Rising Incidence of Lung Cancer in Arab Females, Jewish Females, and Arab Males from 1990 to 2014 in Israel

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ABSTRACT **Background:** Lung cancer is the most common cause of cancer-related death.

Objectives: To identify changing patterns of lung cancer and its histologic subtypes among different population groups in Israel over a 25 year period.

Methods: Primary lung cancers, all types and all stages, diagnosed during 1990–2014 were recorded in the Israel National Cancer Registry database. Demographic information was retrieved from the National Population Register. Age-standardized rates for the different subgroups were calculated for each year. Joinpoint software was used to analyze trends in incidence.

Results: We identified 42,672 lung cancer cases. The most common histology was adenocarcinoma (34%), followed by squamous cell carcinoma (19%), large cell/not-otherwise-specified (19%), other histologies (15%), and small cell lung cancer (11%). The adenocarcinoma incidence rose from 25.7% to 48.2% during the examined period. Large cell/not-otherwise-specified incidence peaked around 2005–2006 and declined after. Lung cancer incidence increased significantly for the population overall and specifically in Arab females, followed by Jewish females and by Arab males. Adenocarcinoma and small cell lung cancer increased in Jewish females and in Arab males. A younger age of diagnosis was seen in Arab compared to Jewish patients.

Conclusions: Jewish females and Arab males and females living in Israel demonstrated a constant increase in lung cancer incidence, mostly in adenocarcinoma and small cell lung cancer incidence. In addition, a younger age of diagnosis in Arabs was noted. Smoking reduction interventions and screening should be implemented in those populations.

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KEY WORDS: Arab ethnicity, female, Jewish ethnicity, lung cancer, registry analysis

Lung cancer is the leading cause of cancer-related death worldwide, accounting for an estimated 1.6 million cancer deaths yearly [1]. In Israel, lung cancer is the third most commonly occurring cancer (following breast and colorectal cancers) and the number one cause of cancer deaths [2]. Precise data about the relative incidence of lung cancer subtypes and their trends over time can contribute insight into this deadly disease and improve approaches to prevention, diagnosis, and treatment.

Israel is a small country with a population of approximately 8 million people, of whom 75% are Jewish, 21% are Arab, and 4% are not classified by population group [3]. The Israel National Health Insurance Law, passed in 1995, guarantees universal coverage, including a defined basket of health services to all legal residents of the country [4]. Documentation of Israeli cancer cases is conducted by the Israel National Cancer Registry (INCR), a population-based passive central cancer registry. Reporting of all new cancer cases to the registry by health care providers has been mandatory since 1982. The completeness of the INCR is estimated to be 94% for solid tumors [5]. In addition, each Israeli citizen has a single unique identification number, allowing retrieval of reliable demographic data from other national databases. These factors result in an optimal scenario for real-world studies [6], allowing in this case insight into the lung cancer landscape.

Health status disparities among the different ethnic groups of Israel have been identified, and multi-disciplinary interventions are conducted at the national level in an attempt to lower their impact. Although for most cancer types, incidence and mortality are higher among Israeli Jews than among Israeli Arabs, lung cancer constitutes an exception [3]. While in the past lung cancer incidence in Israeli Jews was equal to or higher than that in Israeli Arabs [7,8], current data indicate rising lung cancer rates in the Israeli

Arab population [9], particularly among males. We analyzed lung cancer INCR data to characterize incidence trends stratified by sex, population group, and histologic group. We present an analysis of real-world data for the major lung cancer histologic subgroups and their trends in different population groups during a 25-year period.

PATIENTS AND METHODS

DATA EXTRACTION AND ANALYSIS

Data elements on cancer cases recorded in the INCR include tumor site and morphology, coded according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3). Stage is determined according to the U.S. Surveillance, Epidemiology and End-results (SEER) summary staging system, which defines tumors as in situ, locally spread, regionally spread, or metastatic [10]. Demographic data, including sex and population group (Jewish, Arab, or other), were retrieved from the Ministry of Interior's Israel National Population Register. Population group is reported to the Israeli Ministry of Interior by parents at birth or self-reported at immigration. Basis of cancer diagnosis is coded in the INCR database as pathology report, cytology, clinical investigation (indicating medical records but no pathology/cytology report), or death certificate only (DCO). Approximately 5% of new cases in the INCR are currently based on DCO.

