td>1.43</td>
<td>5.8 / 2.1</td>
</tr>
<tr>
<td>Jordan</td>
<td>53.1 (47.9,58.1)</td>
<td>10.5 (7.7,13.7)</td>
<td>5.06</td>
<td>5.8</td>
</tr>
<tr>
<td>Turkey</td>
<td>42.6 (37.2,48.5)</td>
<td>13.5 (9.9,17.8)</td>
<td>3.16</td>
<td>8.6</td>
</tr>
<tr>
<td>USA</td>
<td>33.2 (29.9,36.7)</td>
<td>28.3 (24.2,32.5)</td>
<td>1.17</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Table 6: Age-Standardized Prevalence of smoking and 95% CI for Males and Females in 1980 [20].

Finally a potential role of green vegetables protecting against gene promoter methylation in the aero digestive tract of smokers has been proposed as the mechanism by which they protect against the development of lung cancer [32].

Int J Cancer Res Ther, 2016

Volume 1 | Issue 1 | 5 of 7
reported (Table 3) [9]. Finally the higher proportion of metastatic disease at presentation in Jordan may result in short survival with some cases dying without investigations or treatment, and perhaps without being registered, hence providing another explanation for the low LC incidence in Jordan.

There is a higher proportion of cases over 70 years old, in Cyprus and Israeli Jewish populations (respectively 45% and 51.8%) and similar to the SEER rate (52.8%), whilst the rate is much lower for the Israeli Arab (34.6%), Turkey (31.1%) and Jordan (25.7%). This is likely related to the different age structure of the respective populations with younger populations in Israeli Arab, Turkey and Jordan compared to Israeli Jews and Cyprus [33].

There are significant differences in LC histology type in the four registries with a large proportion of adenocarcinoma and a lower proportion of squamous cell cancer sin Cyprus and Israel (noted also in the previous MECC Cancer Registry publication), compared to the opposite pattern of high squamous and lower adenocarcinoma seen in Turkish and Israeli Arabs [9]. These are likely to be linked to the type of cigarettes smoked/tobacco products used in the different countries. The rise in adenocarcinoma worldwide over the last 2-3 decades and the decline in squamous cell carcinoma is thought to relate to the changing cigarette types, with low-yield filtered cigarettes resulting in greater depth of inhalation and leading to changes in smoking topography with higher order bronchi in the peripheral lung being exposed to carcinogen-containing smoke, resulting in adenocarcinomas, as opposed to the major bronchi alone, where squamous cancers are often seen [12,34,35,36]. Furthermore there is an important difference with the rate of adenocarcinoma being higher in women compared to their men compatriots for all MECC countries and also SEER. This may be due to the fact that women have a larger proportion of non-smoking related LC than men, with one study in the US estimating 19% of LC in women compared to 9% in men and adenocarcinoma being more common in non-smokers compared with smokers [36-38].

The higher rate of metastatic disease at presentation in Jordan raises the issue of late presentation / poor access to appropriate assessment and investigations in Jordan, compared to the other countries, and merits further investigation. The lower rate of metastatic disease in Cyprus, Israeli Jews and SEER in women compared to their male compatriots may be related to women seeking medical attention at an earlier stage than men. In contrast the opposite trend observed in women in Izmir/Turkey may relate to differences in women’s’ behavior to seek medical advice or lack of access to health care in women compared to men, and again merits further investigation.

Conclusions
Despite the close geographic proximity there are significant differences in the four countries in terms of LC incidence, age distribution, histology and staging at presentation. The low LC incidence especially in Jordan in men, despite similar smoking prevalence rates with SEER, remains a paradox. Protective factors especially in relation to diet may also play a role, which merit further investigation. Differences relating to staging at presentation need also to be further investigated, so that corrective interventions can be implemented. Overall these results can help to design cancer control and prevention activities in the four countries.

References


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