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50 Jahre – Forschen für
ein Leben ohne Krebs

Division
Molecular Genetic Epidemiology
C050

Dr. Tianhui Chen

Im Neuenheimer Feld 580
D-69120 Heidelberg
Phone +49.62 21.42-18 05
Telefax +49.62 21.42-18 10
www.dkfz.de
t.chen@dkfz.de

Heidelberg, June 10, 2015

Dear Prof Dr. Schwab,

We would like to submit our manuscript entitled “Distribution and risk of all second primary cancers combined after a specific first primary cancer in German and Swedish cancer registries” to ***Cancer Letters*** as an Original Article.

Using the pooled database from 12 German cancer registries and the nationwide Swedish Family-Cancer Database, we found similar distribution of all second discordant primary cancers (SDPCs) after any specific first cancer in Germany and Sweden and elevated overall risks after 23 cancers (out of 29 cancers in total) in Germany and after 24 cancers in Sweden. Among them, risks after 19 cancers were elevated in both populations, which may suggest common etiology of SDPCs after most of first primary cancers and similar registration practices for those cancers in the two populations. We found substantially higher risk of SDPCs after urinary bladder and upper aerodigestive tract cancers in Germany compared to Sweden, which is likely due to higher incidence of smoking-related cancer for German men compared to Swedish men. While decreased overall risk found only in Germany after five fatal cancers may be attributed to reporting practices or missed death data in Germany.

Our data provide new evidence on the risk of all SDPCs combined after a specific first primary cancer in Germany and Sweden, which offers insight into the epidemiology, etiology and registration practices of SDPCs in different populations and validates their potential use in etiological studies.

The results have not been published in any part elsewhere and we conform to the submission requirements of ***Cancer Letters***. The corresponding author, on behalf of all coauthors, has declared no conflicts of interest.

Sincerely,
Tianhui Chen, MD&PhD

Distribution and risk of all second primary cancers combined after a specific first primary cancer in German and Swedish cancer registries

Tianhui Chen[1*], Mahdi Fallah[1], Lina Jansen[2], Felipe A. Castro[2], Agne Krilavicuite[2], Alexander Katalinic[3], Nora Eisemann[3], Katharina Emrich[4], Bernd Holleczek[5], Karla Geiss[6], Andrea Eberle[7], Jan Sundquist [8,9], Hermann Brenner[2,10,11], Kari Hemminki[1,8] for the GEKID Cancer Survival Working Group[+]

[1] Division of Molecular Genetic Epidemiology, German Cancer Research Center, Heidelberg, Germany;
[2] Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Heidelberg, Germany;
[3] Institute of Cancer Epidemiology, University of Lübeck, Lübeck, Germany;
[4] Cancer Registry of Rhineland-Palatinate, Institute for Medical Biostatistics, Epidemiology and Informatics, University Medical Center, Johannes Gutenberg;
[5] Saarland Cancer Registry, Saarbrüken, Germany;
[6] Bayern Cancer Registry, Munich, Germany;
[7] Cancer Registry of Bremen, Leibniz-Institute for Prevention Research and Epidemiology - BIPS, Bremen, Germany;
[8] Center for Primary Health Care Research, Lund University, Malmö, Sweden;
[9] Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, California 94305-5705, USA;
[10] Division of Preventive Oncology, German Cancer Research Center, Heidelberg, Germany;
[11] German Cancer Consortium (DKTK), Heidelberg, Germany.

[+] Members of the GEKID Cancer Survival Working Group are listed in the Acknowledgement.

*Correspondence to:

Dr. Tianhui Chen

Division of Molecular Genetic Epidemiology

German Cancer Research Center (DKFZ)

Im Neuenheimer Feld 580

69120 Heidelberg

Germany

Tel: +49 6221 421805

Fax: +49 6221 421810

Email: t.chen@dkfz.de

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ABSTRACT

Objectives: We aimed at investigating the distribution and risk of all second discordant primary cancers (SDPCs) after a specific first primary cancer in Germany and Sweden to provide etiological understanding of SDPCs and insight into their incidence rates and recording practices.

