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Trends in rates of inpatients treated for testicular cancer in France, 2000–2014

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SUMMARY

Testicular cancer is rare, accounting for 1–3% of incidence of all malignancies in men. Forecasts predict that the incidence of testicular cancer will increase by 25% in Europe by 2025. We aimed to describe temporal and spatial trends of rates of patients surgically treated for testicular cancer (STTC) in France over the period 2000–2014. Using the International Classification of Diseases and medical procedure codes, from the national hospital discharge database, we selected patients diagnosed with testicular cancer during 2000–2014 who underwent surgery. We used the world's standard population as a reference to standardize rates. We included 29,760 STTC patients. The mean age at diagnosis was 37.4 (±13.5) years. Over the period 2000–2014, the standardized incidence rate of STTC was 6.2 [95% CI: 6.1;6.3] per 100,000 person-years. The overall rate of STTC increased by 21.3% between 2000 and 2014. The annual percentage change (APC) was +1.9% [95% CI: 1.4;2.3] over that period. The incidence rate of STTC was highest among men aged 30–44 (15.0 [95% IC: 14.7;15.2] per 100,000 person-years) and lowest among men aged 0–14 (0.2 [95% IC: 0.16;0.22]). Age-specific STTC incidence rates were similar to indicators from cancer registry data except in elderly men aged 60 years and over. Over the study period, the incidence of STTC increased over the year in all the regions of Metropolitan France. APC varied across regions from 1.0% [95% IC: −4.1;6.1] in Île-de-France to 4.2% [95% IC: −0.8;9.2] in Corse. Hospital discharge data, which are more quickly available than population-based data, are good complementary surveillance source for monitoring testicular cancer, especially in young adult patients and area without population-based registry.

INTRODUCTION

Although testicular cancer (TC) (Sigurdson *et al.*, 1999) is a rare disease, accounting for 1–3% in incidence of all cancers in males in Western countries, it is the most common malignancy among young men (aged 15–34 years) in most European populations (Bray *et al.*, 2006). Its incidence rate has continued to increase since the middle of the twentieth century in many Western countries (Garner *et al.*, 2005). A recent paper by Le Cornet predicted a 25% rise in TC incidence by 2025 in Europe (Le Cornet *et al.*, 2014). In France, 2317 incident cases of TC were estimated from registry data in 2012 (Binder-Foucard *et al.*, 2013).

The etiology of TC is not well understood. Most of the established risk factors are related to early life events, including cryptorchidism, testicular germ cell neoplasia in situ, and in utero exposure to estrogens. Mixed associations with TC have been demonstrated for occupational, lifestyle, socioeconomic, and other risk factors (Dieckmann & Pichlmeier, 2004; Garner *et al.*, 2005; Ylönen *et al.*, 2018). TC treatment always involves surgery before any other intervention.

Warnings around the world about the worsening situation of human reproductive endpoints have become increasingly common in recent decades. There is increasing evidence that impaired prenatal development of testicles leads not only to urogenital anomalies but also to the increased risk of TC and impaired semen quality in adulthood (Skakkebaek *et al.*, 2001; Le Moal *et al.*, 2016). These conditions may reflect testicular dysgenesis syndrome, which is possibly caused by exogenous factors such as exposure to endocrine-disrupting chemicals (EDC) (Skakkebaek *et al.*, 2001).

The objective of the study was to describe temporal and spatial trends of rates and to estimate changes in incidence of patients, surgically treated for TC (STTC) in Metropolitan France over the period 2000–2014.

MATERIALS AND METHODS

Data sources

Hospital discharge database

Data on patients diagnosed with TC over the period 2000–2014 in Metropolitan France were extracted from the French PMSI (Programme de Médicalisation des Systèmes d'Information) system, which is a medico-administrative database, similar to the USA's Medicare Diagnostic-Related Groups (DRG). PMSI provides nationwide data on all patients discharged from public and private hospitals. Each patient stay is documented with the following data recorded: (i) personal information (age, sex, area code of residence) and (ii) clinical and administrative information including the following: diagnoses (principal, related, and associated) codes (according to the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10)), medical procedure codes (according to the French Catalogue of Medical Procedures (FCMP) used until 2004 and subsequently the French Common Classification of Medical Procedures (FCCMP) used from 2002 until today), care center codes, and a systematically generated anonymous individual and common identifier (AICI), which has been used since 2002 to identify all hospital stays of the same patient discharged from different hospitals over time.

