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ORIGINAL ARTICLE

Estimation of Thyroid Cancer Incidence in Kerman Province, Iran Via Three Source Capture-recapture Method During Years 2008-2015

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ABSTRACT

Background: This study aimed to estimate the incidence of thyroid cancer and completeness of thyroid cancer case registration in Kerman province, Iran using three source capture-recapture approach during years 2008-2015.
Methods: All new cases of thyroid cancers reported during 2008-2015 which were registered by pathology, nuclear medicine and medical records were included in this study. Using the personal identifiers, common cases between sources were linked. The log-linear Poisson regression analysis was applied to estimate the number of unregistered cases. The incidence rate per 100,000 population was calculated. To study the trend, Joint-point regression analysis was performed.
Results: Overall, 1153 new cases of thyroid cancer were reported by three sources. Most cases were female (81/7%). The mean age at diagnosis was 41.53±15.69 years. The estimated number of thyroid cancer cases was 1323**.** The estimated incidence per 100,000 population varied from 4.5 in 2011 to 11 in 2015. The female to male ratio varied from 3.1 in 2015 to 6.7 in 2011. The completeness of registration for all three sources varied from 33.7% in 2008 to 95.1% in 2013. The completeness of medical records, pathology reports, and nuclear medicine reports were 33.1%, 50.7%, and 66.2%, respectively.
Conclusion: Despite some improvements in completeness of thyroid cancer registration during the study period, there are still fluctuations within the study period. Furthermore, considering each source separately, the completeness of registration is not satisfactory. Therefore, more effort should be done to increase the completeness of thyroid cancer registration specially through the pathology source.

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Introduction

Population-based cancer registries are the core component of cancer control programs. The primary purpose of population-based cancer registries is to collect, manage and analyze the cancer cases and use these information to estimate the current cancer burden, examine the recent trend and identify affected areas or subpopulations. Such sort of information help the policy makers to establish primary prevention and screening/early detection programs and evaluate the effectiveness of these interventions by comparing the trend of incidence and mortality of cancers in different periods.[1] However, the value of data in policy making will be questionable if cancer registries fail to record all ascertained cases. Therefore, in regions in which the data of cancer registry is imperfect or uncertain, a variety of quantitative and qualitative methods are recommended to be used to estimate the actual incidence and trend of the cancers.[2]

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One of these methods that has been widely used is the "capture-recapture method". It requires access to at least two independent data sources. Based on the ratio of recaptured subjects, the size of the population can be estimated. As the main assumption, independency of data sources are usually violated and statistical techniques including log-linear estimation are applied to tackle this dependency where at least three data sources are available.[3]

Kerman is a province located in the south-east of Iran. Thyroid cancer is the seventh prevalent cancer in Kerman province whiles the ninth common cancer in Iran and also in the globe.[4, 5] Thyroid cancer incidence among women is significantly higher than men. Among women, it is the second common cancer in Kerman, and fifth cancer in Iran and also in the whole world.[5] Evidences indicate the incidence of thyroid cancer is increasing[5]. Improved case ascertainment, and diagnosis of indolent cases are likely to be the main reasons of this increase.[6] However, true increase is also possible because of changes in the prevalence of risk factors.[7] Exposure to ionizing radiation especially during childhood, increased incidence of goiter and benign adenomas, sex (hormone and breeding factors), height and weight at the time of diagnosis, environmental and lifestyle factors such as dietary habits (fish consumption and smoking) and exposure to toxins are among the potential risk factors.

In order to provide an accurate estimate of the actual trend of incidence of thyroid cancer in Kerman, we applied the three-source capture-recapture methodology using data collected from pathology labs, nuclear medicine centers and medical records and estimated the trend of thyroid cancer over the period of 2008-2015 in both genders and three age groups. We also evaluated the completeness of each source separately. The findings of this study may help the policy makers to better understand the current status of thyroid cancer as well as completeness of thyroid cancer registration in Kerman, Iran.

Materials and Methods

Data Collection and Preparation

In this study, all new cases of thyroid cancer in Kerman province during 2008-2015 which were recorded by any of three sources of pathology reports, nuclear medicine center and medical records were recruited to the study. The eligibility criteria were being diagnosed with primary thyroid cancer and being the resident of Kerman province at the time of diagnosis. The duplicated cases in each source were identified and eliminated using Excel software on the basis of the name, family name, national code, father's name, city of residence and date of birth.

