Changing Trends in Bladder Cancer Epidemiology in the Israeli Population: 1996–2016

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ABSTRACT **Background:** There is a rising incidence of bladder cancer (BC) in Israel and worldwide. BC is currently the fourth most common cancer in Israeli males. There are large variations in the incidence of BC observed in different populations, both in Israel and worldwide.

Objectives: To characterize the time trends and epidemiologic profile of BC in Israel regarding various population demographics.

Methods: All cases of BC reported to the Israeli National Cancer Registry between 1996 and 2016 were included. We calculated age standardized rates for BC. Joinpoint regression analysis was used to study trends in incidence as expressed by annual percent change (APC) in incidence.

Results: Between 1996 and 2016, 28,953 cases of BC were diagnosed in Israel. BC rates in Jewish males peaked in 2006 and subsequently declined (APC = -1.69, $P < 0.05$). Between 1996 and 2011, in-situ BC rates increased for both Jewish (APC = 28.2, $P < 0.05$) and Arab males (APC = 16.76, $P < 0.05$). Invasive BC incidence in Jewish males declined from 2005 to 2016 (APC = -7.6, $P < 0.05$) as well as in Arab males from 2006 to 2011 (APC = -12.0, $P < 0.05$).

Conclusions: In the past two decades, in situ BC rates have risen, while invasive BC rates have decreased. BC epidemiology mirrors lung cancer trends, which is expected as smoking is a significant risk factor for both. These trends are important to identify as they can affect clinical guidelines regarding screening in high-risk populations and health care planning.

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KEY WORDS: bladder cancer, epidemiology, Israel, screening

There is a rising incidence of bladder cancer (BC) in Israel and globally [1]. BC is the ninth most common cancer worldwide and is currently the fourth most common cancer in Israeli males [2]. The most common presenting symptom is painless hematuria, which warrants computed tomography (CT) urography, cystoscopy, and biopsy to confirm diagnosis [3]. Some 95% of BC cases are classified as urothelial carcinoma. The remaining types include squamous cell carcinoma, adenocarcinoma, small-cell carcinoma, and sarcoma [4]. Urothelial carcinoma originates from the transitional epithelial cell lining of the urothelial tract [4]. Local BC is subdivided into non-muscle invasive disease, which encompasses carcinoma in situ (CIS), non-invasive papillary carcinoma (AJCC Ta), and tumors invading the subepithelial connective tissue (AJCC T1), and muscle-invasive disease (AJCC T2-3) [5,6].

Non-muscle invasive BC is treated with local resection and adjuvant intravesical therapy with agents such as Bacillus Calmette-Guérin. Still, 50–70% of lesions recur or progress despite optimal management and may ultimately result in radical cystectomy [3].

There is marked variation in incidence in different countries with a higher incidence seen in Europe, North America, Western Asia, and Northern Africa and a lower incidence in mid-Africa and South/Central Asia. Israel has age standardized incidence rates similar to those of developed countries [7].

Recently, BC incidence has significantly increased in both the United States and Europe, with a larger proportion of in situ cancer diagnosed [8]. These trends partially follow smoking trends, a major risk factor for BC [9]. We investigated whether Israel follows similar trends, with an increasing incidence in both BC and bladder carcinoma in situ being diagnosed.

Worldwide, the most prominent risk factors for BC are related to toxin exposure. Tobacco smoking is the greatest known risk factor. The incidence of bladder cancer is approximately three times higher in smokers. In fact, 34% of deaths from BC in males and 13% in females are due

to smoking [2]. Other risk factors include occupational exposure to aromatic dyes, rubber, leather, paint, and arsenic [2]. Additional environmental risk factors for BC are schistosomiasis infection in developing countries as well as indwelling catheters, which cause constant irritation to the bladder wall [9].

In total, 75% of BC cases occur in males, likely due to risk factors such as tobacco and occupational hazards [9]. Some 90% of those diagnosed are over age 55 years, with an average age of 73 years [3]. We used data from the Israel National Cancer Registry (INCR) for the period from 1996 to 2016 to study trends in incidence and epidemiologic profile of BC in Israel.

