Research Article

International Journal of Cancer Research & Therapy

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

Haris Charalambous[1], Pavlos Pavlou[1], Jenny Chang[2], Freddie Bray[3], Ariana Znaor[3], Lisa Stevens[4], Sultan Eser[5], Barbara Silverman[6], Omar Nimri[7], Anna Demetriou[1], Kevin Ward[8], Argyrios Ziogas[2] and Hoda Anton-Culver[2*]

[1]*National Cancer Registry of Cyprus, Cyprus*

[2]*Department of Epidemiology, University of California Irvine, US*

[3]*International Agency of Research on Cancer, France*

[4]*Center for Global Health, National Cancer Institute, USA*

[5]*Izmir Cancer Registry, Izmir &Ha cettepe University, Ankara, Turkey*

[6]*National Cancer Registry of Israel, Israel*

[7]*National Cancer Registry of Jordan, Jordan*

[8]*Georgia Cancer Registry Emory University, Georgia*

[*]Corresponding author
Hoda Anton-Culver, Professor and Chair, Department of Epidemiology, School of Medicine Director, Genetic Epidemiology Research Institute, University of California, Irvine, US, Tel: 949-824-7416; E-mail: hantoncu@uci.edu.

Submitted: 13 Oct 2016; **Accepted:** 25 Oct 2016; **Published:** 30 Oct 2016

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 NC I, 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)

	Cyprus	Israel Jewish	Israel Arab	Izmir-Turkey	Jordan	SEER
Population	789,014	5,499,600	1,454,167	3,778,123	5,789,833	84,271,106
Total cases	1384	10450	1311	12292	1870	308037
Men	1058	6549	1100	10843	1549	163664
Women	326	3901	211	1449	321	144373
Total rate (ASRW)	20.8	24.3	30.7	51.6	11.6	44.0
Men (ASRW)	33.8	33.8	54.3	98.0	19.1	52.5
Women (ASRW)	9.5	16.4	9.4	11.4	3.9	37.5
Ratio (M/W)	3.6	2.1	5.8	8.6	4.9	1.4

Table 1: Total number of Lung and Bronchus Cancer Cases and Age Standardized rates (WHO World Standard Population) by sex, 2005-2010.

	Cyprus						Israel-Jewish						Israel-Arab					
	Total		Men		Women		Total		Men		Women		Total		Men		Women	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
<50	93	7%	52	5%	41	13%	599	5.7%	364	5.6%	235	6.0%	153	11.7%	125	11.4%	28	13.3%
50-59	212	15%	161	15%	51	16%	1797	17.2%	1124	17.2%	673	17.3%	273	20.8%	226	20.5%	47	22.3%
60-69	444	32%	349	33%	95	29%	2649	25.3%	1734	26.5%	915	23.5%	432	33.0%	377	34.3%	55	26.1%
70-79	433	31%	338	32%	95	29%	3350	32.1%	2164	33.0%	1186	30.4%	346	26.4%	294	26.7%	52	24.6%
> 80	194	14%	153	14%	41	13%	2055	19.7%	1163	17.8%	892	22.9%	107	8.2%	78	7.1%	29	13.7%
UNK	8	1%	5	0%	3	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Total	1384	100%	1058	100%	326	100%	10450	100%	6549	100%	3901	100%	1311	100%	1100	100%	211	100%
	Izmir-Turkey						Jordan						SEER					
	Total		Men		Women		Total		Men		Women		Total		Men		Women	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
<50	1328	10.8%	1101	10.2%	227	15.7%	300	16.0%	229	14.8%	71	22.1%	14536	4.7	7044	4.3	7492	5.2
50-59	3149	25.6%	2815	26.0%	334	23.1%	432	23.1%	357	23.0%	75	23.4%	44980	14.6	24867	15.2	20113	13.9
60-69	3962	32.2%	3579	33.0%	383	26.4%	652	34.9%	562	36.3%	90	28.0%	85647	27.8	47124	28.8	38523	26.7
70-79	3137	25.5%	2771	25.6%	366	25.3%	397	21.2%	329	21.2%	68	21.2%	98367	31.9	52511	32.1	45856	31.8
> 80	685	5.6%	556	5.1%	129	8.9%	85	4.5%	69	4.5%	16	5.0%	64500	20.9	32115	19.6	32385	22.4
UNK	31	0.3%	21	0.2%	10	0.7%	4	0.2%	3	0.2%	1	0.3%	7	0.0	3	0.0	4	0.0
Total	12292	100%	10843	100%	1449	100%	1870	100%	1549	100%	321	100%	308037	100%	163664	100%	144373	100%