Methods: Cancer patients diagnosed in 1997-2010 at age ≥15 years and separately selected from nationwide Swedish and German cancer registries were used for this study. Second cancers were defined as SDPCs of any types, except non-melanoma skin cancer. Standardized incidence ratios (SIRs) were used to assess risk of all SDPCs compared with risk of same primary cancers in the corresponding background population.

Results: Among 1,537,004 survivors of first primary cancers in Germany and 588,103 in Sweden, overall 80,162 and 32,534 SDPCs were recorded, respectively. Frequency ranking order of all SDPCs after most of first cancers was similar in the two populations. SIRs of all SDPCs were elevated at levels between 1.1 and 2.1 after 23 (out of overall 29) cancers in Germany and at levels between 1.1 and 1.6 after 24 cancers in Sweden, and among them, elevated SIRs were found after 19 cancers in both populations. Decreased SIRs at levels ranging from 0.5 to 0.9 were found for some cancers with poor prognosis in Germany only.

Conclusions: We found elevated risk after 19 out of 29 cancers in both countries, suggesting common etiology of SDPCs after most of first cancers and registration similarity. Decreased risks after some fatal cancers were found only in Germany, which may be attributed to reporting practices or missed death data in Germany.

INTRODUCTION

Second primary cancers (SPCs) have become a long-term outcome with increasing importance because of their steadily growing numbers as a result of continued improvement in early detection, treatment, and supportive care (1). For instance, the total number of SPCs accounted approximately for one sixth of all cancers reported to the US Surveillance, Epidemiology, and End Results (SEER) program in 2012 (1), while this number reached one fifth of all registered cancers in Sweden in 2012 (2). SPC can be classified as second concordant primary cancer (the same type of cancer as first cancer, e.g., newly diagnosed left breast cancer after right breast cancer) and second discordant primary cancer (SDPC, e.g., newly diagnosed breast cancer after melanoma).

Carcinogenesis of SPCs is a complex process as many risk factors could contribute to the etiology, including intensive medical surveillance after the diagnosis of the first primary cancer, therapy effect of first cancer, shared genetic or lifestyle factors between first cancer and SPC, or interactions among aforementioned factors (3, 4). Numerous studies on SPCs have been published, originating from the Nordic cancer registries (e.g., Sweden), the US SEER Program, and the International Agency for Research on Cancer (IARC) coordinated collaborations (5-7). Although recent European studies showed steady increases in survival and incidence rates for cancer patients, persistent difference between countries has been reported despite general improvement in overall cancer treatment (though detailed treatment information is commonly absent in population-based cancer registries) (8-12), which may influence SPC rates in different populations. Nevertheless, to our knowledge, investigations on the risk of SPCs after first primary cancers in different populations have not been reported. Addionally, the distribution of all SPCs combined after a specific first primary cancers has also not been reported, though our group has reported the distribution of five most common SPCs after ten common first cancers in the present populations (13).

We aimed at investigating the distribution and risk of all SDPCs combined (except for non-melanoma skin cancer) after a specific first primary cancer in the two populations, using the pooled database from 12 German cancer registries (14) and the nationwide Swedish Family-Cancer Database (FCD) (15). While investigations on the distribution of all SPCs combined in different populations may provide an overall picture on SPCs. Investigations on the risk of all SDPCs combined after a specific first primary cancer in two populations may provide insight into the epidemiology, etiology and registration practices of SDPCs in different populations. The findings may validate the use of data on SPCs in etiological studies, particularly regarding side effects of treatment when therapies are changing.