Principal diagnosis is defined as the main reason which most mobilized the medical effort (up to 2008), the main reason for patient admission to hospital (since 2009). Related diagnosis aims to best explain the principal diagnosis in the absence of reliable information. Associated diagnosis is defined as symptoms or other significant reasons that necessitate increased involvement of health professionals in patient care, in addition to the care provided for the principal and related diagnoses.

Population-based cancer registry data

Population-based cancer registration represents the gold standard for the provision of information on cancer incidence in a defined population. There is no national cancer registry in France. Information of all cases of malignant tumors located in the testicle which were reported to district cancer registry of 18 subregional territories (called *départements* in France) Bas-Rhin, Calvados, Charente, Charente-Maritime, Deux-sèvres, Doubs, Gironde, Haut-Rhin, Haute-Vienne, Hérault, Isère, Loire-Atlantique, Manche, Somme, Tarn, Territoire de Belfort, Vendée, and Vienne between 2008 and 2012 were used to compare indicators from a selection algorithm in the PMSI with those from registries.

Census data

We used census data by age from 2000 to 2015, provided by the French National Institute of Statistics and Economics Studies to calculate rate. As populations are given for 1 January each year, we calculated the number of person-years for year y as the mean of populations for years *y* and *y*+1 (Estève *et al.*, 1994). We used the world's standard population (Estève *et al.*, 1994) as a reference to standardize rates.

Patient selection

Based on the ICD-10 revision cancer codes and FCMP/FCCMP codes of surgical treatment, we selected hospital stays of patients suffering from TC (C62), where this cancer code was recorded as the principal or related diagnosis in PMSI between 2000 and 2014. Hospital stays, from 2002 to 2014, without an AICI or with a non-valid AICI, as well as patients living outside of France, were excluded.

As a rule, radical orchiectomy is performed before any further treatment on patients with TC. Accordingly, we assumed that a hospital stay for TC diagnosis treated by orchiectomy represented a patient suffering from TC and an incident case of TC. Patients diagnosed for TC and surgically treated represent the study population.

Statistical analysis

Data analysis was primarily descriptive in nature. The rates of STTC patients were analyzed at three levels—national, regional, and district (regions comprise several districts).

At the national level, we calculated, for each year of the study period, the crude rate of patients who underwent surgery for TC as the number of cases divided by the French mid-year population and age-standardized this rate to the world's standard population (Estève *et al.*, 1994), expressed in 100,000 person-years for comparison. These age-standardized rates were calculated with the standard 5-year segmentation of age, from 0 to 85 years of age and over. We also calculated the age-specific incidence rates of patients who underwent surgery over 2000–2014. To assess trends over this period, we estimated the annual percentage change (APC) in age-adjusted incidence rates and their 95% CI by Poisson regression, for example $[\exp(\beta)-1]\times 100$, where β denotes the regression coefficient of time (change per year). For temporal analysis, years of diagnosis were grouped into four periods (2000–2002; 2003–2005; 2006–2009; and 2010–2014) after visual inspection (Wagner *et al.*, 2002) of data over time using graph on trends of incidence rates.

At the regional level, we calculated—for each French region where patients were resident—the age-standardized incidence rates for STTC for each year and for the period 2000–2014. Age standardization was performed using the world's standard population. Poisson regression analysis was used to evaluate the annual changes in STTC over time in each of the Metropolitan French region.

To test the validity of the algorithm used to select patients in the PMSI, we calculated the age-specific incidence rates in the 18 district cancer registries and compared them with those of the same districts from PMSI data.

All analyses were performed using SAS ENTERPRISE GUIDE software version 7.1 (SAS Institute, Cary, NC, USA). All confidence intervals were at 95%, and the level of significance for the test was 5%.

