National surveillance of cancer survival in Iran (IRANCANSURV): analysis of data from 90,862 cancer patients for 15 cancers from 9 population-based cancer registries

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Abstract

Objectives: Cancer survival is a key indicator for the national cancer control program. However, survival data in the East Mediterranean region (EMRO) are limited. We designed a national cancer survival study in Iran based on population-based cancer registries from 9 provinces.

Methods: The current study reports 5-year net survival of 90,862 cancer patients from 15 cancer in Iranian adults (15-99 years) during 2014-2015 in 9 provinces of Iran. We used data linkage between the cancer registries and the causes of death registry and vital statistics and active follow-up approaches to ascertain the vital status of the patients. Five-year net survival was estimated through the relative survival approach. We applied the international cancer survival standard weights for age standardization.

Results: Overall, 5-year relative survival was 49.70% (95% CI 49.25, 50.15). The overall 5-year survival for men and women was 45.89 (95% CI, 45.34, 46.52), and 52.40 (95% CI, 51.68, 53.12), respectively. Five-year survival was highest for prostate cancer (78.18%), followed by breast (74.24%, 95% CI 72.50, 75.88), bladder (70.70%, 95% CI 69.36, 71.94) and cervix (65.4%, 95% CI 61.1, 69.3). Survival was below 25% for cancers of the pancreas, lung, liver, stomach, and esophagus.

Conclusion: Iranian cancer patients experience a relatively poor prognosis as compared to those in high-income countries. Introducing early detection programs and improving the quality of care is therefore recommended. Further studies are needed to monitor the outcomes for cancer patients in Iran and other EMRO countries.

Keywords: Cancer, Population-Based Survival, Population-based Cancer Registries, Cancer Control Program, IRANCANSURV

Introduction

Cancer is a life-threatening global public health challenge that is increasing worldwide, particularly in low- and middle-income countries (1). The estimated number of deaths due to cancer reached 9.9 million in 2020, and it is projected that in 2040 the number of cancer-related mortality will exceed 16.3 million(2). Cancer has a severe effect on the burden of disease through decreasing life expectancy. Therefore, several cancer control programs have been developed to prolong the survival of cancer patients and improve their quality of life (3). Cancer control includes primary prevention, early detection, treatment, and palliative care (4, 5).

Cancer survival is a key indicator for the evaluation of cancer control programs. Population-based cancer survival is the most comprehensive approach since it provides information on the prognosis of all cancer patients in the target population (6). Population-based cancer survival covers different contributing factors such as patient's socioeconomic status, their access to health care, the effectiveness of the health care system for early detection, and treatment (6). Therefore, estimation of population-based cancer survival is a useful approach for monitoring and evaluating cancer control programs. Several global, regional, and national attempts have already been made to draw a comprehensive picture regarding the survival of cancer worldwide (6, 7). However, there is a lack of evidence from low- and middle-income countries, particularly countries from the EMRO region.

Establishing population-based cancer registries in most provinces of Iran over the recent years, along with the increasing quality of the national mortality database, has provided enough infrastructure to estimate population-based cancer survival (8). We conducted a national study called IRANCANSURV including data from 9 provincial registries across Iran, in which the quality of data was higher than in other regions. We aimed to provide age-standardized 5-year survival estimates for adult patients diagnosed with one of 15 cancers during 2015-2016.

Material and method

Cancer Patients

The study included 90,862 cancer patients from 9 provincial registries in Iran located in Tehran, East Azerbaijan (1), West Azerbaijan, Mazandaran(2), Isfahan, Fars (3), Kerman (4), Kermanshah, and Khuzestan (5) provinces. We obtained baseline data of the cancer patients including first name, last name, father’s name, national identification code, birth date, date of

diagnosis, topography, morphology, contact information, and source of diagnosis from the selected registries.

We used both passive and active approaches to follow up the cancer patients, respectively. First, we traced registered patients through the national causes of death registry and national vital statistics to ascertain vital status and date of death for those who had died during the follow-up. We applied both deterministic (using national identification) and probabilistic (using first name, last name, father name, and age) approaches for the data linkage and managed to determine the vital status of 57,817 (63.3%) patients through record linkages. Afterward, we retrieved the patient's contact information from the registries and contacted the patients or their next of kin to ascertain their vital status. Active follow-up was only performed for the missing cases in the prior phases and provided vital status information for 14,279 (15.7%) additional patients. For all the traced cases, the full date of death or last contact was completed. We followed up all the patients up to five years after the diagnosis, unless those who were died earlier. Total follow-up percent reached 79.4% at the end of the follow-up, and the vital status remained missing for 18,766 (20.6%) patients.