Statistical Model

We used the "capture-recapture approach" to estimate the number of missing cases and completeness of cancer registration over the study period. The main underlying assumption of this method is independency of the sources. As this assumption is usually violated in cancer registration, we used the log-linear model in which the dependency between the sources would be considered by entering all two interactions between the three sources in the model. Accordingly, there were eight possible models including one independent model without any interaction term, three model with one interaction term, three model with two interaction terms and one model with three interaction terms (saturated model). The final model was chosen based on the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). We stratified the analysis by gender and three different age groups. The age groups were categorized in three groups: <49, 50-65 and >65 years.

Calculating the Incidence Rate

To calculate the observed incidence rate (based on cancer registry data) and estimated incidence rate (based on capture-recapture method) for each study year, we divided the number of new cases in each sex/age group by the population of Kerman province in the same gender/age category. The corresponding rates were multiplied by 100,000. Given that the national census in Iran is conducted every 5 years, we used the continuous exponential growth formula to estimate the size of population for the interval years between two censuses. To do this, first we reviewed the official reports of statistics center of Iran[8] and extracted the number of population reported for 2011 and 2016. Then we used the following formula to estimate the size of population for the years in which no census data was available.

$P_{t+1}=P_t\ e^{rt}$, where P_{t+1}: the estimated population for the target year, P_t: the number of population in the last census, r: population growth rate, t: the time (year) that has passed, e (exponential e): 2.71.

The population growth rate(r) was estimates as below:

$r=Ln(P_t/P_0)/t$

Where P_t: The number of population in latest census, P_0: The number of population in penultimate census and t: the time interval (year) between two censuses.

Trend Analysis

The trends in incidence of thyroid cancer over the study period was expressed as annual percentage of change (APC) and average annual percentage of change (AAPC). To find the best-fit line, we fitted the jointpoint model to the data using Joinpoint Regression Program (Version 4.7.0.0 National Cancer Institute; 2019).The trend was considered to be significant (increasing or decreasing) if the P-value was less than 0.05.

Study Ethics

During all stages of this study, personal information including name, family name, national code, phone number, address and other personal identifiers were kept confidential. The study protocol was reviewed and approved by ethic committee of Kerman University of Medical Sciences (Ethic code: IR.KMU.REC.1397.266.)

Results

Demographic Characteristics

A total of 1153 new cases of thyroid cancer, registered from April 2008 to March 2015 were included in the

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analysis. Of these, 671 cases were found from pathology department, 876 from nuclear medicine department and 439 from hospital medical records. Majority of the cases were female (81/7%). The mean age was 41.53±15.69 years. There was no significant difference regarding the mean age between two genders (41.16±15.30 in women vs. 43.15±17.31 in men, p-value: 0.09).

Estimated Cases Based on Three Source Capture-recapture

Linkage of the cases indicated that 8.58% of registered cases were reported by all three sources. That is, a total of 1153 cases were reported by any sources of hospital medical records, pathology and nuclear medicine department, 99 of them shared these three sources (figure 1). The result of the three-source capture-recapture method using log-linear modeling is presented in table 1. Out of eight possible model fitted, the model in which medical records and pathology reports as well as medical records and nuclear medicine reports had interaction effect was chosen as it was the best model with the lowest value of both AIC and BIC. According to this model, the total number of cases which were not recorded by any source (counting down) was estimated to be 187. As a result, the estimated total number of thyroid cancers within the study period was 1323.41 (95% CI: 1252.66 to 1396.25) (table 1). The estimated incidence per 100,000 population varied from 4.5 in 2011 to 11 in 2015.The incidence in women was higher than men. The female to male ratio varied from 3.1 in 2015 to 6.7 in 2011. In all study years; except two (2013 and 2015), the ratio was over 5 (table 2).

The overall completeness of registration considering all three sources was 87.1%. Furthermore, the completeness of registration by all three sources varied from 33.7 in 2008 to 95.1 in 2013. The completeness of medical records, pathology reports, and nuclear medicine reports were 33.1%, 50.7%, and 66.2% respectively (table 3).