RESULTS

Characteristics of patients selected

From 2000 to 2014, of the 251,478 hospitalizations for diagnosed TC in Metropolitan France, 207,697 (83%) were coded as principal or related diagnosis. Of the latter, 30,320 with a surgical code for treatment—corresponding to 29,802 (98%) patients—were identified. After the exclusion of 42 patients for missing information on age, the number of patients we considered to be incident TC cases was 29,760 (study population). Mean age at diagnosis for the study population was 37.4 (±13.5) years. Median age was 35 [Q25–Q75: 28–43] years. Details on the characteristics of the study population by year are depicted in Table 1.

Table 1 Data description and age-standardized rates of surgically treated testicular cancer according to the year of diagnosis, PMSI 2000–2014

Year of diagnosis	Number of stays[a]	Number of stays with valid AICI[b]	Corresponding number of patients	Mean number of stays per patient	Number of study patients[c]	Mean age at diagnosis (SD)[d]	Age-standardized rate (per 100,000)	
							Crude [95% CI]	World's standard population [95% CI]
2000	1736	–	1736	–	1729	36.7 (13.8)	5.5 [4.3;6.7]	5.5 [5.2;5.8]
2001	1745	–	1745	–	1743	37.7 (14.9)	5.9 [4.5;7.2]	5.5 [5.2;5.7]
2002	1794	1724	1704	1.01	1700	36.8 (13.5)	5.4 [4.2;6.5]	5.4 [5.1;5.7]
2003	1878	1825	1808	1.01	1804	36.5 (13.3)	5.7 [4.5;6.9]	5.8 [5.5;6.0]
2004	1888	1863	1834	1.01	1832	37.5 (14.1)	5.9 [4.6;7.1]	5.8 [5.5;6.1]
2005	1875	1850	1830	1.01	1825	37.0 (13.7)	5.7 [4.6;6.9]	5.8 [5.5;6.0]
2006	2065	2030	2015	1.01	2011	37.0 (13.2)	6.2 [5.0;7.4]	6.3 [6.1;6.6]
2007	2086	2086	2065	1.01	2060	37.9 (14.1)	6.5 [5.3;7.8]	6.4 [6.1;6.7]
2008	2096	2096	2074	1.01	2071	37.5 (13.7)	6.5 [5.3;7.8]	6.5 [6.2;6.7]
2009	2229	2229	2200	1.01	2199	36.8 (13.0)	6.7 [5.5;8.0]	7.0 [6.7;7.3]
2010	2146	2146	2117	1.01	2117	38.2 (13.5)	6.6 [5.4;7.8]	6.5 [6.3;6.8]
2011	2080	2080	2054	1.01	2054	37.4 (13.2)	6.4 [5.2;7.5]	6.5 [6.2;6.7]
2012	2224	2224	2190	1.02	2190	37.7 (12.9)	6.8 [5.5;8.0]	6.8 [6.5;7.1]
2013	2314	2314	2291	1.01	2286	38.1 (13.4)	7.0 [5.8;8.3]	7.1 [6.8;7.4]
2014	2164	2164	2139	1.01	2139	37.9 (12.9)	6.5 [5.4;7.7]	6.7 [6.4;7.0]
2000–2014	30,320		29,802		29,760	37.4 (13.5)	6.2 [5.9;6.5]	6.2 [6.1;6.3]

[a]Hospital stays for surgical treatment of testicular cancer coded in principal or related diagnosis. [b]Anonymous and individual common identifier was not available for data for 2000 and 2001. [c]Patients with valid information on age. [d]Standard deviation.

Incidence of surgically treated testicular cancer and trends over time

Over the period 2000–2014, the standardized incidence rate of STTC was 6.2 [95% IC: 6.1;6.3] (Table 1). It increased by 21.3% between 2000 and 2014, corresponding to an increase in APC of 1.9% [95% CI: 1.4;2.3] (Fig. 1A, Table 2). This overall 1.9% increase included a significant decrease in APC in 2000–2002 (−1.1 [95% IC: −1.3; −0.9]) and a significant increase in APC in 2006–2009 (2.9 [95% IC: 0.6;5.2]) (Table 2).