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 men 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

	Cyprus			Israel			Israel-Arab			Izmir-Turkey			Jordan			SEER		
	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women
Number of MV cases	1179	901	278	10450	5679	3302	1311	998	181	10532	9364	1168	1825	1510	315	272330	145656	126674
% MV	85.2	85.2	85.3	86.0	86.7	84.6	89.9	90.7	85.8	85.7	86.4	80.6	97.6	97.5	98.1	88.4	89.0	87.7

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

	Cyprus						Israel-Jewish						Israel-Arab					
	Total		Men		Women		Total		Men		Women		Total		Men		Women	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Squamous	236	20.0%	200	22.2%	36	12.9%	1603	17.9%	1236	21.8%	367	11.1%	280	23.8%	260	26.1%	20	11.1%
Adenocarcinoma	549	46.6%	390	43.3%	159	57.2%	3525	39.3%	1956	34.4%	1569	47.5%	373	31.6%	291	29.2%	82	45.3%
Small cell	189	16.0%	162	18.0%	27	9.7%	997	11.1%	708	12.5%	289	8.8%	165	14.0%	151	15.1%	14	7.7%
Large cell	24	2.0%	19	2.1%	5	1.8%	635	7.1%	404	7.1%	231	7.0%	80	6.8%	68	6.8%	12	6.6%
All others	181	15.4%	130	14.4%	51	18.3%	2221	24.7%	1375	24.2%	846	25.6%	281	23.8%	228	22.9%	53	29.3%
Total	1179	100%	901	100%	278	100%	8981	100%	5679	100%	3302	100%	1179	100%	998	100%	181	100%
	Izmir-Turkey						Jordan						SEER					
	Total		Men		Women		Total		Men		Women		Total		Men		Women	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Squamous	2967	28.2%	2800	29.9%	167	14.3%	365	20.0%	335	22.2%	30	9.5%	57706	21.2%	36476	25.0%	21230	16.8%
Adenocarcinoma	2429	23.1%	1961	20.9%	468	40.1%	519	28.4%	389	25.8%	130	41.3%	105399	38.7%	51192	35.2%	54207	42.8%
Small cell	1796	17.1%	1595	17%	201	17.2%	264	14.5%	227	15%	37	11.8%	41071	15.1%	20603	14.1%	20468	16.2%
Large cell	366	3.5%	317	3.4%	49	4.2%	141	7.7%	113	7.5%	28	8.9%	13381	4.9%	7642	5.3%	5739	4.5%
All others	2974	28.2%	2691	28.7%	283	24.2%	536	29.4%	446	29.5%	90	28.6%	54773	20.1%	29743	20.4%	25030	19.8%
Total	10532	100%	9364	100%	1168	100%	1825	100%	1510	100%	315	100%	272330	100%	145656	100%	126674	100%

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

	Cyprus						Israel-Jewish						Israel-Arab					
	Total		Men		Women		Total		Men		Women		Total		Men		Women	
Localized	115	13.6%	75	11.5%	40	20.9%	1404	24.9%	789	22.5%	615	28.8%	147	22.1%	118	19.6%	29	27.9%
Regional	233	27.6%	184	28.1%	49	25.7%	1264	22.4%	801	22.9%	463	21.7%	147	22.1%	130	23.1%	17	16.3%
Distant	497	58.8%	395	60.4%	102	53.4%	2965	52.6%	1909	54.6%	1056	49.5%	372	55.9%	314	55.9%	58	55.8%
Total	845	100.0%	654	100.0%	191	100.0%	5633	100.0%	3499	100.0%	2134	100.0%	666	100.0%	562	100.0%	104	100.0%
	Izmir- Turkey						Jordan						SEER					
	Total		Men		Women		Total		Men		Women		Total		Men		Women	
Localized	990	9.3%	877	9.3%	113	9.5%	114	11.5%	94	11.7%	20	10.9%	54329	19.0%	26266	17.2%	28063	21.0%
Regional	3143	29.5%	2834	30.0%	309	25.9%	172	17.4%	136	16.9%	36	19.7%	67521	23.6%	36017	23.6%	31504	23.6%
Distant	6514	61.2%	5744	60.8%	770	64.6%	702	71.1%	575	71.4%	127	69.4%	164578	57.4%	90443	59.2%	74135	55.4%
Total	10647	100.0%	9455	100.0%	1192	100.0%	988	100.0%	805	100.0%	183	100.0%	286428	100.0%	152726	100.0%	133702	100.0%

