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ORIGINAL ARTICLE

Reproductive Health

Risk of second primary cancers after testicular cancer in East and West Germany: a focus on contralateral testicular cancers

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Testicular cancer survival rates improved dramatically after cisplatin-based therapy was introduced in the 1970s. However, chemotherapy and radiation therapy are potentially carcinogenic. The purpose of this study was to estimate the risk of developing second primary cancers including the risk associated with primary histologic type (seminoma and non-seminoma) among testicular cancer survivors in Germany. We identified 16 990 and 1401 cases of testicular cancer in population-based cancer registries of East Germany (1961–1989 and 1996–2008) and Saarland (a federal state in West Germany; 1970–2008), respectively. We estimated the risk of a second primary cancer using standardized incidence ratios (SIRs) with 95% confidence intervals (95% CIs). To determine trends, we plotted model-based estimated annual SIRs. In East Germany, a total of 301 second primary cancers of any location were observed between 1961 and 1989 (SIR: 1.9; 95% CI: 1.7–2.1), and 159 cancers (any location) were observed between 1996 and 2008 (SIR: 1.7; 95% CI: 1.4–2.0). The SIRs for contralateral testicular cancer were increased in the registries with a range from 6.0 in Saarland to 13.9 in East Germany. The SIR for seminoma, in particular, was higher in East Germany compared to the other registries. We observed constant trends in the model-based SIRs for contralateral testicular cancers. The majority of reported SIRs of other cancer sites including histology-specific risks showed low precisions of estimated effects, likely due to small sample sizes. Testicular cancer patients are at increased risk especially for cancers of the contralateral testis and should receive intensive follow-ups.
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Keywords: cancer registry; incidence; neoplasms; second primary; testicular neoplasms

INTRODUCTION

Testicular cancer is the most frequently occurring cancer among men aged 15–44 years in Europe, Australia and North America, and the incidence has substantially increased in recent decades.[1,2] Testicular cancer incidence in Germany is among the highest observed in Europe;[3] however, the etiology of testicular cancer is not well-understood. Undescended testis (cryptorchidism), family history and contralateral testicular cancer are considered to be well-established risk factors.[4] The rapid increase in incidence over the past 40 years suggests that critical changes in environmental factors are contributing to the development of these tumors.[5]

Testicular cancer survival rates improved dramatically when cisplatin-based therapies were introduced in the 1970s. Because of drug shortages, the use of cisplatin in East Germany was limited until 1989.[3] Currently, the mean age-adjusted 5-year survival is 97% in Europe.[6] The primary treatment of testicular cancer is orchiectomy. Depending on the spread of disease (localized or metastatic), further treatment strategies may include surveillance, chemotherapy and radiation therapy.[7] However, patients with testicular cancers have an increased risk of developing second primary cancers of the contralateral testicle and other sites. Chemotherapy or radiation therapy could induce future carcinogenic sequelae. A limited number of population-based publications have reported the risk of second primary cancers, and in particular, the risk of contralateral testicular cancer.[8–13]

The aim of this study was to evaluate the risk of developing second primary cancers among testicular cancer survivors by analyzing data from population-based cancer registries in Germany. We were especially interested in histology-specific relative risks of contralateral testicular cancers and other second primary cancers. The risk estimates during the virtually cisplatin-free era in East Germany from 1961 to 1989 were analyzed. Additionally, we compared the relative risks of contralateral testicular cancer by primary histologic type (seminoma and non-seminoma) reported in published studies from population-based cancer registries and in the current study.

MATERIALS AND METHODS

Men who were newly diagnosed with a first primary cancer of the testis were identified in the National Cancer Registry of the German Democratic Republic (GDR) and its successor, the Common Cancer

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Registry of the New Federal States (1961–2008) and the Saarland Cancer Registry (1970–2008).