We searched the INCR database for all diagnoses with ICD-O-3 typography site code 34.* (cancers of the lung and bronchus), with behavior code 3 (invasive) and diagnosis year between 1990 and 2014, excluding hematologic malignancies. Identified cases were categorized into histology groups based on the World Health Organization classification [11]. Number of cases diagnosed per year by sex and by population group (Jewish, Arab, or other) was calculated. For the Jewish and Arab population groups, age-standardized incidence rates (ASR) per 100,000 were calculated using direct standardization and the Segi World standard as the standard population. ASR were not calculated for the group categorized as 'other' due to its small size (3.9% of the cohort) and because age- and sex-specific data were not available for age standardization for the entire follow-up period for the 'other' group. Standard errors for ASR were calculated using the binomial approximation. Joinpoint software [12] was used to assess trends in incidence of lung cancer overall and by histologic groups for the study period. Ages at diagnosis in different population groups were compared by *t*-test or ANOVA test. Statistical analysis was performed using SAS Enterprise Guide version 7.1 software (SAS Institute Inc., Cary, NC, USA).

ETHICS

This study was performed in accordance with the Israel National Cancer Registry's mandate to perform surveillance of cancer incidence and characteristics and therefore was not subject to institutional review board approval.

RESULTS

LUNG CANCER INCIDENCE TRENDS

We identified 42,672 cases of lung cancer during the study period: 23,554 Jewish males, 13,189 Jewish females, 3638 Arab males, 604 Arab females, 1249 'other' males, and 438 'other' females. The large majority of diagnoses (68.7%) were based on pathology reports, 16.9% were based on cytology reports, 7.6% were based on clinical investigation, and 5.9% were based on DCO. Regarding the entire studied population (Jewish and Arabs), a steady increase in incidence was seen throughout the study period, from 18.6 to 21 cases per 100,000 person-years. The highest incidence of lung cancer throughout the study period was seen in Arab males (up to 52.9 per 100,000 person-years), followed by Jewish males. The lowest incidence of lung cancer was seen in Arab females (as low as 2 per 100,000 person-years). Join point analysis indicated that among Jewish males, total lung cancer incidence was stable for the period from 1990 to 2007, and mildly decreased from 2007 to 2014 [Table 1]. Lung cancer incidence increased significantly in Jewish females and in Arab males and

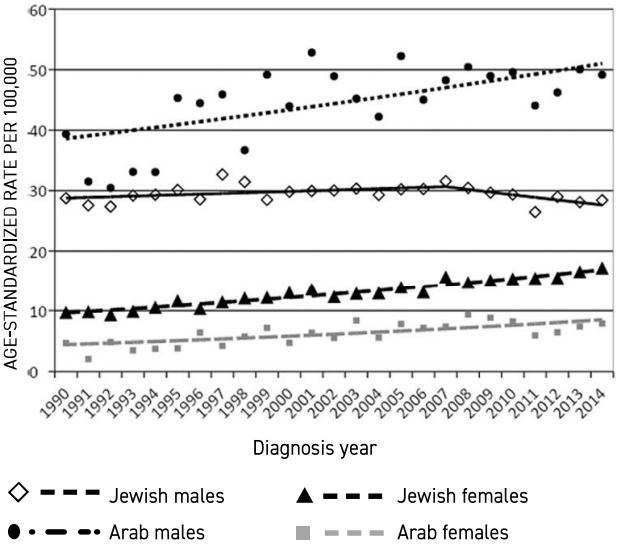
Table 1. Joinpoint analysis, annual percent change in incidence of lung cancers, by population group and sex, Israel 1990–2014