PATIENTS AND METHODS

THE ISRAELI NATIONAL CANCER REGISTRY

The INCR was founded in 1960. Reporting to the registry has been required since 1982 and is required for all in situ and invasive tumors with the exception of non-melanoma skin cancers. Reporting is also required for benign tumors and uncertain behaviors of the brain and central nervous system tumors. The registry covers the entire population of citizens and permanent residents of Israel. In 2020, the population of Israel numbered approximately 9 million, of whom 74% were Jewish, 21% Arab, and 5% were neither Jewish nor Arab (labeled *Other*) [10].

BLADDER CANCER REGISTRATION

All diagnoses are registered according to the ICD-O-3 coding system, and each diagnosis is assigned topography and morphology codes. Tumor behavior is represented by the fifth digit of the morphology code (2 = non-invasive/in situ, 3 = invasive). According to the guidelines of the Surveillance, Epidemiology and End Results (SEER) program of the U.S. National Cancer Institute, behavior code 2 is assigned to cases of BC described in the pathology report with terms such as *non-invasive*, *intraepithelial*, *non-infiltrating*, *carcinoma in situ/CIS*, or *stages 0 or Ta* [11].

Stage at the time of diagnosis is recorded for cases diagnosed in 2000 and onward using the SEER summary stage 2000 classification system [12] rather than AJCC stage. The SEER system classifies AJCC T1 (invasion of subepithelial connective tissue) and T2 (muscle invasion) together as localized tumors, while AJCC stages T3a and b (microscopic/macroscopic extension into perivesical tissue would be classified as SEER summary stage 2: regional by direct extension) [5]. Cases with behavior code 2 are by default coded as SEER summary stage 0 (in situ, epithelial, non-invasive). Recurrences of BC after treatment are not entered in the registry as new cases.

DATA ACQUISITION AND ANALYSIS

We identified all cases of in situ or invasive BC reported to the INCR meeting the following criteria:

- Year of diagnosis 1996–2016
- International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) topography codes C67.0-C67.9
- ICD-O-3 4-digit morphology codes not equal to 9050-9055, 9140, 9590-9989
- ICD-O-3 behavior 2 (in situ) or 3 (malignant)

Cases of BC were categorized into histologic groups, as follows:

- Urothelial tumors
  - In situ (ICD-O-3 codes 8120/2, 8130/2)
  - Invasive (ICD-O-3 codes 8120/3, 8130/3)
- Other tumors of the bladder

Age standardized rates were computed for BC overall and for invasive and in situ histologies separately using the Segi World Population Standard. Joinpoint regression analysis was used to identify trends in incidence over the period of the study and expressed as annual percent change (APC) in incidence. A P-value < 0.05 is indicative of an APC different from zero, signaling a significant upward or downward trend during the period of the study. We also examined trends in the distribution of stage at diagnosis for the period from 2000 through 2016, when stage data were available. Life table analysis was used to calculate cumulative survival overall and by stage at diagnosis.

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 23 (SPSS, IBM Corp, Armonk, NY, USA) and Joinpoint version 4.7.0 (National Cancer Institute, USA).

RESULTS

BLADDER CANCER IN ISRAEL

We identified a total of 28,953 cases of BC diagnosed in Israel from 1996 through 2016. The proportion of total BC cancers that were classified as in situ at diagnosis increased during the study period, from 1.2% in 1996 to 50% in 2016 [Figure 1]. Ninety-five percent of BC cases were urothelial tumors. The remaining cases were composed of other tumors such as adenocarcinoma, squamous cell carcinoma,

or histologies not otherwise specified. The distribution of diagnoses by histologic subtype did not change during the study period. Mean age at diagnosis for the entire period was 70 years, and the median age was 71 years.

Overall BC incidence was higher in men than in women, regardless of population group. In 2017, age-adjusted BC incidence was 23.2/100,000 in Jewish men, 4.3/100,000 in Jewish women, 27.7/100,000 in Arab men, 4.0/100,000 in Arab women, 26.3/100,000 in Other men, and 3.8/100,000 in Other women. Overall BC incidence in Jewish men was stable from 1996 to 2006 and decreased significantly from 2006 to 2017 (APC = -1.69, $P < 0.05$). In all other sex-population groups, BC incidence rates remained stable throughout the study period.