Ethics approval

The study was approved by the Ethics committee of Tehran University of Medical Sciences (Ethics Code: IR.TUMS.VCR.REC.1397.612)

Statistical analysis

We performed multiple imputation for the censored cases to ascertain the vital status. MI was performed in three stages: A) generating multiple imputed data sets: the vital status for LTFU cases were defined based on patients' data collected through active follow-up, assuming that the LFTU was missing at random. Sex, age (age as a continuous variable), cancer site, calendar year, and place of residence were potential covariates. We performed multiple imputations with chained equation (MICE) approach in Stata software to replace each missing value with a set of m imputations (m=10) (6). B) Analysis of the multiple imputed data sets: we analyzed each imputed and completed data set separately and estimated 5-year net survival for each data set. C) Combining analysis from different data sets: we applied Rubin's rules to estimate mean and standard error for each survival rate from the m estimates obtained in the m data sets.

The observed data for multiple imputations were those cases that had already been followed in

We used a complete approach and used all available follow-up data to estimate 5-year net survival (7). We used national all-cause mortality rates for each calendar year, sex, and age during 2010- 2020 in the general population in Iran. We provide age-standardized 5-year net survival and corresponding 95% confidence intervals (CI) for 15 cancers in each province and for all nine provinces combined. For standardization, we first categorized patients into five age groups15-44, 45-54, 55-64, 65-74, and 75-99. Then, we applied weights from International Cancer Survival Standard (ICSS) weights. We used two groups of ICSS weights based on cancer sites (8). We used ICSS group 2 weights (Melanoma of skin, cervix uteri, and brain) for cancers sites that their incidence rates do not increase by age, while group 1 weights were used for the other sites that are associated with age (Esophagus, stomach, colon, rectum, liver, pancreas, lung, breast, ovary, and prostate).

Results

The total number of patients was 90,862, for the 15 cancer sites in 9 provinces across Iran. The proportion of Death Certificate Only (DCO) cases was 15.42% (N=14,013). We followed up 58,083 (63.92%) cases and 18,766 (20.65%) patients the loss to follow-up (Figure 1). The highest DCO was in the liver (41.24%), lung (32.98%), and pancreas (30.77%). We also observed the highest proportion of lost to follow-up in breast (28.23%), melanoma of skin (28.21%), and bladder cancer (27.49%) (Table 1).

Overall, 5-year relative survival was 49.70% (95% CI 49.25, 50.15). The overall 5-year survival for men and women was 45.89 (95% CI, 45.34, 46.52), and 52.40 (95% CI, 51.68, 53.12), respectively.

Prostate cancer had the highest 5-year survival (78.18%, 95% CI 76.50, 79.98), followed by cancers of the breast (74.24%, 95% CI 72.50, 75.88), bladder (70.70%, 95% CI 69.36, 71.94) and cervix (65.4%, 95% CI 61.1, 69.3). The lowest survival estimates were for cancers of the pancreas (11.30%, 95% CI 9.77, 12.91), lung (14.17%, 95% CI 13.11, 15.25), liver (14.39%, 95% CI 12.73, 16.31), stomach (19.49%, 95% CI 18.61, 20.39) and esophagus (23.40%, 95% CI 21.0, 24.4). (Table 2) (Figure 1).

Discussion

We conducted the IRANCANSURV study as a national cancer surveillance project. This is so far the most extensive and up-to-date report on population-based cancer survival in Iran and the EMRO region, including more than 90,000 cancer patients diagnosed with one of 15 cancers

during 2014-2015 from 9 population-based cancer registries, representing about 75% of the cancer patients in each region. This study provides important clues about cancer control status at the national and provincial levels in Iran, and its results can be applied to improve the infrastructure for the diagnosis and treatment of all cancer patients in the country. In addition, the results for each type of cancer can be used to introduce and monitor focused interventions to improve the outcomes for each type of cancer. In summary, this study has shown that prostate, breast, and bladder cancers had the highest 5-year survival reaching 70%, while patients with cancers of the pancreas, lung, liver, stomach, and esophageal had less than 25% survival at five years.

In Iran, the combined 5-year survival of all 15 cancer sites was lower than those reported from the high-income countries, including the United States (9, 10), Japan (11), Sweden (12), and the UK (13). However, the results of this study were more comparable with the survival reported from low- and middle-income countries. Five-year survival for breast and prostate cancers was higher than 70%, which was close to the levels reported from Kuwait (14), Mongolia, and Turkey (9). Survival for cervix and colorectal cancer patients was lower than the high-income countries but similar to Turkey, Kuwait, and Israel (9).