After the reunification of East and West Germany in 1990, the National Cancer Registry of East Germany ceased to exist, and the West German healthcare system was adopted in East Germany. Cancer registration in the new federal states including Berlin was continued as the 'Common Cancer Registry of the New Federal States including Berlin'. Between 1990 and 1995, the completed registration was too low for a meaningful data analysis. Since 1996, three (Mecklenburg-Western Pomerania, Saxony, Brandenburg, abbreviated as MSB) out of the five new federal states have provided cancer incidence data (including death certificate only cases), with an estimated completed registration of at least 90%. The estimated completed registration of the remaining registries of the New Federal States including Saxony-Anhalt, Thuringia and Berlin is below 90%. Therefore, we based our analysis on the entire East German population for the years from 1961 to 1989 and only used MSB for the years 1996–2008.

Testicular cancers were coded using the International Classification of Diseases (ICD) version 9 (topography code 186) and version 10 (topography code C62).[14,15] We defined three major histologic groups of testicular cancer: seminoma (9060/3-9062/3, 9064/3), non-seminoma (9065/3, 9070/3-9073/3, 9080/3-9085/3, 9100/3-9102/3) and cancers of other or unspecified histological types (8000/3-8004/3) according to the 3rd edition of International Classification of Diseases for Oncology.[16,17] The patients were followed from the date of diagnosis until whichever came first of the following: detection of any second primary cancer, death, loss to follow-up or until 31 December 2008. Second primary cancers were classified according to the rules for multiple primary cancers outlined by the International Agency for Research on Cancer and coded as 104-208 (ICD-9) or C00-80 (ICD-10).[18] Because other malignant skin neoplasms (ICD-9: 173; ICD-10: C44) were not completely captured by the registries, these cancers were excluded from the analysis. Invasive primary cancers occurring at least 6 months after testicular cancer diagnosis were defined as metachronous, and thus were classified as second primary tumors. Cancers occurring less than 6 months after testicular cancer diagnosis were considered to be synchronous tumors and were excluded: 37 in East Germany, 41 in MSB and 6 in Saarland. Analyses of the treatments and stage were not possible due to the large proportion of missing data.

Table 1 presents an overview of the primary testicular cancer cases in the registries. The proportion of histological verification was generally high and ranged from 97% to 99%, and verification ranged from 95% to 99% for cases of any second cancer.

We estimated the standardized incidence ratio (SIR) of all second cancers together and by the specific cancer site. The SIR was determined as the ratio of the number of observed cases (O) to the number of expected cases (E). The E was calculated by multiplying accumulated person-years at risk according to the detection date of a second primary cancer, death, loss to follow-up or the closing date of 31 December, 2008 and cancer incidence rates specific for gender (male), age (0–4, 5–9,…, 80–84, > 85 years), and a 5-year calendar period. For each SIR, an exact 95% confidence interval (95% CI) was calculated assuming a Poisson distribution of O.

To calculate the trend across annual SIRs, we plotted the estimated annual SIRs and fitted a weighted penalized smoothing spline (P-spline) model for the annual SIRs with the corresponding 95% CI. The weights for the annual SIRs were defined, in the standard meta-analytic sense, as inverted estimated variances. To avoid the arbitrariness of choosing the smoothing parameter, we used the equivalence of the P-spline and mixed models as implemented via the TYPE = RSMOOTH-option in the RANDOM statement in PROC GLIMMIX of SAS® (SAS Inc., Cary, NC, USA).[19]

The entire Medline database was searched in a systematic manner up to 16 July 2012 to identify population-based studies that reported a risk of contralateral testicular cancer determined with major histologies (seminoma and non-seminoma) using the following keywords: testicular cancer, risk, second primary and cancer registry. The references of all publications were searched for additional studies. We identified 4 publications and extracted the SIR estimates and corresponding 95% CIs for any testicular cancer and histology-specific SIR for seminoma and non-seminoma. To quantify the heterogeneity of seminoma and non-seminoma, we calculated the ratio of SIR estimates (RoSIR). To estimate the 95% CI for this ratio, we estimated the variance of the difference between the natural logarithms of the effect estimates. We back transformed this CI to the linear scale after calculating the CI for the difference in the estimated variance.