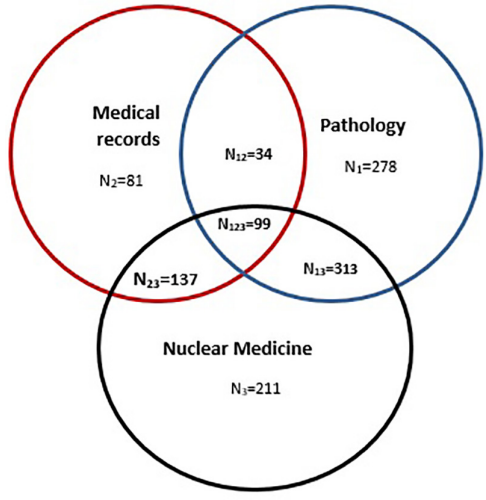


Figure 1: The Venn diagram of thyroid cancer cases in Kerman province that were recorded by three source of pathology, medical records and Nuclear Medicine

Thyroid Cancer Trend

Using the joint-point regression analysis, we assessed the trend of thyroid cancer over the study period in three different age groups including ≤49, 50-65 and >65 years. Combining all age groups and both gender, the overall trend of thyroid cancer in Kerman province was increasing (figure 2). The trend in women, men and both genders that aged ≤49years was increasing (figure 3a) while in other age groups, the trend showed a slight decrease. (figures 3b, 3c). The highest AAPC in men and women was estimated for the age group ≤49 years (17.8% in men vs 4.4% in women), while combining men and women, the highest AAPC was estimated for the age group >65 years (18.6%).

Table 1: Specifications of linear log models fitted to data extracted from three thyroid cancer registry sources during years 2008 to 2015

Log linear model**	X***	N****	95 %CI	Df**	*G2	*BIC	*AIC
P/M/N*	194.39	1330.39	(125.47-1403.44)	4	72.67	127.27	127.48
PM/N	144.51	1280.51	(1211.80-1353.11)	3	29.41	85.96	86.23
PN/M	186.44	1322.44	(1251.68-1395.23)	3	75.54	129.09	129.23
MN/P	255.61	1391.61	(1319.82-1467.09)	3	32.72	89.27	89.54
PM/PN	97.03	1233.03	(1165.13-1303.79)	2	20.36	78.85	79.18
PM/MN	187.41	1323.41	(1252.66-1396.25)	2	1.13	59.62	59.94
PN/MN	500.4	1636.4	(1557.67-1717.24)	2	20.73	79.22	79.54
PM/PN/MN	243.76	1379.76	(1308.14-1454.77)	1	<0.001	60.43	60.81

* Akaike's Information Criterion/Bayesian Information Criterion/Goodness of fit; **Degree of freedom; ***Estimation of number of thyroid cancer cases not recovered in any of the sources; ****Estimation of the total number of thyroid cancer cases in Kerman province during years 2008 to 20015; *P:Patology reports source، M:Medical records documentation، N: Nuclear Medicine; P/M/N model: Model that has only Main effect .PM/N model: A model that in addition to the main effect is the interaction between pathology and medical records in the model..PM/PN model: A model that in addition to the main effect is the interaction between pathology and medical records and the interaction between pathology and Nuclear Medicine in the model..PM/MN model: A model that is in addition to the main effect, the interaction between pathology and medical records, and the interaction between medical records and Nuclear Medicine in the model.PN/MN model: A model that is in addition to the main effect, the interaction between pathology and Nuclear Medicine , and the interaction between medical records and Nuclear Medicine in the model. PM/PN/MN model: A model that is in addition to the main effect, the interaction between pathology and medical records, and the interaction between pathology and Nuclear Medicine, and the interaction between and medical records and Nuclear Medicine in the model. (Saturation model).

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Table 2: Estimation of total reported and estimated incidence in terms of number of reported and estimated thyroid cancer cases during years 2008 to 2015