CARCINOMA IN-SITU

In Jewish men, the incidence of in situ BC increased significantly from 2000 to 2011 (APC = 28.7, $P < 0.05$) and stabilized thereafter. In Jewish women, the increase in incidence was most marked from 2000 to 2009 (APC=40.8, $P < 0.05$) and remained significant from 2009 to 2016 (APC = 4.6, $P < 0.05$). Among Arab men, in situ BC incidence increased steadily from 2000 to 2016 (APC = 17.4, $P < 0.05$). Insufficient cases were reported for Other men, as well as Arab and Other women to allow for an analysis of trends [Figure 2].

INVASIVE BLADDER CANCER

The incidence of invasive bladder carcinoma decreased among men in all population groups and among Jewish and Other women [Figure 3]. Among Jewish men, invasive BC incidence was stable during the period from 1996 to 2006, (APC = -0.8, $P = 0.6$) and decreased significantly thereafter (APC = -8.2, $P < 0.05$). For Jewish women, invasive BC rates were stable from 1996 to 2007 and decreased significantly from 2007 to 2016 (APC = -8.8, $P < 0.05$). In Arab men, incidence increased significantly from 1996 to 2006 (APC = 3.9, $P < 0.05$), decreased from 2006 to 2011 (APC = -12.3, $P < 0.05$), and then stabilized from 2011 to 2016. In the Other male population, a decrease was observed from 1996 to 2016 (APC = -5.5, $P < 0.05$). In Other women, the corresponding APC was -6.0 ($P < 0.05$).

Figure 1. Distribution of total bladder cancer cases by tumor behavior (in situ or invasive), Israel, 1996–2016