The incidence rate of STTC during 2000–2014 was highest among men aged 30–44 (15.0 [95% IC: 14.7;15.2] per 100,000 person-years) and lowest among men aged 0–14 (0.2 [95% IC: 0.16;0.22]). Incidence rates of STTC by age class and year of diagnosis are shown in Fig. 1B. The age-specific incidence in 2000–2004 was highest in the age group of 25–29 years, while in 2005–2009 and 2010–2014, the peak incidence was detected in the age group of 30–34 years (Fig. 2).

As shown in Table 2, the STTC incidence rate decreased significantly in 2000–2002 for men aged 0–14 (APC = −27.5 [95% IC: −45.3; −9.8]) and 45–59 (APC = −6.2 [95% IC: −9.5; −2.9]), in 2003–2005 for men aged 15–29 (APC = −3.0 [95% IC: −c3.3; −2.6]), and in 2010–2014 for men aged 75 and over (APC = −9.3 [95% IC: −13.8; −4.8]). It rose significantly in 2006–2009 for men aged 30–44 (APC = 5.1 [95% IC: 3.6;6.5]) and 45–59 (APC = 1.1 [95% IC: 0.2;2.0]).

Comparison between rates of STTC and incidence rates of testicular cancer from population-based cancer registries

Both age-specific incidence estimates based on the nationwide PMSI and the pooled analysis of data from 18 available district cancer registries for 2008–2012 showed similar results until 60 years of age, with a peak at 30–34 years (Fig. 3). Incidence rates from PMSI were higher in men aged 60 and over than those in registry data.

Incidence of surgically treated testicular cancer by region

The world standardized rate (WSR) of STTC varied across regions of residence from 5.3 to 7.5. Over the period 2000–2014 (Fig. 4), regions in the east (Grand-Est, WSR = 7.4 [95% IC: 7.1;7.7] and in the west (Brittany, WSR = 7.5 [7.2;7.9]) of France had a higher STTC incidence, while the Île-de-France (WSR = 5.3 [5.1;5.4]) region had a lower incidence.

From 2000 to 2014, the incidence rate of STTC increased over the years in all the regions, but this increase was not significant. The APC varied across regions from 1.0% [95% IC: −4.1;6.1] in Île-de-France region to 4.2% [95% IC: −0.8;9.2] in Corse.

DISCUSSION

The objective of this study was to describe temporal and spatial trends of rates of patients diagnosed and treated for TC over the period 2000–2014. The primary treatment for TC, as for any solid tumor, is surgery, radiotherapy, and chemotherapy. As a rule, radical orchiectomy is performed before any other treatment. Accordingly, like Stang (Stang *et al.*, 2009), we assumed that a recorded hospital stay for TC diagnosis with orchiectomy represented a patient suffering from TC who was an incident TC case.

The main findings of the study are that (i) mean age at diagnosis of males suffering from TC was 37.4 years over the study period, and most cases occurred between 30 and 34 years; (ii) the age-standardized rate increased from 5.5 per 100,000 person-years in 2000 to 6.7 in 2014, with an annual percentage change (APC) of 1.9%; and (iii) rates of STTC varied across French regions. TC rates in western (Brittany) and eastern (Grand-Est) regions were higher than rates in the Ile-de-France (i.e., Paris) region. Between the period 2000 and 2014, the APC of STTC patients increased in all the 13 regions of Metropolitan France.

There is no national cancer registry in France. The estimation of cancer incidence is based on incidence/mortality ratio observed in district registries which cover approximately 20% of the adult population (defined as being over 15 years of age) (Colonna *et al.*, 2008; Binder-Foucard *et al.*, 2013). However, this method cannot be applied at the regional level for rare cancers like TC. Another method based on either the incidence/inpatient ratio or the incidence/'long-term illness status beneficiary' ratio provides a more accurate estimation of cancer incidence at the regional and district levels (Colonna *et al.*, 2014). Accordingly,

Figure 1 Trend of incidence rates of patients surgically treated for testicular cancer, all patients (A) and by age class (B), PMSI 2000–2014.