Table 5: Stage at presentation among cases with known stage.

there is a large proportion of cases in all registries with unknown staging; this varies between 13.4% in Izmir/Turkey to 28% in Cyprus, 46.1 % in Israel Jew, 47.2% in Jordan and 49.2% in Israeli Arabs, compared to 7.0% for SEER. Stage at presentation in LC cases with known stage can be seen in table 5. The main finding relates to the proportion of patients with metastatic disease being between 52-60.8% for Cyprus, Israel, Izmir Turkey and SEER, but higher at 71.1% in Jordan. Also of note that women in Cyprus, Israeli Jews and SEER appear to present less often with metastatic disease compared to their male compatriots, whilst the opposite trend is observed in women in Turkey.

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).

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

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

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 less 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-

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

1. http://www.cancer.gov/aboutnci/organization/global-health/research-programs-initiatives/mecc
2. Freedman LS, Barchana M, Al-Kayed S, Qasem MB, Young JL, et al. (2003) A comparison of population-based cancer incidence rates in Israel and Jordan. Eur J Cancer Prev 12: 359-365.
3. Middle East Cancer Consortium (2009) MECC Manual of Coding and Staging, 5th Edition, Version 5.1.
4. Pavlos Pavlou, Director Cyprus Cancer Registry. "Report of the Quality Control Audit of the Cyprus Cancer Registry and a Brief Report on other Quality Control Activities". Ministry of Health. Cyprus.
5. Eser S, Ozdemir R, Yakut C, Karakilinc H, Ozen E, et al. (2010) Estimating Completeness of Selected Cancer Registries Data in Turkey; an Evaluation Using the Capture-Recapture Method, The 32nd Annual Meeting of International association of Cancer Registries. Japan 12: 14.
6. Fishler Y, Shetrit A, Barchana M, Modan B (2003) Assessment of the Completeness of the Israel Cancer Registry Database - Methods and Findings [in Hebrew]. Israel Center for Disease Control.
7. http://seer.cancer.gov/about/overview.html
8. Young JL Jr, Roffers SD, Ries LAG, Fritz AG, Hurlbut AA (2001) SEER Summary Staging Manual 2000: Codes and Coding Instructions. National Cancer Institute NIH Pub. No. 01-4969.
9. http://seer.cancer.gov/archive/publications/mecc/mecc_monograph.pdf
10. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, et al. (2015) Global cancer statistics, 2012. CA Cancer J Clin 65: 87-108.
11. Thun M, Peto R, Boreham J, Lopez AD (2012) Stages of the cigarette epidemic on entering its second century. Tob Control 21: 96-101.
12. Alberg AJ, Brock MV, Ford JG (2013) Epidemiology of Lung Cancer: Diagnosis and Management of Lung Cancer, (3rd edn.) American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 143:e1S-e29S.
13. Farazi PA (2014) Cancer trends and risk factors in Cyprus. E cancer medical science 24: 388-389.
14. Sherwood AR, Wang N, Carlile AL, Neumann JM, Wolfgruber TK, et al. (2012) The Hawaiian Freshwater Algal Database (HfwADB): a laboratory LIMS and online biodiversity resource. BMC Ecol 12: 22.
15. Israel Centre for Disease Control (ICDC) 2003b report. MABAT: First Israeli National Health and Nutrition Survey 1009-2001: Part 2-what Israelis eat (in Hebrew) 228.
16. Israel Centre for Disease Control (ICDC) 2006 report. INHIS: Israeli National Interview Survey 2003-2004, part of the