Population group	Sex	Period	Annual percent change	95% confidence interval
All lung cancers				
All*		1990–2014	+0.9**	+0.7, +1.1
Jewish	Male	1990–2007	+0.4	-0.1, +0.8
Jewish	Male	2007–2014	-1.5**	-2.8, -0.1
Jewish	Female	1990–2014	+2.4**	+2.1, +2.7
Arab	Male	1990–2014	+1.2**	+0.5, +1.8
Arab	Female	1990–2014	+2.8**	+1.4, +4.1
Adenocarcinoma only				
Jewish	Male	1990–1995	+6.7**	+1.7, +12.0
Jewish	Male	1995–2003	-1.3	-3.7, +1.1
Jewish	Male	2003–2014	+4.9**	+3.9, +6.0
Jewish	Female	1990–1995	+10.1**	+3.1, +17.5
Jewish	Female	1995–2005	+0.9	-1.1, +2.9
Jewish	Female	2005–2014	+6.6**	+5.0, +8.1
Arab	Male	1990–2014	+3.4**	+2.1, +4.8
Arab	Female	1990–2014	+3.8**	+2.0, +5.6

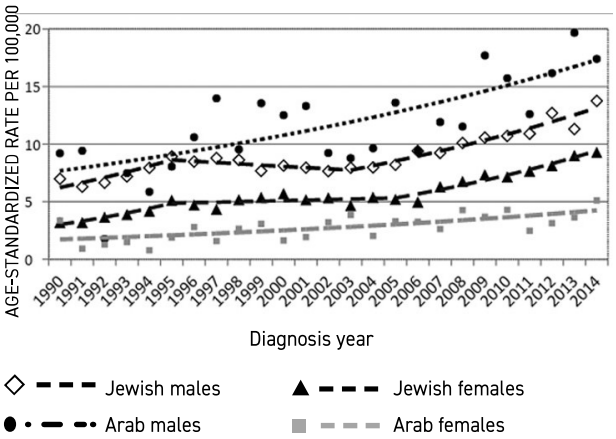
*Includes all Jewish and Arab patients, excluding 'others'
**$P < 0.001$ regarding the change in the incidence during the specified period for the specified ethnic group

Figure 1. Age-standardized incidence of invasive cancer of the lung by sex and population group. Points represent data for each year. The lines represent trends as analyzed by Joinpoint software

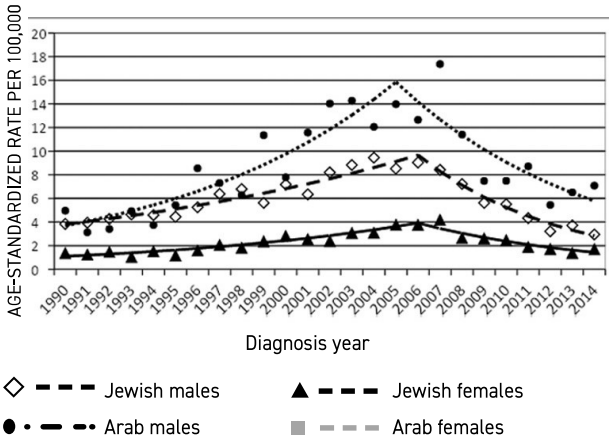
[A] Lung cancer: data are shown for the 40,985 cases



[B] Adenocarcinoma: data are shown for the 14,137 cases



[C] Large cell or NSCLC non-otherwise specified: data are shown for the 7703 cases



females throughout the period of the study. The annual percent increase was numerically largest in Arab females, followed by Jewish females and then by Arab males [Table 1].

HISTOLOGIC SUBTYPES OF LUNG CANCER

The diagnoses included number of cases and their designated groups can be seen in Figure 3. Overall, the most common histologic type was adenocarcinoma. The next most commonly occurring types of lung cancer were squamous cell and large cell/non-otherwise specified (NOS) with an almost identical number of cases in each group. The next common group (n=6514, 15% of the cohort) was classified as 'other histologies'. The most common diagnosis (86%, 5570 of 6514) within this poorly-defined group was tumor malignant NOS (ICD-O-3 code 80003). As expected, the large majority of these cases (84%) was diagnosed based on clinical investigation or DCO. The next common diagnoses were small cell lung cancer (SCLC 11%), carcinoid (2%), and sarcoma (0.3%). Following these were a large number of relatively rare diagnoses. A significant number of different pathologic diagnoses were identified among cases defined as lung cancer. For many of these only a handful of cases have been recorded per diagnosis.