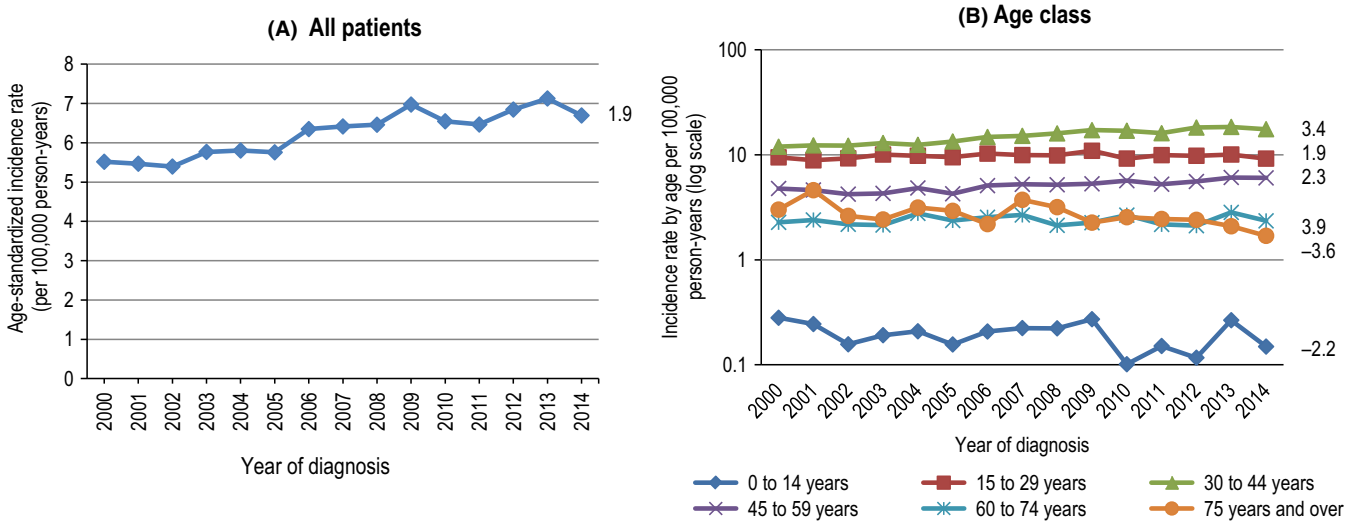


Table 2 Annual percentage change and 95% confidence interval by age group (in year) and periods

	2000–2014	2000–2002	2003–2005	2006–2009	2010–2014
All ages	1.9 [1.4;2.3]	−1.1 [−1.3;−0.9]	−0.09 [−0.9;0.7]	2.9 [0.6;5.2]	1.4 [−0.9;3.7]
0–14	−2.2 [−5.6;1.1]	−27.6 [−45.3;−9.8]	−9.5 [−31.3;12.3]	8.3 [2.7;13.9]	13.5 [−11.1;38.1]
15–29	0.3 [−0.3;0.9]	−1.1 [−7.2;5.0]	−3.0 [−3.3;−2.6]	1.8 [−2.5;6.2]	0.1 [−2.9;3.2]
30–44	3.4 [2.8;3.9]	1.1 [−1.1;3.2]	1.7 [−4.6;8.0]	5.1 [3.6;6.5]	2.0 [−1.2;5.2]
45–59	2.3 [1.6;3.0]	−6.2 [−9.5;−2.9]	−0.4 [−14.5;13.8]	1.1 [0.2;2.0]	2.7 [−0.4;5.8]
60–74	0.3 [−0.9;1.5]	−2.1 [−10.5;6.4]	4.6 [−19.4;28.6]	−5.8 [−13.6;2.0]	0.1 [−9.0;9.2]
75 and over	−3.7 [−6.1;−1.2]	−5.7 [−65.3;54.0]	8.9 [−10.4;28.3]	−1.2 [−29.2;26.8]	−9.3 [−13.8;−4.8]

Figure 2 Age-specific incidence of surgically treated testicular cancer per 100,000 person-years in 2000–2004, 2005–2009, and 2010–2014, PMSI 2000–2014.