European Health Interview Survey (EURO-HIS) (in Hebrew) 249.
17. Kivity S, Sade K, Abu-Arisha F (2001) Epidemiology of bronchial asthma and chronic rhinitis in schoolchildren of different ethnic origins from two neighboring towns in Israel. Pediatr Pulmonol 32: 217-221.
18. Wu WS, Lai FJ (2015) Properly defining the targets of a transcription factor significantly improves the computational identification of cooperative transcription factor pairs in yeast. BMC Genomics 16 Suppl 12: S10.
19. http://www.infoplease.com/ipa/A0762370.html#ixzz3QRN1rHWr
20. Ng M, Freeman MK, Fleming TD, Robinson M, Dwyer-Lindgren L, et al. (2014) Smoking prevalence and cigarette consumption in 187 countries, 1980-2012. JAMA 311: 183-192.
21. Dresler C (2013) The changing epidemic of lung cancer and occupational and environmental risk factors. Thorac Surg Clin 23: 113-122.
22. Parkin DM1, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. CA Cancer J Clin 55: 74-108.
23. Tarabeia J, Green MD, Barchana M (2008) Increasing lung cancer incidence among Israeli Arab men reflects a change in the earlier paradox of low incidence and high smoking prevalence. Eur J of Cancer Prevention 17: 291-296.
24. Gnagnarella P, Maisonneuve P, Bellomi M, Rampinelli C, Bertolotti R, et al. (2013) Red meat, Mediterranean diet and lung cancer risk among heavy smokers in the COSMOS screening study. Ann Oncol 24: 2606-2611.
25. Fortes C, Forastiere F, Farchi S, Mallone S, Trequattrinni T, et al. (2003) The protective effect of the Mediterranean diet on lung cancer. Nutr Cancer 46: 30-37.
26. Gonzalez CA, Riboli E (2010) Diet and cancer prevention: Contributions from the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Eur J Cancer 46: 2555-2562.
27. Brennan P, Fortes C, Butler J, Agudo A, Benhamou S, et al. (2000) A multicenter case-control study of diet and lung cancer among non-smokers. Cancer Causes Control 11: 49-58.
28. Lam TK, Gallicchio L, Lindsley K, Shiels M, Hammond E, et al. (2009) Cruciferous vegetable consumption and lung cancer risk: a systematic review. Cancer Epidemiol Biomarkers Prev 18: 184-195.
29. Wu QJ, Xie L, Zheng W, Vogtmann E, Li HL, et al. (2013) Cruciferous vegetables consumption and the risk of female lung cancer: a prospective study and a meta-analysis. Ann Oncol 24: 1918-1924.
30. Stidley CA, Picchi MA, Leng S, Willink R, Crowell RE, et al. (2010) Multivitamins, Folate, and Green Vegetables Protect against Gene Promoter Methylation in the Aerodigestive Tract of Smokers. Cancer Res 70: 568-574.
31. Berk S, Yalcin H, Dogan OT, Epozturk K, Akkurt I, et al. (2014) The assessment of the malignant mesothelioma cases and environmental asbestos exposure in Sivas province, Turkey. Environ Geochem Health 36: 55-64.
32. Gunduz O, Bakar C, Simsek C, Baba A, Elci A, et al. (2015) Statistical analysis of causes of death (2005-2010) in villages of Simav Plain, Turkey, with high arsenic levels in drinking water supplies. Arch Environ Occup Health 70: 35-46.
33. Hajjar RR, Atli T, Al-Mandhari Z, Oudrhiri M, Balducci L, et al. (2013) Prevalence of aging population in the Middle East and its implications on cancer incidence and care. Ann Oncol 24 Suppl 7: vii11-24.
34. Travis WD, Brambilla E, Muller-Hermenlink HK, Harris CC (2004) Tumours of the Lung, Pleura, Thymus and Heart. Lyon, France International Agency for Research on Cancer 9-124.
35. Wynder EL, Hoffmann D (1994) Smoking and lung cancer: scientific challenges and opportunities. Cancer Res 54: 5284-5295.
36. Dela Cruz CS, Tanoue LT, Matthay RA (2011) Lung cancer: epidemiology, etiology, and prevention. Clin Chest Med 32: 605-644.
37. Wakelee HA, Chang ET, Gomez SL, Keegan TH, Feskanich D, et al. (2007) Lung cancer incidence in never smokers. J Clin Oncol 25: 472-478.
38. Toh CK, Gao F, Lim WT, Leong SS, Fong KW, et al. (2006) Never-smokers with lung cancer: epidemiologic evidence of a distinct disease entity. J Clin Oncol 24: 2245-2251.