RESULTS

The SIR of second primary cancer of any location (excluding other malignant cancers of skin) among testicular cancer survivors was 1.9 (95% CI: 1.7–2.1) in East Germany. In comparison, the SIR was 1.6 (95% CI: 1.3–1.8) in MSB and 1.3 (95% CI: 1.1–1.6) in Saarland. **Table 2** shows cancer-site specific SIRs for the registries that include only sites with at least five total cases. Supplementary Information displays corresponding cancer-site specific SIRs by primary histologic type seminoma and non-seminoma, respectively.

Increased risks were observed for contralateral testicular cancers in all registries. The highest SIR was observed in East Germany (SIR: 13.9; 95% CI: 11.2–17.0), and the lowest SIR was observed in Saarland (SIR: 6.0; 95% CI: 3.3–10.1). The SIR for seminoma, in particular, was higher in East Germany (SIR: 17.7; 95% CI: 13.5–22.8) than in other registries. The SIRs for seminoma in MSB (SIR: 7.2; 95% CI: 4.6–10.8) and Saarland (SIR: 5.2; 95% CI: 1.9–11.3) were similar to the SIRs for all testicular cancers. In addition to contralateral testicular cancer, we observed elevated SIRs for malignant melanoma of the skin, kidney cancer and leukemia in East Germany and MSB, albeit with borderline precision of effects. The SIRs of other specific second cancer sites showed low precisions of effects with correspondingly wide 95% CIs of the estimated SIRs. With the exception of second primary cancers of any location and contralateral testicular cancers, the precision in the histology-specific SIRs by seminoma and non-seminoma was low and was likely due to the small sample size (Supplementary Information).

In the analysis of the model-based SIR trend, we observed a decrease in SIRs from 2.3 (95% CI: 1.6–3.0) in year 1 to 0.8 (95% CI:

Table 1: Baseline characteristics of testicular cancer from cancer registries in Germany

	East Germany 1961–1989	*MSB 1996–2008*	*Saarland 1970–2008*
Registered cases of first primary testicular cancer (*n*)	11 445	5545	1401
Age of first primary testicular cancer, median (IQR)	31 (25–39)	37 (30–44)	34 (27–41)
Person years of observation	70 475	34 174	22 415
Years of follow-up, median (IQR)	3.3 (0.9–9.4)	5.6 (2.5–9.0)	10.9 (4.6–18.6)
Registered cases of any second cancer[a] (*n*)	301	159	104

IQR: interquartile range; MSB: Region of Mecklenburg-Western Pomerania; Saxony, Brandenburg. [a]Occurring at least 6 months after diagnosis of testicular cancer

0–2.0) in year 27 for a second primary cancer of any location in East Germany. The decrease in SIRs among seminomas accounted for the majority of the decrease (**Figure 1**). In MSB, the model-based SIR trends were constant (results not shown). In analyses where we excluded contralateral testicular cancer model-based SIR trends, the patterns in East Germany and MSB were similar (results not shown). In Saarland, the observed number of second primary cancer cases was too low for meaningful analysis. Based on the model-based SIR trend, the risk of contralateral testicular cancer in East Germany was constant over time (**Figure 2**). Similarly, the histology-specific SIR trend of seminoma risk was stable over 18 years of follow-up, while the trend of non-seminoma risk increased from 7.7 (95% CI: 2.9–12.4) in year 1 to 13.9 (95% CI: 0–32.5) in year 18 (**Figure 2**). In MSB, the histology-specific SIR trend of seminoma showed a gradual decrease from 20.3 (95% CI: 13.3–27.2) in year 1 to 11.4 (95% CI: 3.6–19.3) in year 9; whereas, the trend for non-seminoma was constant (results not shown).

Table 2: Standardized incidence ratios for any second primary cancer (occurring at least 6 months after diagnosis of testicular cancer) in patients diagnosed with testicular cancer from cancer registries in Germany