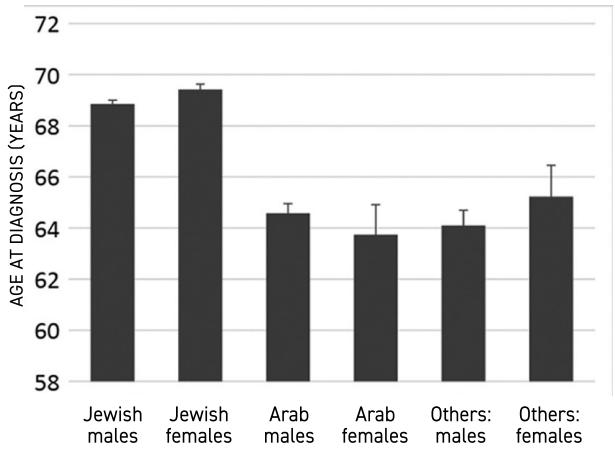
TRENDS IN HISTOLOGIC SUBTYPES

Adenocarcinomas constituted 25.7% of lung cancer cases in 1990 and 48.2% of diagnoses in 2014 (summarized by 5-year periods in Figure 1C). For squamous cell carcinoma, the corresponding figures were 24.0% and 16.8%. Small cell cancers made up between 8–12% of cases throughout the years, and sarcomas and carcinoid malignancies taken together made up less than 4% of lung cancer cases in any given year.

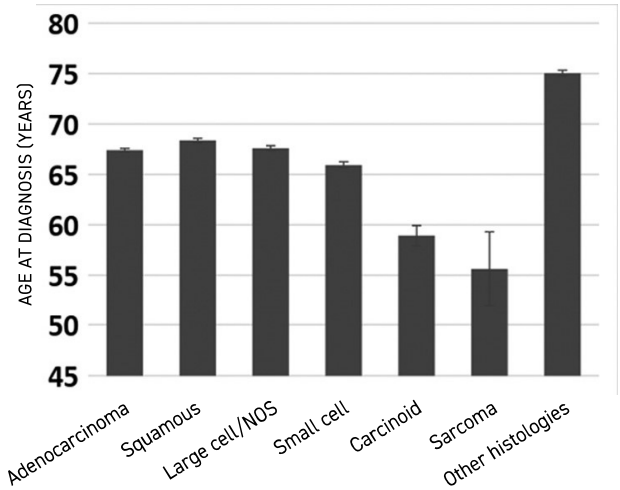
Analysis of trends in age-standardized incidence rates by histologic group was carried out for Jewish males and females and for Arab males. The number of lung cancer cases diagnosed in Arab females was insufficient to allow for trend analysis for most histologic groups with the exception of adenocarcinoma. Incidence of adenocarcinoma increased during the study period for all of the population/sex groups studied, despite a brief period during which rates stabilized among Jewish males and females [Figure 1B, Table 1]. In contrast, the incidence of squamous cell carcinomas dropped significantly among Jewish males during the period of the study (annual percentage change [APC] = -1.9, 95%

Figure 2. Age at diagnosis

[A] Age at diagnosis of the different sex/population groups in the study



[B] Age at diagnosis of different histologic groups. Bars represent mean ages; error b ars indicated 95% confidence interval of the mean NOS = non-otherwise specified



confidence interval [95%CI] -2.4 – -1.4), and remained stable in Jewish females (APC = 0.1, 95%CI -0.9–1.0) and Arab males (APC=0.4, 95% CI -0.5,1.3). The rate of SCLC remained stable among Jewish males, and increased for Arab males (APC = 2.4, 95%CI 1.2–3.5) and Jewish females (APC = 1.8, 95%CI 0.– 3.6). The rate of cancers classified as 'large cell/NOS' rose sharply in all population groups studied until 2005-2006, and dropped sharply thereafter [Figure 1C].