Year	Sex	Reported cases*	Estimated cases	Reported incidence rate(I1)	Estimated incidence rate(I2)	95% CI for I2	Completeness** (percent)	Female/ Male ratio
2008	Female	55	187.2	4.12	14.04	12.09-16.2))	33.75	5.4
	Male	20	35	1.49	2.60	(1.82-3.63)		
	Total	75	222.2	2.80	8.30	(7.25-9.47)		
2009	Female	80	158.2	5.94	11.75	(9.98-13.72)	54.13	9.3
	Male	15	17.3	1.09	1.26	(0.72-1.99)		
	Total	95	175.5	3.50	6.49	(5.56-7.52)		
2010	Female	107	118.07	7.87	8.68	(7.19-10.4)	92.03	5.7
	Male	21	21	1.50	1.50	(0.93-2.3)		
	Total	128	139.07	4.64	5.04	(4.24-5.96)		
2011	Female	102	111.5	7.42	8.12	(6.65-9.75)	91.05	6.8
	Male	15	17	1.05	1.19	(0.69-1.91)		
	Total	117	128.5	4.13	4.53	(3.57-5.37)		
2012	Female	98	117.45	7.06	8.47	(7.04-10.19)	85.43	5.3
	Male	22	23	1.51	1.58	(1-2.38)		
	Total	120	140.45	7.55	8.84	(7.47-10.47)		
2013	Female	122	126.59	8.71	9.03	(7.56-10.79)	95.19	3.9
	Male	31	34.2	2.09	2.30	(1.59-3.21)		
	Total	153	160.79	5.31	5.57	(4.76-6.52)		
2014	Female	148	230.42	10.46	16.28	(14.29-18.58)	80.24	5.07
	Male	40	48.57	2.63	3.21	(2.4-4.29)		
	Total	224	278.99	7.65	9.53	(8.45-10.72)		
2015	Female	194	244.61	13.57	17.12	(15.07-19.44)	73.56	3.1
	Male	47	83	3.05	5.38	(4.29-6.68)		
	Total	241	327.61	8.11	11.03	(9.88-12.31(		

*Reported case by three sources of pathology, medical records and Nuclear Medicine after removal of duplicates; **Number of registered cases divided by the number of estimated incidences multiplied by 100

Table 3: The Trends of Age-Standardized Incidence Rate of thyroid Cancer Incidence in kerman province by jointpoint analysis during years 2008 to 2015

Age group	Sex	JOINPOINT				
		Trend1	APC	Trend2	APC	AAPC
Less than or equal to 49 years	Female	1387-1390	-22.79	1390-1394	30.97	4.4
	Male	1387-1392	-11.80	1392-1394	143.1	17.8
	Both gender	1387-1390	-8.99	1390-1394	23.20	8.2
50-64 years	Female	1387-1392	-9.67	1392-1394	25.51	-0.8
	Male	1387-1389	-33.22	1389-1394	23.24	3.4
	Both gender	1387-1392	-6.43	1392-1394	20.11	0.5
Over 65 years	Female	1387-1391	-19.23	1391-1394	17.42	-5.2
	Male	1387-1390	-17.59	1390-1394	30.70	7.3
	Both gender	1387-1392	-17.43	1392-1394	193.49	18.6

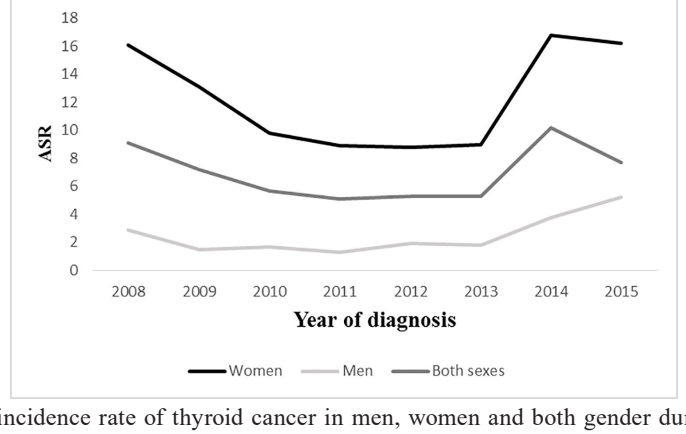


Figure 2: Age-standardized incidence rate of thyroid cancer in men, women and both gender during 2008 to 2015 in Kerman province, Iran