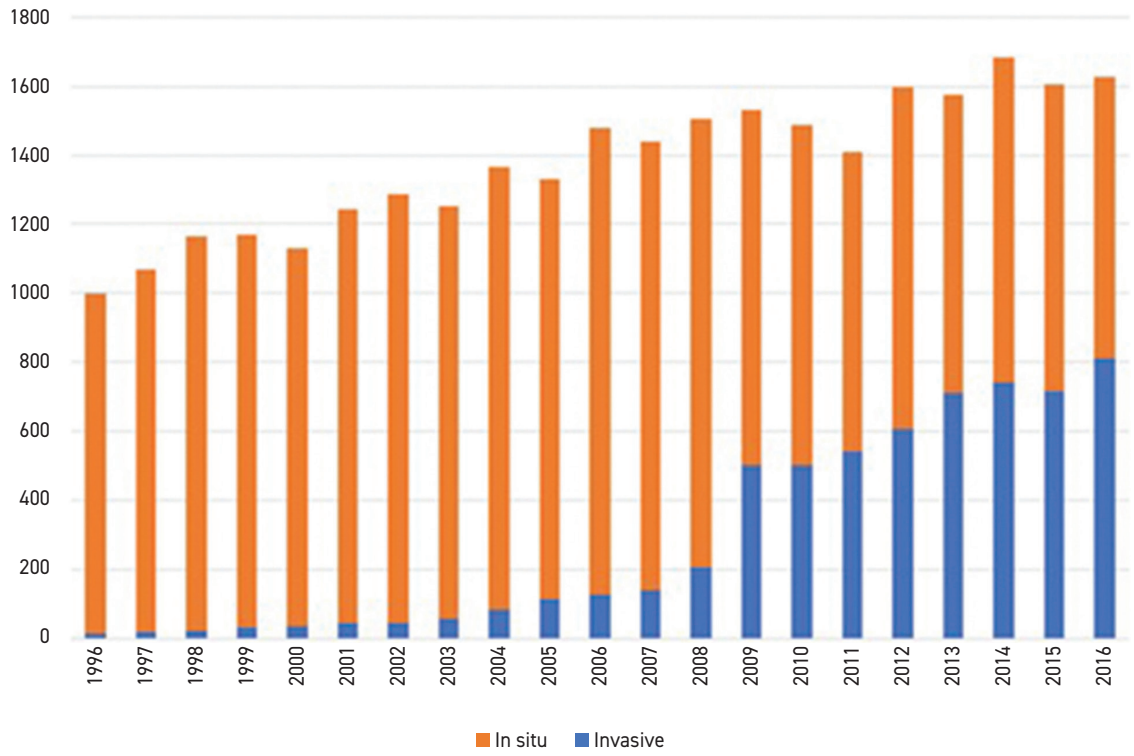


Figure 2. Joinpoint analysis, trends in age-adjusted incidence of in situ bladder cancer, Israel 1996–2016*