Because established and effective early detection programs are available for breast, cervix, and colorectal cancers, we expect higher survival for these cancers. Although early detection programs and the high quality of care in high-income countries is the main reason for higher survival for breast, colorectal and cervical cancers, part of this gap may be due to over-diagnosis and the lead-time bias in high-income countries (15, 16). Human Development Index (HDI), a complex indicator including life expectancy at birth, knowledge (mean and expected year of schooling), and standard of living (national income per capita) is associated with patient outcomes (17). Population awareness and access to screening programs, timely diagnosis, and treatment are considerably more advanced in high-HDI countries than countries with a low HDI (18, 19).

For the more lethal cancers like esophagus, stomach, liver, lung, and pancreas, we observed poor survival rates, similar to the results from other developing countries (9). According to the SurvCan2 project conducted by the international agency for research on cancer (IARC), esophageal cancer survival varied from 5% to 30% in the low and middle-income countries, supporting the findings of this study (20). Five-year survival for esophageal cancer was similar to that reported from a hospital-based study in the cancer institute of Iran in the same period (21). The patterns for other cancers like stomach and pancreas cancer were also similar to the rates reported by LMICs because most of these patients tend to be diagnosed at an advanced

stage with metastatic cancer in these countries. The survival outcome is strongly associated with tumor extension and lymph node involvement (22, 23). However, according to CONCORD-3, the developed countries had better performance even in lethal cancers, indicating that timely and efficient diagnosis and treatment will improve these patients' outcomes (9).

Screening programs have improved the survival for esophageal and stomach cancers in Japan and South Korea (11, 24-26). As esophageal and stomach cancer are two high incidence cancers in Iran, implementing early detection programs and providing a high quality of care for these cancers will considerably impact the prognosis of these patients and the overall cancer survival in Iran (9).

However, the screening procedures for upper GI cancers are invasive and require financial and technical resources. In addition, GI cancer screening might be cost-effective only in more high-risk regions of Iran. A pilot study was conducted in Golestan province, located at the beginning of the Asian esophageal cancer belt (27). It showed that the non-invasive sponge capsule-based method was effective for screening esophageal cancer. Further research is required to provide more stable results from this screening method and to implement it as a routine feature of the public health system (28).

Similar to other low- and middle-income countries, the prognosis of lung cancer was poor in our study (20). Except for a modest five-year survival of 33% in Japan, survival for lung cancer is lower than 20% in all countries worldwide (9). Lung cancer screening is not considered to be cost-effective universally, and its effect on overall lung cancer mortality reduction is negligible (20). Moreover, therapeutic options are limited for lung cancer patients, and patients will die even when the best treatments are provided (20). The experience of high-income countries implies that mortality due to lung cancer could significantly decrease with vigorous and comprehensive anti-tobacco policies, such as proposed by *Framework Convention on Tobacco Control* (FCTC) that cover various areas, including tobacco consumption measurement, a ban on tobacco advertisements, education, legislation, and taxation and pricing (20). Such anti-tobacco activities might be more effective in the Middle East, where tobacco smoking, including cigarettes and water-pipe, is increasing, especially among women and young people (29-31).

We believe that the results from this study can be seen as representing an accurate picture of the average cancer survival in most parts of Iran, but not all. We could include some provinces, especially the low-resource areas like Sistan and Baluchestan, Bushehr, Kohkiluye and Boyrahamd, North Khorasan, Ilam, Ardabil, and Golestan provinces, where survival maybe

even lower, as reported for Golestan (32). In these poorer areas of the country, diagnostic and treatment facilities are usually lacking, and not all cancer patients can travel to larger cities for their care (33). Given challenges in completing treatment in such circumstances, the overall outcome will be lower in these areas.

The Ministry of Health and Medical Education recently established a national program and launched cancer registries in all provinces of Iran (34). However, the quality of data is not yet sufficient to involve all registries in this study. We strongly advocate supporting these registries to improve their quality indicators and gradually enhance their capacity to provide survival results in the future. The situation is almost the same for different countries in the EMRO region. With further support to registries in this region, it would be possible to estimate cancer survival in different countries and apply it for planning and monitoring of cancer control programs.