MATERIALS AND METHODS

German data

Details on the pooled German database were described elsewhere (14). Briefly, data were originally collected from cancer registries covering 13 of 16 German federal states. According to the criteria related to data quality, e.g., cancer patients who had a Death Certificate or autopsy only (DCO) cancer were all excluded (14). Finally, data from 12 cancer registries, covering a population of 26.7 million people (33% of the total German population), were retained in the pooled German database for further analyses (14). According to the rules set up by the IARC (16), Germany cancer registries did not register tumors occurring at the same organ or at the contralateral organ for SPCs; non-melanoma skin cancers were not collected. Therefore, second cancers in this study were only limited to second discordant primary cancers of any types except non-melanoma skin cancer (simply called SDPCs). Cancers were recorded according to the International Classification of Diseases, 10th version (ICD-10) (16) and the percentage of microscopically verified cancer diagnosis was larger than 95% in all registries (14). Patients with a primary malignant tumor diagnosed in 1997-2010 at age ≥15 years and with follow-up information until the end of December 2010 were included in the current analyses.

Swedish data

Swedish FCD2010 (updated in 2013) was used for the current study and its details were described elsewhere (15). For comparability and consistency, same criteria for German data were adopted for Swedish data, e.g., the definition of primary cancers was recoded and restricted to the study period 1997-2010; cancer DCO cases were excluded and only SDPCs (second concordant cancers and non-melanoma skin cancers were excluded) diagnosed in 1997-2010 at age ≥15 years were selected. Briefly, we used all first primary cancer (except non-melanoma skin cancers) patients diagnosed 1997-2010, covering approximately 9 million Swedish population. Information on cancer cases were retrieved from the Swedish Cancer Registry for the years 1997-2010, relying on separate compulsory notifications from clinicians, pathologists and cytologists (17); cancers during the study period were recorded according to both ICD-7 and ICD-10 codes. The Swedish Cancer Registry only records primary cancers. Metastasized cancers to other sites were only registered at primary sites; for multiple primary cancers occurring in same organ or same organ system, only clearly separated malignancies were accepted as multiple primaries and registered (18). Close to 100% of the registered neoplasms were histologically verified and approximately 98% of second neoplasms were correctly verified according to a re-evaluation study of 209 multiple primary tumors (17).

Statistical analyses

For both German and Swedish datasets, standardized incidence ratios (SIRs), calculated as the ratio of observed to expected numbers of cases, were used to assess the risk of all SDPCs combined after a specific first primary cancer. The expected numbers of all SDPCs combined after a specific first primary cancer were calculated from the strata-specific incidence rate of the combination of first primary cancers (except non-melanoma skin cancer) in the Swedish and German general population, respectively, multiplied by the corresponding person-years in survivors of first primary cancer. Person-years at risk were accumulated for each patient, starting at the date of diagnosis of the first primary cancer

(diagnosed from 1997 to 2010), and terminating on the date of SDPCs of any type, date of death, date of emigration, or December 31st, 2010 (end of the study), whichever came earliest.

All SIRs for Germany and Sweden were adjusted for three identical variables [sex, age (5-year bands), and calendar period (1995-2000, 2001-2005, and 2006-2010)] and a regional category (12 states in Germany and 4 categories in Sweden). The 95% confidence intervals (CIs) for SIRs were calculated assuming that the cases followed a Poisson distribution. Statistical significance for SIRs higher or lower than 1.00 was assessed by whether or not 95% CIs for those SIRs included 1.00. Further analyses were stratified by characteristics of cancer patients [sex, age at diagnosis of first cancer (<65 years, 65-74, and ≥75 years), and follow-up time after first cancer (<1 year, 1-4, and ≥5 years)]. In order to avoid chance findings, we set up rules for showing results. Only cancer sites with a total number of all SDPCs ≥100 in both countries are presented in tables. Additionally, sensitivity analyses restricted to eight (out of 12 in total) German cancer registries with full follow-up period 1997-2010 were conducted because four German registries started cancer registration later than 1997, i.e., Lower Saxony in 2003, Schleswig-Holstein in 1999, and Bremen and Rhineland-Palatinate in 1998. SAS software (version 9.3, SAS Institute Inc., Cary, NC) was used for the data analyses.