*Insufficient cases in the database for the analysis of trends in Arab women and Other men and women

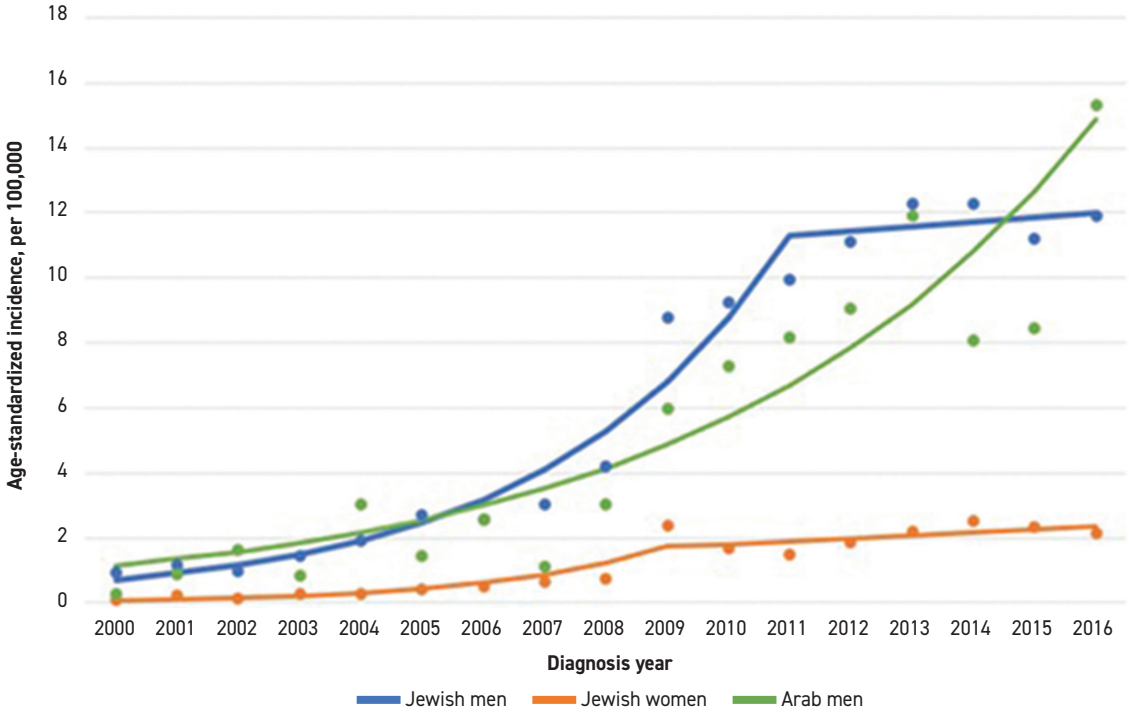
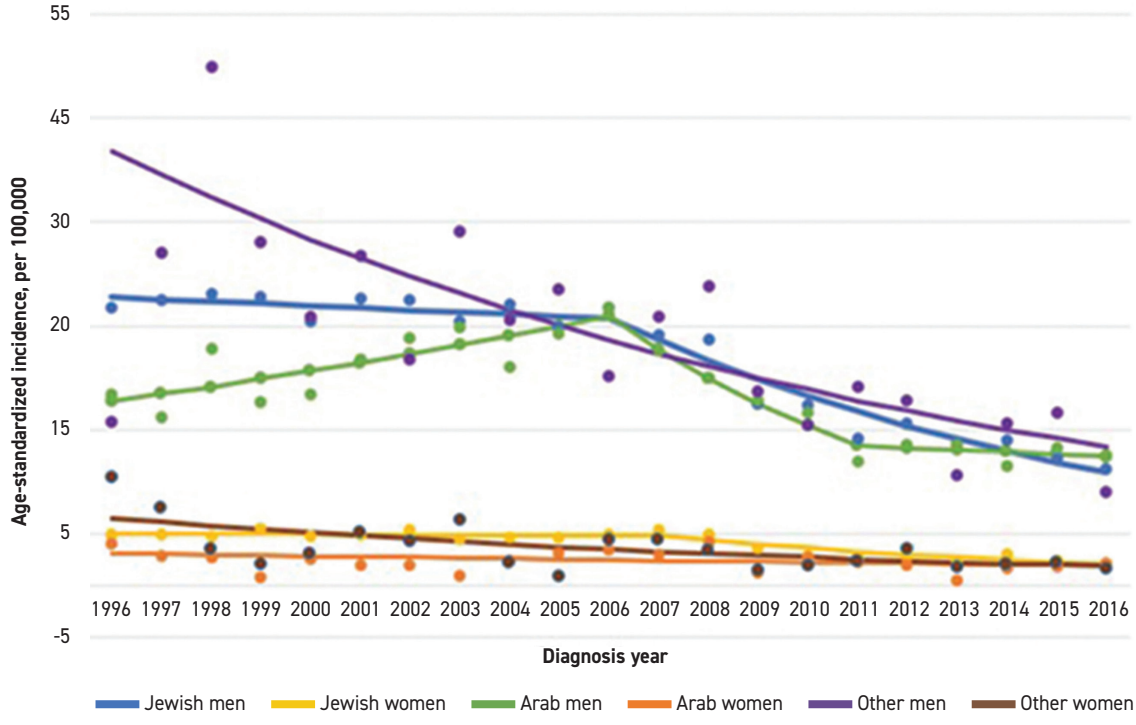