This study had some limitations, in particular loss to follow-up that could reduce the validity of our findings. The proportion of loss to follow-up varied from 7.4% to 38.3% in different regions. Although we applied a multiple-imputation approach to solving this problem, survival estimates from population-based registries with loss to follow-up over 15.0% must be flagged as less reliable estimates (9). Moreover, we observed a high proportion of DCO in some registries. A high proportion of DCOs will remove a sizable number of patients from survival analyses and is likely to lead to over-estimation of survival (35, 36). Attempts should be made to improve the registration process and increase the completeness of cancer registration.

In conclusion, in a large and comprehensive study, we reported 5-year survival for all cancers combined and by type of cancer in Iran. Survival is typically lower than those in the high-income countries, including for cancer types that could be diagnosed through screening programs. Our results suggest that there is room for improvement in the design and implementation of interventions for cancer control. These could include improving access to diagnostic and therapeutic services, and increasing public awareness, particularly in the marginal and more deprived provinces. Implementing early detection programs should be on the agenda to respond to lower survival for cancers of the breast, colon, and cervix.

Despite recent progress in cancer registration in Iran, further resources are required to improve the quality of these registries and to support them in collecting follow-up data to enable accurate estimation of cancer survival. We hope IRANCANSURV will promote the networking of all population-based cancer registries in Iran and regular reporting of survival for each type of

cancer. It will be a powerful policy tool to evaluate the health system and improve the national cancer control program.

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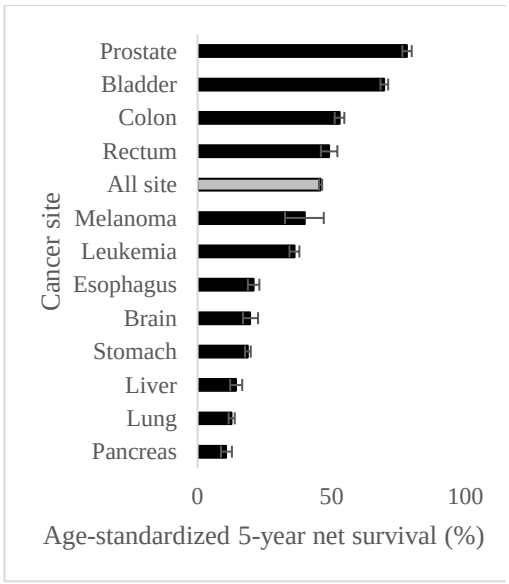
Table 1: Definition of malignancies and number and proportion of excluded and included patients diagnosed during 2014-2015 in Iran by cancer site

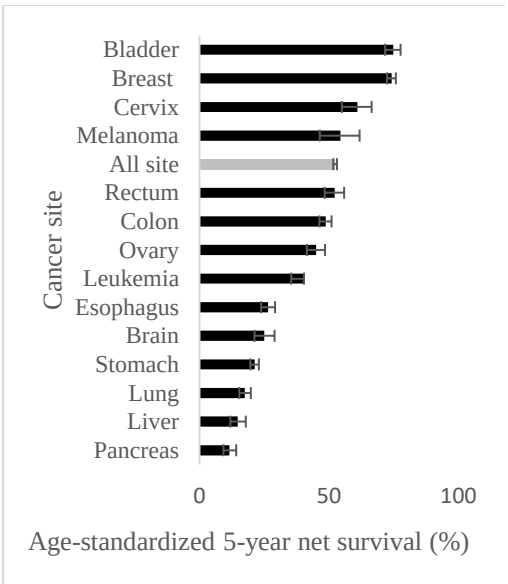
Cancer site	ICD-0	N of registered	DCO (%)	Lost to follow-up (%)	N of Included (%)
Esophagus	C15.0–C15.5, C15.8–C15.9	3,211	474 (14.76%)	526 (16.38%)	2,211 (68.86%)
Stomach	C16.0–C16.6, C16.8–C16.9	10,711	2,324 (21.70%)	1,447 (13.51%)	6,939 (64.79%)
Colon	C18.0–C18.9, C19.9	9,103	1,064 (11.69%)	1,958 (21.51%)	6,081 (66.80%)
Rectum	C20.9, C21.0–C21.2, C21.8	2,828	100 (3.54%)	648 (22.91%)	2,080 (73.55%)
Liver	C22.0–C22.1	2,767	1,141 (41.24%)	345 (12.47%)	1,281 (46.30%)
Pancreas	C25.0–C25.4, C25.7–C25.9	2,564	789 (30.77%)	249 (9.71%)	1,526 (59.52%)
Lung	C34.0–C34.3, C34.8–C34.9	7,204	2,376 (32.98%)	862 (11.97%)	3,966 (55.05%)
Breast (Women)	C50.0–C50.6, C50.8–C50.9	18,623	940 (5.05%)	5,258 (28.23%)	12,425 (66.72%)
Cervix	C53.0–C53.1, C53.8–C53.9	1,043	47 (4.51%)	282 (27.04%)	714 (68.46%)
Ovary	C48.0–C48.2, C56.9, C57.0–C57.4, C57.7–C57.9	2,606	265 (10.17%)	543 (20.84%)	1,798 (68.99%)
Prostate	C61.9	8,756	1,299 (14.84%)	2,297 (26.23%)	5,160 (58.93%)
Brain	C71.0–C71.9	4,276	1,232 (14.84%)	2,297 (26.23%)	5,160 (58.93%)
Melanoma	8720–8790 if topography was C44.0–C44.9, C51.0, C51.9, C60.9, or C63.2	507	13 (2.56%)	143 (28.21%)	351 (69.23%)
Leukemia	9590-9992	8,349	1,535 (18.39%)	1,341 (16.06%)	5,473 (65.55%)
Bladder	C67.0-67.9	8,315	414 (4.98%)	2,286 (27.49%)	5,615 (67.53%)
All site	--------	90,862	14,013 (15.42%)	18,766 (20.65%)	58,083 (63.92%)