Second cancer site	*East Germany (n=11 445)*			*MSB (n=5545)*			*Saarland (n=1401)*		
	O	*SIR*	*95% CI*	*O*	*SIR*	*95% CI*	*O*	*SIR*	*95% CI*
All sites[a]	286	1.9	1.7–2.1	145	1.6	1.3–1.8	89	1.3	1.1–1.6
Lip, oral cavity and pharynx	7	1.1	0.5–2.3	9	1.1	0.5–2.1			
Esophagus	5	1.9	0.6–4.4				5	3.1	1.0–7.1
Stomach	21	1.3	0.8–2.0	5	1.1	0.4–2.6			
Colon	10	1.2	0.6–2.1	5	0.8	0.2–1.8	10	1.8	0.9–3.3
Rectum, rectosigmoid junction and anus	14	1.5	0.8–2.5	5	0.9	0.3–2.0	8	1.7	0.7–3.3
Pancreas	10	2.1	1.0–3.9						
Trachea, bronchus and lung	35	0.9	0.6–1.3	15	1.1	0.6–1.8	11	0.8	0.4–1.5
Malignant melanoma of skin	8	2.5	1.1–4.8	8	2.3	1.0–4.5			
Prostate	14	1.3	0.7–2.2	17	1.1	0.6–1.7	16	1.4	0.8–2.3
Testis	91	13.9	11.2–17.0	39	7.0	4.9–9.5	14	6.0	3.3–10.1
Kidney	9	2.5	1.2–4.8	7	2.4	1.0–5.0			
Bladder	9	1.1	0.5–2.0						
Hodgkin lymphoma	5	2.2	0.7–5.2						
Non-Hodgkin lymphoma	7	2.0	0.8–4.2						
Leukaemia	13	2.9	1.5–4.9	8	2.9	1.2–5.6			

MSB: Region of Mecklenburg-Western Pomerania, Saxony, Brandenburg; O: observed number of cases; SIR: standardized incidence ratio; 95% CI, 95% confidence interval. [a]ICD-9, 104-208 excluding 173; ICD-10, C00-97 excluding C44

Table 3 provides a summary of SIRs for contralateral testicular cancer according to the histology of the first cancer reported in previous studies and our study. Estimated SIRs of MSB and Saarland were considerably lower than SIRs in previous studies. The range of RoSIR from 0.6 to 2.3 indicated broad heterogeneity across both major histologic groups for contralateral testicular cancer.

DISCUSSION

In the current study, men with a history of testicular cancer were at increased risk of second primary cancers in all three German registries. In particular, the risk of contralateral testicular cancer was increased. This risk was very high within the 1st year of initial diagnosis, remained high more than 15 years after diagnosis, and is consistent with the previous observations.[8,12] The constant model-based SIR trends for contralateral testicular cancer; however, do not imply a stable risk; rather, data may be too sparse to identify changes in the trend.

While there was an approximate 14-fold increased risk of contralateral testicular cancer in East Germany from 1961 to 1989, we observed only a 7-fold risk increase in the New Federal States of MSB from 1996 to 2008. Several factors may explain this lower SIR in MSB. First, in East Germany, due to drug shortages, cisplatin-based chemotherapy was rarely used for treating testicular cancers.[3] As discussed by Fosså *et al*.,[10] the introduction of cisplatin as the standard therapy in many countries reduced the risk of metachronous contralateral testicular cancer. A recent study from the Cancer Registry of Norway separately analyzed the diagnostic periods (I) 1953–1979 and (II) 1980–2007 to evaluate the possible protective effects of cisplatin-based chemotherapy. However, the SIRs were virtually identical. The observation of a continued cumulative incidence increase, after 15 years in period (II) compared to period (I), supports the hypothesis that cisplatin delays tumor development as a result of its influence on the premalignant germ cell epithelium.[13] Second, in the 1990s, there was an increased awareness of testicular intraepithelial neoplasia (TIN), a precursor of testicular cancer, in the contralateral testis of testicular cancer patients. Approximately 5% of men with testicular cancer have been reported to have contralateral TIN.[20] However, international guidelines differ regarding the importance of diagnosing TIN in the contralateral testis. The treatment options range from orchiectomy and chemotherapy to radiotherapy, and in rare cases, surveillance.[21,22] However, biopsies and treatments for TIN in Germany are not extensively practiced. Third, and likely most important, second cancer cases in testicular cancer survivors could be underreported in the registry of MSB. The

Table 3: Comparison of standardized incidence ratio (corresponding 95% CI) for contralateral testicular cancer in patients diagnosed with testicular cancer according to histological type in population-based cancer registries and ratio of SIR estimates of seminoma and non-seminoma