Figure 3. Joinpoint analysis, trends in age-adjusted incidence of invasive bladder cancer, Israel 1996–2016



For cases diagnosed in 2000, the SEER summary stage could be determined for only 28% of cases of BC. By 2016, this figure had increased to 84%. During the same period, the percentage of cases for which advanced stage was recorded remained relatively constant, ranging from 0.8% to 1.5% (an average of 17.8 cases per year). Given the large number of cases with unknown stage, particularly earlier in the study, it is likely that the registry data provide an underestimate of the total number of metastatic cases diagnosed per year. Together in situ and localized cases comprised 18.0% of cases in 2000 and 76.6 in 2016 [Figure 4].

BLADDER CANCER SURVIVAL

Cumulative 5-year survival for all BC patients was 69.7%. Five-year survival in people with in situ or SEER stage 1 cancer at time of diagnosis was 78.5% (95%CI 77.0–79.2) compared to 62.5% (95%CI 61.7–63.3) in those with a higher or unknown stage at diagnosis. This finding indicates a significant survival advantage for early stage disease ($P < 0.0001$, log-rank test).

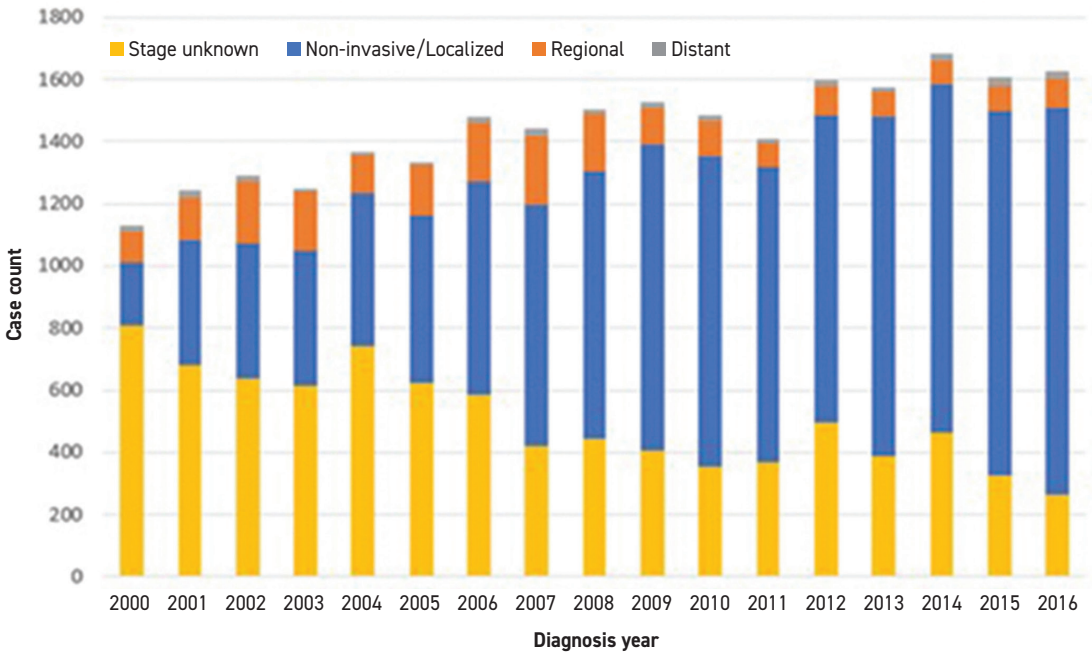
DISCUSSION

In this study, we described the changing trends observed in BC in Israel from 1996 to 2016. Data from the INCR for this period show stable rates of overall BC in all population groups studied, with the exception of Jewish males, among whom a significant decrease in incidence occurred from 2006 to 2016. Stratification of BC rates by tumor behavior as reflected by the ICD-O-3 morphology code recorded at presentation demonstrate a significant rise in in situ BC concurrent with the decrease in invasive BC. In situ BC was rare prior to the year 2000; however, it has been steadily increasing in most population-sex groups.

The trends observed in Israel are similar to those seen in other Western nations. In Western and Northern European countries rates of BC have been stabilizing or decreasing since the late 1990s [9]. Throughout the world BC is more common in males than females. Higher BC rates observed in male populations can be partially explained by higher rates of smoking and increased exposure to occupational

Figure 4. Distribution of total bladder cases by SEER summary stage at time of diagnosis*, 2000–2016

SEER = Surveillance, Epidemiology and End Results program of the U.S. National Cancer Institute
*SEER summary stage recorded in the cancer registry for cases diagnosed 2000 and later



hazards among men [13]. In all Israeli ethnic groups, males were observed to have higher rates of BC compared to females. In the United States, BC rates have been increasing over the past 40 years [14]. Specifically, urothelial cancer rates rose to a peak in 2007 and then declined [14]. A similar trend was observed in the Israeli Jewish male population. BC rates increased from 1996 to 2006 and then declined. In the United States, different trends in BC incidence were observed in different ethnic groups. Increased rates have been reported in African Americans, and a decreasing trend has been shown in most other populations [14]. This trend mirrors those observed in this study where different rates are seen in different ethnic groups living in Israel. These differences may be explained by differences in genetics, nutrition, lifestyle habits, or occupational exposures.

Comparing BC incidences across different countries can be difficult as there is large variation in the reporting of in situ and invasive tumors [2]. Specific differences in in situ and invasive cancer rates have not been analyzed in other countries [15]. Our analysis is among the first to sub-stratify BC into in situ and invasive cancer and elucidate changing trends.