Table 2: Age- standardized 5-year net-survival with 95% CI in adult cancer patients diagnosed in Iran during 2014-2015

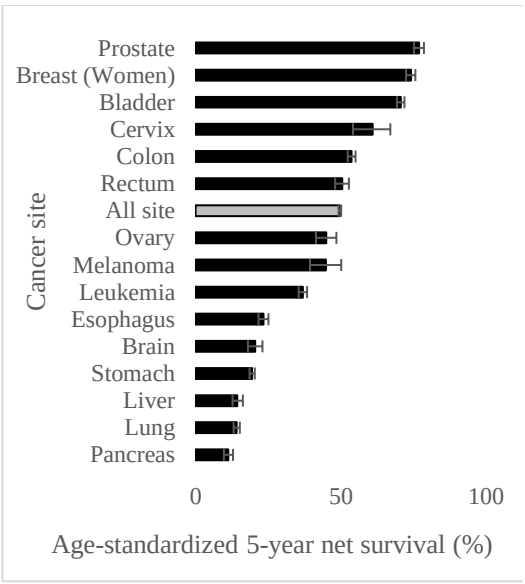
Cancer site	Men	Women	Both sexes
Esophagus	20,87 (18.78, 23,06)	26.46 (23.81, 29.19)	23.40 (21.71, 25.11)
Stomach	18.80 (17.72, 19.87)	21.30 (19.64, 22.94)	19.49 (18.61, 20.39)
Colon	53.04 (51.21, 54.81)	48.78 (46.32, 51.04)	53.70 (52.40, 55.10)
Rectum	49.16 (46.04, 52.20)	52.20 (48.38, 55.90)	50.49 (48.08, 52.82)
Liver	14.28 (12.17, 16.67)	14.73 (11.91, 17.89)	14.39 (12.73, 16.31)
Pancreas	10.60 (8.74, 12.81)	11.59 (9.26, 14.19)	11.30 (9.77, 12.91)
Lung	12.67 (11.57, 13.87)	17.54 (15.39, 19.84)	14.17 (13.11, 15.25)
Breast (Women)	----	74.24 (72.50, 75.88)	74.24 (72.50, 75.88)
Cervix	----	60.99 (55.03, 66.52)	60.99 (55.03, 66.52)
Ovary	----	45.05 (41.47, 48.51)	45.05 (41.47, 48.51)
Prostate	78.18 (76.50, 79.98)	----	78.18 (76.50, 79.98)
Brain	19.63 (16.98, 22.59)	25.02 (21.25, 29.00)	20.51 (19.04, 23.05)
Melanoma	39.99 (32.63, 47.13)	54.48 (46.47, 61.86)	44.86 (39.41, 50.18)
Leukemia	36.21 (34.34, 38.00)	40.30 (35.47, 40.37)	36.92 (35.51, 38.41)
Bladder	69.73 (68.28, 71.18)	74.92 (71.75, 77.71)	70.70 (69.36, 71.94)
All site	45.89 (45.34, 46.52)	52.40 (51.68, 53.12)	49.70 (49.25, 50.15)



Men



Women



Both Sexes

Figure 1: Age- standardized 5-year net-survival with 95% CI in adult cancer patients diagnosed in Iran during 2014-2015 by sex and cancer site