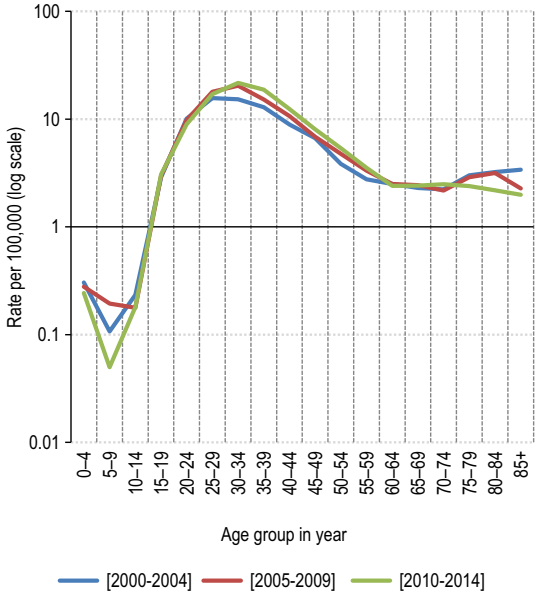
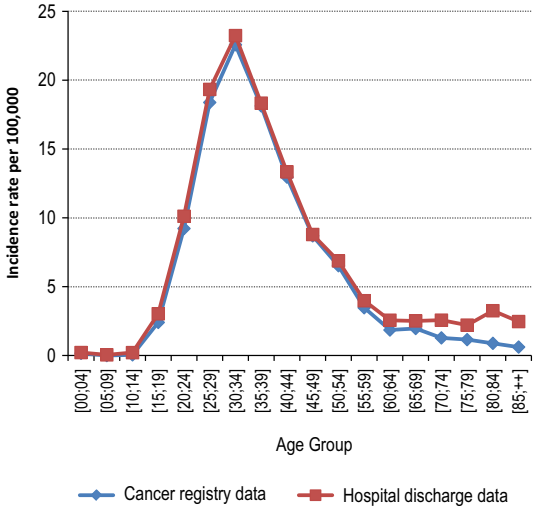


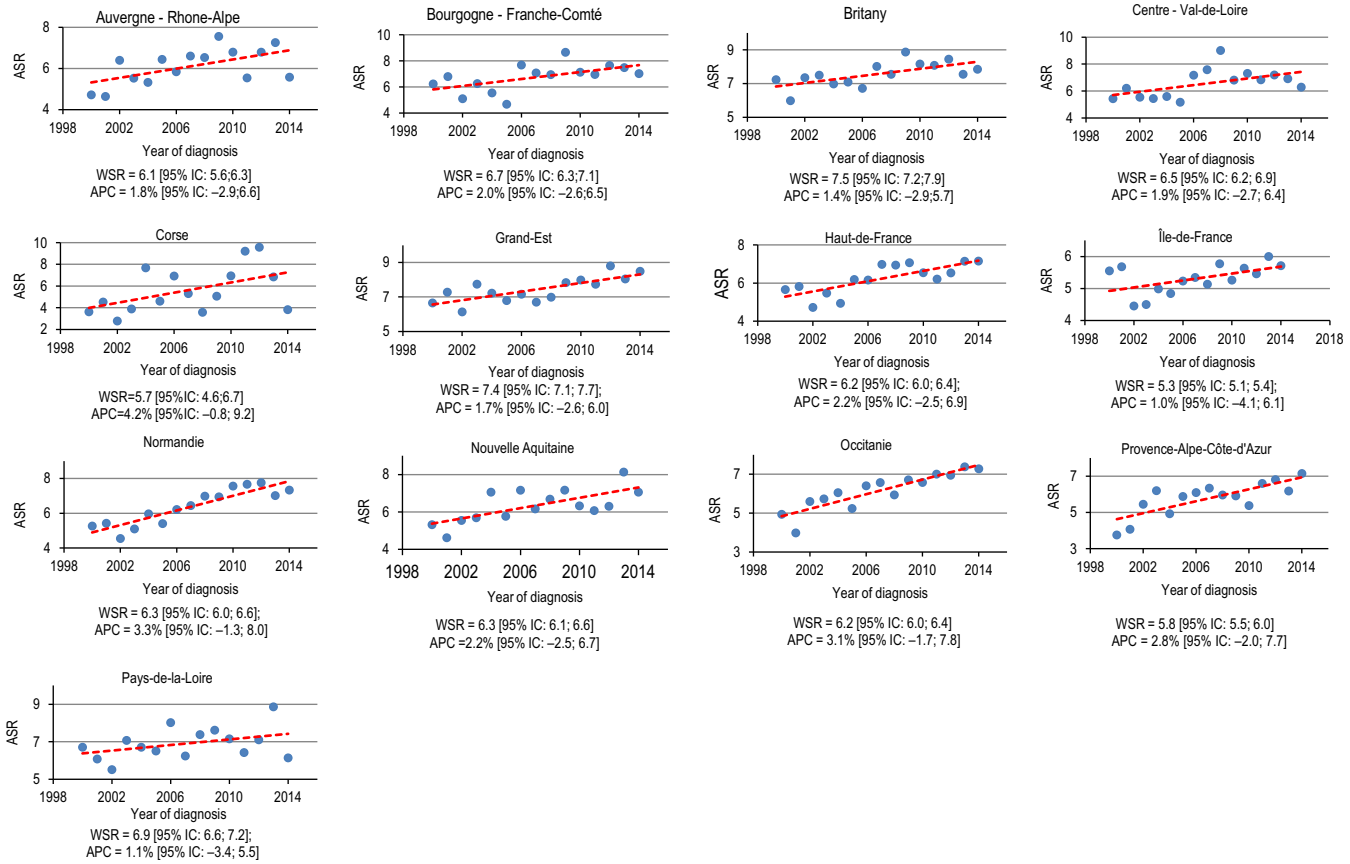
Figure 3 Comparison of age-specific incidence rates of testicular cancer from 2008 through 2012 between hospital discharge data and cancer registry based.