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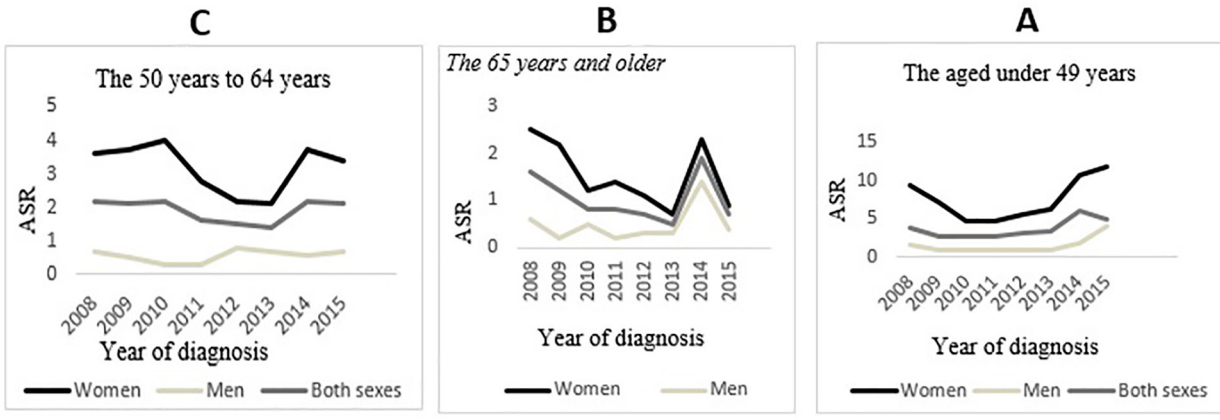


Figure 3: Gender-based age-Standardized incidence rate of thyroid cancer in three age group during 2008 to 2015, Kerman province, Iran

Discussion

In the present study, we used three source "capture-recapture" approach to estimate the incidence and trend of the thyroid cancer and completeness of cancer registry data in Kerman province of Iran. We showed an increasing trend of thyroid cancer in men and women especially among the age group less than 49 years. The incidence was higher among young women. The overall completeness of cancer registry within the study period was 87.1%. Overall, the completeness of the registration increased during the study period.

In our study, the mean age at diagnosis was 41.53±15.69 years which is consistent with the mean age reported in other parts of the Iran.[9, 10] So, it seems that the most affected population in Iran is mostly at their early forty. In a study conducted on data collected from 1974-2013 in the U.S, the mean age at diagnosis reported to be 48±16 years.[11] The results of other studies around the world indicate that the mean age at diagnosis recently decreased compared to the past. In a study on five high income countries, the researchers concluded that the decrease in age at diagnosis may be mainly due to introduction of new imaging techniques followed by intense search for thyroid nodules that very seldom lead to death in young and middle-age individuals.[12]

The female to male ratio in most study years was over 5 and varied from 3.1 in 2015 to 6.7 in 2011. The fluctuation in sex ratio within the study period is somehow implausible and may be attributed to imprecision and incompleteness of case registration or case reports. Based on the estimates of Global cancer observatory, 2018, the female to male ratio for thyroid cancer estimated to be 3.3 in Iran, 3.1 in Eastern Mediterranean Region and 3.2 worldwide which are lower than our estimates.[4]

It has been stated that the higher incidence of thyroid cancer among women is mainly the result of overdiagnosis of thyroid tumors that, if left undiagnosed, would cause no harm or death.[13] Vaccarella et al. in a study conducted in 12 high income countries estimated that more than 470,000 women compared to 90,000 men may have been over diagnosed with thyroid cancer over the past two decades.[14] Nevertheless, the higher incidence among women may be somehow related to reproductive factors. The findings of a meta-analysis in 2019 indicated an association of reproductive factors including age at menarche, increased parity, miscarriage/abortion, and artificial menopause with increased risk of thyroid cancer. This association may explain the female preponderance of this disease.[15]

The estimated ASR per 100,000 population within the study period varied from 4.5 in 2011 to 11 in 2014. In most of the studied years, the ASR was more than 6. In the latest two years of the study, the ASR was 9.5 and 11, respectively. According to the latest estimates of the "Global Cancer Observatory" in 2018, the ASR of thyroid cancer per 100,000 population is estimated to be 6.5 for Iran, 3.0 for EMRO and 6.7 worldwide. Comparing our finding indicated that the incidence of thyroid cancer in Kerman province specially in the recent years was higher than global, regional and national estimates.

We found that the overall incidence of thyroid cancer in Kerman province shows an increasing trend similar to the recent trends of thyroid cancer all around the world.[6, 11]

The reason for this increasing trend is a matter of debate. There are two possible explanations for this increase: 1) overdiagnosis and 2) the real increase in thyroid cancer incidence. It is argued that widespread use of sensitive diagnostic techniques such as ultrasound, fine needle aspiration biopsy, CT scan and MRI and also increasing the number of endocrinologists, pathologists and radiologists during the recent years resulted in detection of indolent small size thyroid nodules which if left undiagnosed, rarely progress to higher stages or cause death.