The observed rise in the rate of in situ and localized cancer observed is intriguing. There have been no systematic screening programs for BC in the past 50 years [16]. The U.S Preventive Services Task Force does not recommend screening in asymptomatic adults as testing has a low positive predictive value and there is little evidence that early treatment improves long term outcomes [3]. Despite the lack of official screening guidelines, the increase in early-stage BC observed may be partly due to increased awareness of both patients and physicians as well as the availability of imaging techniques such as cystoscopy (the gold standard), ultrasound, and CT urography [3,17,18]. Classification of BC tumors has remained variable and is not always reflective of heterogeneous clinical and genetic nature of the disease [19]. There are also differences in recommendations between regulatory bodies like the International Union Against Cancer and the American Joint Committee regarding classification [5]. The rise in early BC rates and the declining rates of invasive disease observed may be attributed to improved diagnosis techniques and treatment of early-stage lesions thus preventing progression of those lesions to invasive disease.

For most cancers, rates in the Arab population are lower than in the Jewish population [1]. This is not the case for lung cancer and BC, two diseases tightly linked to smoking. Lung cancer rates in Israel are higher in Arab men than in any other population group, while the gap in BC incidence between the Jewish and Arab populations has narrowed. These trends are most likely due to the changes in smoking habits in both populations. Smoking rates are higher in the Arab population than in the Jewish population [1]. As of 2015, 25.2% of the Arab population smoke vs 18.5% of the Jewish population [1]. Smoking rates in the Jewish population have decreased over time, resulting in a larger difference in smoking rates between the two populations.

The main strength of our study is that it is based on data from a long-standing, national, population-based cancer registry with a high level of completeness allowing the analysis of long-term trends in cancer incidence [20]. Vital status of individuals registered in the database is updated annually, allowing calculation of survival. The availability of histological classification and SEER stage allowed us to stratify by level of invasiveness when calculating five-year survival.

Our study has several limitations. The INCR collects limited clinical information about BC cases and does not have access to information on risk factors such as smoking status or occupational hazard exposure in cases. Furthermore, population data on risk groups is also unavailable. Therefore, we are unable to address the extent to which personal and occupational risk factors affect disease incidence in the Israeli population. Because stage at diagnosis is coded according to SEER summary stage, in contrast to AJCC stage, there may be an overestimation of the proportion of cases diagnosed as in situ or localized. As incidence of overall BC is quite low in female populations for all groups, it is difficult to draw conclusions about those population groups.

CONCLUSIONS

We described the changing trends in BC in Israel over the past two decades. While overall rates of BC remained stable, other than a slight decline in BC cases in Jewish males, we observed an increase in the proportion of cases diagnosed at an early stage. Early stage BC is a chronic disease. As in situ disease has a high recurrence rate and variable risk of progression to invasive disease, considerable resources are required for treatment [2]. Data regarding the epidemiology of BC in the Israeli population are important for formulating guidelines regarding screening, diagnosis, and treatment of this disease. The data also allow more accurate resource allocation among government decision makers. Research collaborations between the registry and treating institutions would allow us to access more specific clinical information about BC cases and enrich our knowledge of the disease burden due to BC in Israel.

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Capsule

SARS CoV 2 mRNA vaccines sensitize tumors to immune checkpoint blockade

Immune checkpoint inhibitors (ICIs) extend survival in many patients with cancer but are ineffective in patients without pre-existing immunity. Although personalized mRNA cancer vaccines sensitize tumors to ICIs by directing immune attacks against preselected antigens, personalized vaccines are limited by complex and time-intensive manufacturing processes. **Grippin** and colleagues showed that mRNA vaccines targeting SARS-CoV-2 also sensitize tumors to ICIs. In preclinical models, SARS-CoV-2 mRNA vaccines led to a substantial increase in type I interferon, enabling innate immune cells to prime CD8+ T cells that target tumor-associated antigens. Concomitant ICI treatment is required for maximal efficacy in immunologically cold tumors, which respond by increasing PD-L1 expression. Similar correlates of vaccination response are found in humans, including increases in type I interferon, myeloid–lymphoid activation in healthy volunteers, and PD-L1 expression on tumors. Moreover, receipt of SARS-CoV-2 mRNA vaccines within 100 days of initiating ICI is associated with significantly improved median and 3-year overall survival in multiple large retrospective cohorts. This benefit is similar among patients with immunologically cold tumors. Together, these results demonstrate that clinically available mRNA vaccines targeting non-tumor-related antigens are potent immune modulators capable of sensitizing tumors to ICIs.

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