the PMSI approach provides relevant information on TC indicators at the subnational level.

The mean age at diagnosis of our patients was 37 years as opposed to 33 years in the USA (American Cancer Society, 2018) and 38 years in Germany (Stang *et al.*, 2009). The age-specific incidence distribution was similar to that in Germany for the period 2009–2010 (Robert Koch institute, 2014) and in the UK for 2011–2013 (Cancer Research UK, 2015). In 2012, the incidence rate from registry data in Metropolitan France was 7.2 person-years (Binder-Foucard *et al.*, 2013) compared with 6.8 for the

Figure 4 Annual age-standardized rate (ASR) of testis cancer in regions with linear regression lines, annual percentage change (APC), and world standardized rate (WSR): period 2000–2014.



same year in our study. The incidence rate in France was higher than that in Belgium, Portugal (5.9), and Finland (5.8; IARC, 2012). It was comparable with the rate in the UK (7.1), but lower than that in Italy (8.8), Germany (10.0), Switzerland (12.0), Denmark (12.5), and Norway (12.7; IARC, 2012).

As in most European countries, France showed an annual increase in TC incidence over the period studied. More specifically, based on the registry data, annual incidence continued to rise from 1980 (+2.4% per year) onward, with a moderate increase of +1.6% per year between 2005 and 2012 (Binder-Foucard *et al.*, 2013). This is consistent with the APC of +1.9% and +1.7% observed in our study during the periods 2000–2014 and 2005–2012 (data not shown), respectively. The annual percentage change of 1.9% was lower than 6% and 4%, observed for the 10 years of available registry data up to 2010, in Spain and Finland, respectively. It was comparable with the rate in Switzerland (1.7%) and higher than that observed in Germany (1.4%) (Znaor *et al.*, 2014). Temporal incidence decreased significantly between 2000 and 2002 (1.1%) and increased significantly between 2006 and 2009 (2.9%). The decrease can be explained as follows: In 2000 and 2001, as the anonymous individual common identifier, which allowed identifying a patient, was not available, the number of STTC was equal to the number of hospital stays instead of the number of patients as in 2002. With respect to the significant increase of temporal incidence observed between 2006 and 2009, it was in line with the global increase of TC incidence rate of these four last decades.