For overdiagnosis to be the only explanation of increasing trend of thyroid cancer, we should have expected an increase in the trend of tumors with small size, while stable or decreasing trend for tumors diagnosed at larger size as well as more new cases among population with higher access to medical services.[16] Unfortunately, we did not study the change in incidence based on the size of tumors or access of population subgroups to health services. However, the role of overdiagnosis has been supported in variety of studies that showed the shift of recent detected tumors toward earlier stages.[17] The overdiagnosis usually brings about overtreatment of indolent cases. Unnecessary treatment of such cases will result in both more adverse effects and financial costs. For

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example, overdiagnosis may cause psychologic burden of a cancer diagnosis. In addition, overtreatment and interventions such as partial or total thyroidectomy may be followed by parathyroidectomy, injury to the vocal cords and lifelong thyroid hormone replacement therapy.[12, 18, 19] To reduce the overdiagnosis, approaches such as risk-based screening combined with biomarkers, avoiding routine screening of thyroid cancer, reclassification of low-risk thyroid cancers with terms other than cancer, development of less aggressive national guidelines for management of thyroid nodules may be beneficial.[12, 18]

Although the overdiagnosis is a more plausible explanation, the possibility of actual increase in thyroid cancer incidence could not be ruled out. The real increase in thyroid cancer incidence may be the result of increased exposure to significant risk factors. More than 80% of thyroid cancers are papillary carcinoma[9] which has been associated with exposure to ionizing radiation especially during childhood.[20] By widespread use of medical diagnostic imaging techniques, exposure to ionizing radiation has been increased all around the world including Iran. Furthermore, increased risk factors including obesity, cigarette smoking and exposure to environmental carcinogens during the recent years may also be responsible for increased incidence of thyroid cancers.

The overall completeness of the three source capture-recapture methodology of our study within the study period was 87.1%. Considering each year separately, the estimated completeness of cancer registry data varied from 33.7% in 2008 to 95.1% in 2013. In the first two years of the establishment of registration, the completeness was low (33.7% in 2008 and 54.1% in 2009) which increased to more than 80% within the next five years. In the latest studied year; year 2015, the completeness decreased to 73% which may be due to the time gap between case diagnosis and case registration. The completeness of a variety of cancer registrations has been assessed in Iran. Mohammadi et al. in 2017 studied the completeness of Tehran, Iran cancer registration and showed 49% under reporting of the cases.[21] In another study conducted in Kohgiluyeh and Boyer-Ahmad, Iran, only 31% of cancer cases were registered by cancer registration.[22] In another study conducted in Ardabil, the completeness of registration for gastric cancer reported to be 36%.[23] Although we did not find any similar study on thyroid cancer registration to compare our results with, it seems that registration of thyroid cancer in Kerman province, especially during the recent years to be accurate, but still not satisfactory and more efforts still should be made to reach the ideal completeness of 90%-100%.

Considering each source separately, the highest completeness was estimated for nuclear medicine reports (66.2%), while the lowest belonged to the medical records (33.1 %). This finding was expected since all thyroid cancers who receive treatment at nuclear medicine center must have been confirmed pathologically.

Although the morality and burden of the thyroid cancer is low compared to other common cancers, strengthening the completeness of thyroid cancer registration, especially through the pathologic source is vital. Having accurate information on size and stages of the tumor may inform policy makers about the rate of overdiagnosis and probably overtreatment. This information provides valuable inputs for updating clinical guidelines for diagnosis and management of thyroid cancers and reclassification of the disease.

We would like to admit the limitations of our study. There is possibility of violation of capture-recapture assumptions which may affect the validity of our results. Furthermore, one of our sources was nuclear medicine reports which mainly registers the cases of papillary and follicular thyroid cancers, and therefore, other types of thyroid cancers are being missed using this source. Finally, we linked the three-source data using personal identifiers including national code, first name, family name and father's name which might not have been recorded accurately.

Conclusion

The results of the present study indicated that thyroid cancer in Kerman, Iran is common, and the trend is increasing. Regarding the completeness of thyroid cancer registration in our study in Kerman province of Iran, its completeness showed fluctuations within the study period. Therefore, extensive efforts are needed to improve the coverage and accuracy of thyroid cancer registration especially the completeness of pathology reports which provide information about type, size and stage of the tumors. Finally, three source capture-recapture method could be used as a simple and feasible approach to estimate the completeness of thyroid cancer registration.

Conflict of Interest: None declared.

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