References	*Patients, n (country/region)*	*Period*	*Total*	*Seminoma*	*Non-seminoma*	*RoSIR*
Østerlind *et al*.[8a]	2850 (Denmark)	1960–1979	24.8 (19.3–31.4)	22.5 (16.1–30.8)	27.1 (18.5–38.4)	0.8 (0.5–1.4)
Fosså *et al*.[10b]	29 515 (USA.)	1973–2001	12.4 (11.0–13.9)	14.7 (12.6–17.0)	10.0 (8.2–12.0)	1.5 (1.2–1.9)
Hemminki *et al*.[12c]	5533 (Sweden)	1980–2006	20.5 (16.6–25.0)	29.3 (22.5–37.5)	13.0 (8.9–18.2)	2.3 (1.5–3.5)
Andreassen *et al*.[13b]	1843 (Norway)	1953–1979	16.7 (11.8–22.9)	13.1 (7.6–21.0)	21.4 (13.2–32.7)	0.6 (0.3–1.2)
	5259 (Norway)	1980–2007	15.9 (13.3–18.8)	18.0 (14.0–22.6)	14.1 (10.9–18.0)	1.3 (0.9–1.8)
Current study[b]	11 445 (East Germany)	1961–1989	14.6 (11.9–17.9)	18.6 (14.3–23.8)	11.3 (7.6–16.0)	1.7 (1.1–2.6)
	5545 (MSB)	1996–2008	7.1 (5.1–9.7)	7.5 (4.9–11.1)	7.2 (4.0–11.9)	1.0 (0.5–2.1)
	1401 (Saarland)	1970–2008	6.4 (3.6–10.6)	5.2 (1.9–11.3)	8.0 (3.7–15.2)	0.7 (0.2–2.0)

95% CI: 95% confidence interval; MSB: Region of Mecklenburg-Western Pomerania, Saxony, Brandenburg, [a]Metachronous NOS. [b]Metachronous (≥2 months). [c]Including synchronous. RoSIR: ratio of SIR

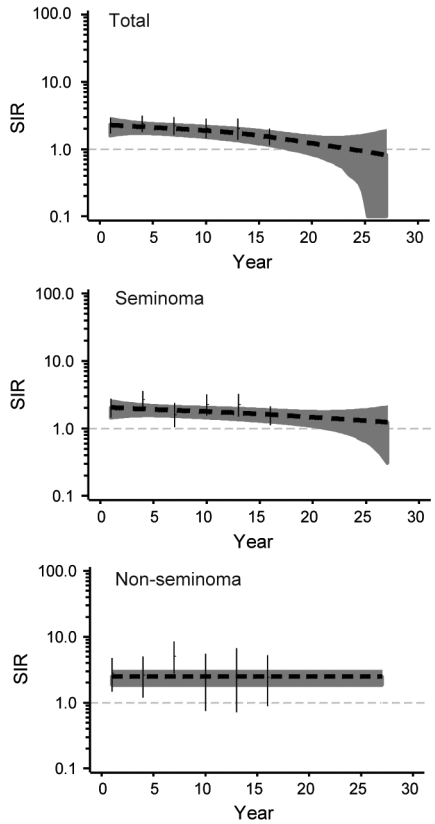

Figure 1: Model-based standardized incidence ratio (SIR) trend (dashed line) and corresponding 95% confidence interval (95% CI) (grey shaded area) for any second primary cancer (excluding other malignant cancer of the skin) in patients diagnosed with testicular cancer according to histological type in East Germany, 1961–1989. Observed specific 3-year-period SIRs (dot) and corresponding 95% CI (bar). The dot and corresponding bar in year 16 averaging observed SIRs and corresponding 95% CI from year 16 to 27.