In 2002, Hédelin & Remontet (2002)observed a high TC incidence rate in the administrative district of Bas-Rhin (part of the Grand-Est region and covered in our study). A previous study (Kudjawu *et al.*, 2012) showed that the region of Brittany in the west of Metropolitan France together with and Alsace and Lorraine (former regions now under the umbrella of the larger new region of Grand-Est, created in 2016) in the east were the three national regions where the TC incidence was highest. Moreover, results for each of the 13 regions of Metropolitan France for the period 2000–2014 are consistent with those from a study on TC based on incidence/'long-term illness status beneficiary' at the French regional level (Colonna *et al.*, 2014). The reasons for the high incidence in some regions are as yet unknown. However, the recent rise in incidence of TC in developed countries indicated the possible involvement of environmental or lifestyle factors in the etiology of this cancer (Rajpert-De & Hoei-Hansen, 2007).

When comparing TC incidence indicators from population-based registry data to those of STTC from PMSI, for validation test of algorithm used to select patients, we found that results obtained from the latter were very much in line with the incidence observed from the former, except for patients over 60 years of age. Our observation of higher STTC PMSI-based incidence rates among the elderly men (60 years and over) than registry-based rates has also been observed in a study performed by Stang in Germany (Stang *et al.*, 2009). The latter argued that the reason for this difference was because the registration of TC by district registries among elderly men was incomplete.

Instead, we hypothesize that this difference may indicate that errors in coding TC diagnosis in PMSI are more significant in elderly men than in other age groups for men. In elderly men, certain surgically treated non-cancer conditions of the testis or the scrotum (e.g., hydrocele, varicocele, cyst, or tumor of epididymis) may be coded sometimes in the PMSI as malignant testis tumors without histological evidence, because these non-cancer diseases could hide much more serious pathologies. Such incorrect coding may explain the higher incidence of STTC in elderly men observed in the PMSI data compared with that observed in the cancer registry data.

The data we used to perform this study did not allow us to calculate the sensitivity or the predictive value of the algorithm. However, Grosclaude *et al.* (2012), who performed a validation study using a selection algorithm for patients suffering from TC based only on diagnosis codes from PMSI, measured 83% sensitivity and 61% for the positive predictive value. They concluded that adding surgical procedure codes to this algorithm provides a reasonably high sensitivity and positive predictive value for the detection of TC.

Cancer incidence as well as survival and mortality are essential population-based indicators for public health and cancer control. Data on TC survival from population-based cancer registry showed that the net survival of TC at 5 years (96%) was the highest for all cancers diagnosed between 2005 and 2010 in France (Cowppli-Bony *et al.*, 2016). Moreover, the already low mortality rate associated with TC decreased from 0.7 to 0.2 person-years between 1980 and 2012, with an APC of −3.5% per year (Binder-Foucard *et al.*, 2013).

Some limitations associated with the data used in this work must be underlined. Due to the absence of information on pathology in PMSI, we were not able to enhance the analysis, either in terms of histology (seminoma and non-seminoma) or in terms of evaluation of the stage of TC. However, a study by Hédelin & Remontet (2002), based on the registry data, suggested that rate for seminoma and non-seminoma evolved the same way in men born from 1940. This is also the case in the Nordic countries where the incidence rates of seminoma and non-seminoma have increased quite similarly between 1961 and 2010 (Ylönen *et al.*, 2018).

Patients suffering from synchronous or metachronous TC within the same 2000–2014 period were counted once for analysis in our study, whereas population-based cancer registries counted both events as two separate incident cases of TC, if the histology of the two tumors differed. Despite this, epidemiological evidence suggests that this limitation is not statistically relevant, as in a population-based study in the USA, the prevalence of synchronous contralateral TC was very low in men diagnosed with unilateral TC (Fossa *et al.*, 2005).

CONCLUSION

During the period 2000–2014, the incidence rate of STTC increased in France by 1.9% per year. It varied across regions. Brittany in the west and Grand-Est in the east were the regions with the highest incidence. Given that systematic surgical treatment of TC takes place during hospitalization, hospital discharge data, which are more quickly available than population-based data, are good complementary surveillance source for monitoring this cancer, especially in young adult patients and at subnational level without population-based registry.

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CONFLICT OF INTEREST

The authors declare no conflict of interests and have no financial disclosures to make.

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