AGE AT DIAGNOSIS

The mean age at diagnosis for the entire study cohort increased from 67.5 (95%CI 67.2–67.8) in 1990–1994 to 69.1 (95%CI 2010–2014; ANOVA test for significance $P < 0.001$). The mean age of Jewish patients at diagnosis was 69.1 years (95%CI 68.9–69.2), while the Arab patients mean age at diagnosis was 64.5 years (95%CI 64.1–64.8) and was 64.4 (95%CI 63.9–64.9) for the small 'others' group (ANOVA test for significance $P < 0.0001$). The mean age of diagnosis was 68.1 years (95%CI 68.0–68.2) for males and 69.0 (95%CI 68.8–69.3) for females (*t*-test, $P < 0.0001$). Mean age of diagnosis of the different sex/population groups is depicted in Figure 2A. The mean age at diagnosis was within the same range for adenocarcinoma, squamous cell carcinoma, large cell/NOS and SCLC, but was higher for 'other histologies' and lower for carcinoid and for sarcoma (Figure 2B; ANOVA test for significance with $P < 0.0001$).

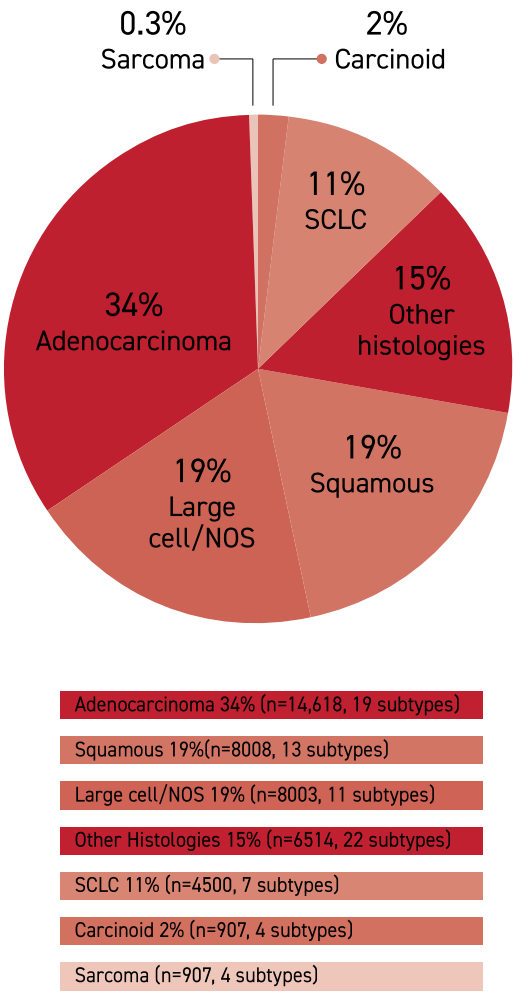
DISCUSSION

The data for this study were derived from a population-based registry with a high capture rate, mostly based on pathology or cytology reports. Our data document an ongoing rise in lung cancer incidence in Israel for most population subgroups over a 25-year period. The only exception is Jewish males, for whom a modest decrease in incidence has been seen since 2007. The highest increase in lung cancer incidence was seen in Arab females, followed by Jewish females and then by Arab males. Among the Jewish population, a narrowing the gap of lung cancer incidence between males and females can be seen, as reported in other countries [13]. The most common histologic subtype in Israel is adenocarcinoma, with an incidence that keeps rising in all population groups. The incidence of SCLC is also rising but only among Jewish females and Arab males. Age at diagnosis was lower in the Arab population compared to the Jewish population.

Smoking rates in Israel vary markedly by sex and population group, with the highest rates in the Arab male population and the lowest among Arab females [14]. Furthermore, while smoking rates have declined markedly among Israel Jews during the past two decades, a parallel trend has not been observed among Arab males [15-17]. This smoking rate is related to the high incidence of lung cancer in Arab males [18,19]. Trends in lung cancer incidence commonly follow the trends in smoking incidence, with a delay of around two decades. The reason for the ongoing increase in lung cancer incidence in Arab females might be a gradual uptake of smoking, although no clear data are available regarding this question. A confounding factor of the changes in lung cancer incidence is the accuracy of diagnostic tools, which is expected to increase. A younger age of diagnosis in the Arab population is intriguing in light of an older age of smoking initiation in this group. Jewish smokers started to smoke at a mean age of 18.9 for males and 19.6 for females, and Arab smokers started to smoke at 20.1 for males and 24.7 for females [16]. The earlier age of diagnosis can be explained by higher carcinogen exposure or possibility by the potential existence of a genetic predisposition to lung cancer that may be