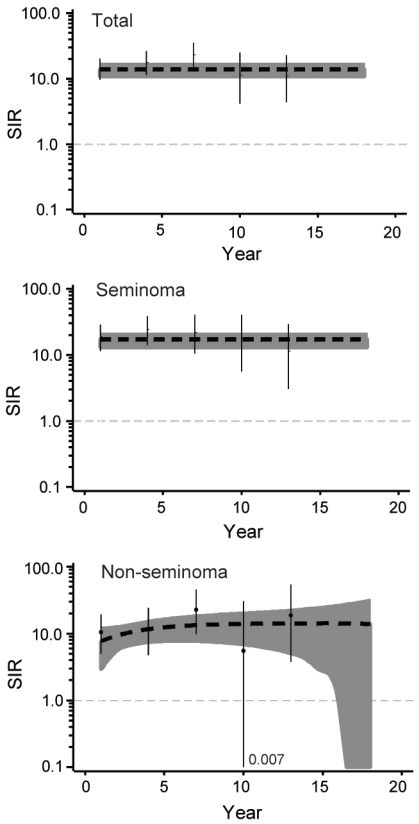

Figure 2: Model-based standardized incidence ratio (SIR) trend (dashed line) and corresponding 95% confidence interval (95% CI) (grey surface) for contralateral testicular cancer in patients diagnosed with testicular cancer according to histological type in East Germany, 1961–1989. Observed specific 3-year-period SIRs (dot) and corresponding 95% CI (bar). The dot and corresponding bar in year 13 averaging observed SIRs and corresponding 95% CI from year 13 to 18.

estimated completed registration is at least 90%. However, due to the low mortality of testicular cancer, using a ratio of the mortality to the incidence as a measure for the completeness of registration for testicular cancer is highly unreliable. Furthermore, patients emigrating from the registries' catchment area could have contributed to the underreporting of cancer survivors.

We observed heterogeneity of seminoma and non-seminoma in the risk of contralateral testicular cancers summarizing SIRs from previously published studies and our results. The available data are not sufficient to explain this heterogeneity. Specifically, the heterogeneity was not explained by factors such as the time-period, pre-cisplatin and cisplatin era, or ethnicity. A comparison of histology-specific SIRs across the studies remains complicated due to the various registration techniques, coding standards, and follow-up lengths. Only two of the previous studies provide the length of follow-up (Østerlind *et al.*[8]: average length of follow-up 8.6 years; Andreassen *et al.*[13]: median follow-up length over the whole period (1953–2007) 10.9 years). Although we contacted the corresponding authors of the remaining previously published studies for median length of follow-up, we were unable to obtain that information.

The current study also found risks of cancer in other sites among men with prior testicular cancers. There was an approximate 3-fold increased risk of leukemia in men from East Germany and MSB. In the absence of cisplatin-based chemotherapy, in East Germany, our study emphasizes that both chemo- and radio-therapy have a leukemogenic effect. The majority of previous studies focused on chemotherapy inducing leukemogenicity, while Travis *et al.*[25] were the first authors to link leukemia to previous radiation treatments for testicular cancer.[23–25] Radiotherapy without chemotherapy or cumulative dose of 650 mg cisplatin was associated with a three fold elevated risk; larger doses were linked with a six fold increased risk.[25] The increased risk of malignant melanoma of the skin was previously reported and is more likely due to increased medical surveillance than treatment.[11] In contrast to other population-based studies, we observed marginally increased risks, low precision of effects or both, for second primary cancers of the gastrointestinal and urinary tracts. The previously observed increased risks of these cancers are consistent with a radiogenic effect, as they are located in the treatment field during standard radiation of the paraaortic lymph nodes.[9,11] In the current study, the sample size of the cancer registries may not have permitted the detection of a sufficient number of cases to evaluate the risk of other, rarer, second primary cancers.

In conclusion, among men with a prior testicular cancer, the risk of second cancers was markedly increased for testicular cancer, and the risk remained high even more than 15 years after the initial diagnosis. Our findings support the recommendation of an intensive follow-up of testicular cancer survivors, particularly for the development of contralateral testicular cancer.

AUTHOR CONTRIBUTIONS

CR and AS were responsible for the conception, design, analysis, interpretation and preparation of the manuscript. BS and CS provided data and contributed to the preparation of the manuscript. PT and OK contributed to analysis, interpretation and preparation of the manuscript. KAM and BT contributed to analysis expertise and preparation of the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

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Supplementary information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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