Figure 3. Lung malignancies subtypes distribution

Pie chart demonstrating distribution of the major histologic subtypes among the cohort throughout the study period (1990–2014) for the entire population of Israeli lung cancer patients (N=42,672)



more prevalent among the Arab population. Data indicating that Arab smokers consume a higher number of cigarettes than Jewish smokers [16] point to a higher carcinogen exposure as the culprit. Additional factors such as second-hand smoke, water-pipe smoking, radon exposure, diet, or other life style changes besides cigarette smoking might play a role in the younger age of diagnosis of Arabs and in the different trends between Jewish males and the other population groups examined in this study [9]. It can be speculated that the Arab population group would benefit from initiation of screening for lung cancer at an earlier than currently recommended.

Our data verify the increase in adenocarcinoma and the decrease in squamous cell carcinoma reported elsewhere [19,20]. This change is thought to result from the increased use of filtered vs. non-filtered cigarettes and thus higher carcinogen exposure of the peripheral lung tissue [19,20]. In addition, adenocarcinoma is the most common type of lung cancer in never-smokers. The rate of lung cancer in never-smokers is suggested to increase in incidence [21]. Unfortunately, the INCR data do not include smoking habits, precluding us from investigating the trends in the never-smoking subgroup. Another change evident in our data is the increase followed by a decrease in the proportion of large cell/NOS diagnoses, with incidence peaking around 2004–2006 [Figure 1C]. Large cell/NOS is defined by lack of features indicating a specific subtype. The marked changes in incidence may be an artifact of variations in the efforts to sub-classify non-small cell lung cancer (NSCLC) to its histologic subtypes. The timing of the marked reduction of incidence roughly fits the time when emerging data indicated that histologic sub-type is predictive of benefit from specific chemotherapeutic agents [22]. We regarded the trends in the 'other histologies' as another subgroup of lung cancer diagnoses, which are not one of the major recognized subgroups. No similar trends were seen in the incidence changes of 'other histologies' in the registry (data not shown). The reason for the marked increased incidence of large cell/NOS up to 2004–2006 is not evident to us.

Another unexpected result of our study was the incidence of SCLC [Figure 3], found to be about 11% compared to 13–17% reported, for example, in the SEER database [23]. The smoking rate is a bit lower in Israel compared to the United States [24], possibly explaining this difference. However, the level of consumption of tobacco is higher in Israel among smokers [24]. Since SCLC is linked to higher cigarette consumption rate more than other cancers, it might have been expected for SCLC relative incidence to be higher in Israel vs. the United States. However, in our study, we did not see evidence for a decrease in SCLC incidence during 1990–2000 as reported from the SEER data [23]. It should be noted that the decreased SCLC incidence reported from the SEER data was seen mostly in males. In our data SCLC incidence increased in Arab males and in Jewish females. The increased SCLC incidence in Jewish females is another example of the narrowing of the male-female gap in lung cancer incidence, as previously reported [13,25].

CONCLUSIONS

The incidence of lung cancer is rising in all population/sex groups in Israel. Adenocarcinoma is the most common type of cancer, and its incidence is rising in all population groups. SCLC incidence is rising only in Jewish women and Arab men. These data, and the earlier age of diagnosis of lung cancer in the Arab minority (despite the older age of smoking initiation), are worrisome for a high carcinogen exposure of this population group and/or a possible genetic predisposition for lung cancer. The trends we identified need to be examined in other countries, especially regarding the Arab population.

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Capsule

Sensing an allergen

Dendritic cells (DCs) can initiate allergic immune responses, but how allergens influence DCs is unclear. Using a mouse model in which the allergen papain was injected into the skin, **Perner** and colleagues reported that TRPV1$^+$ sensory neurons were required for an immune response to allergens. Allergen-driven activation of TRPV-expressing neurons caused the release of the neuropeptide substance P, which resulted in the migration of CD301b$^+$ DCs to the draining lymph nodes. The induction of adaptive T helper 2 immunity, including itching and pain responses, was observed.

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