RESULTS

Distribution of all SDPCs after a specific first primary cancer in the two populations

The distribution of all SDPCs after a specific first primary cancer is presented in Table 1. We found 80,162 SDPCs in Germany and 32,534 in Sweden. Overall, frequency ranking order of all SDPCs after a specific first primary cancer was similar in Germany and Sweden, i.e., the ranking order of the four most frequent SDPCs was identical in Germany and Sweden in the sequence of prostate, colorectal, breast and urinary bladder cancers, while the ranking order after other cancers was generally similar, except for nervous system cancer (27th versus 12th) and unknown primary cancer (21st versus 15th). The

total number of any first primary cancers (except non-melanoma skin cancer) diagnosed at age ≥15 years during the 1997-2010 period was 1,537,004 in Germany and 588,103 in Sweden (Appendix Table 1). Among them, the percentages for unknown primary, nervous system and non-thyroid endocrine cancers were low in Germany with 1.9% (28,418), 1.4% (20,872) and 0.1% (850), respectively, while in Sweden these were 3.5% (20,287), 2.8% (16,371) and 1.4% (8,402), respectively. The percentages of other cancers were rather similar between Germany and Sweden (Appendix Table 1).

SIRs of all SDPCs after a specific first primary cancer in the two populations

The overall SIRs of all SDPCs after a specific first primary cancer and the stratification by sex are presented in Table 2. We found that SIRs of all SDPCs were elevated at levels between 1.1 and 2.1 after 23 (out of overall 29) cancers in Germany and at levels between 1.1 and 1.6 after 24 cancers in Sweden and among them, SIRs after 19 cancers were elevated in both Germany and Sweden. It shall be noted that elevated overall SIR reached ≥2.0-fold in Germany after urinary bladder cancer (2.1) and upper aerodigestive tract cancer (2.0), while it was slightly elevated in Sweden (1.3 and 1.2, respectively). Decreased SIRs at levels ranging from 0.5 to 0.9 were found for five cancers with poor prognosis (pancreatic, lung, nervous system and unknown primary cancers, and multiple myeloma) in Germany only. Additionally, SIRs of all SDPCs after most of first cancers were similar between men and women in both countries, with three exceptions, i.e., higher SIR in men than in women was found after urinary bladder cancer in Germany (2.3 for men versus 1.3 for women) and in Sweden (1.4 for men versus 1.2 for women), while lower SIR in men than in women was found only in Germany after lung cancer (0.9 versus 1.1) and connective tissue cancer (1.2 versus 1.7).

We observed a declining trend of SIRs along with increasing age at diagnosis after most of first cancers in Germany and after a few first cancers in Sweden (Table 3). Decreased SIRs at levels ranging from 0.3 to 0.9 were found only in Germany, i.e., for diagnosis age <65 years after nervous system cancer, for

diagnosis age at 65-74 years after four fatal cancers (pancreatic, lung and nervous system cancers, and multiple myeloma), and for diagnosis age ≥75 years after eight fatal cancers (stomach, liver and gallbladder, pancreatic, lung, nervous system and unknown primary cancers, multiple myeloma and leukemia).

The SIRs stratified by follow-up time after first primary cancer (<1 year, 1-4, and ≥5 years) are presented in Table 4. While a tendency of deceasing SIR along with prolonged follow-up time was observed after the majority of first cancers in both Germany and Sweden, we found elevated SIR (≥1.5-fold) for ≥5 years follow-up in Germany after upper aerodigestive tract cancer (1.9), Hodgkin lymphoma (1.8) and thyroid cancer (1.5) and in Sweden after esophageal cancer (1.6). Additionally, SIRs for <1 year follow-up were elevated at levels between 1.2 and 4.0 after 21 cancers in Germany and at levels between 1.4 and 2.5 after 15 cancers in Sweden. Nevertheless, decreased SIRs at levels ranging from 0.4 to 0.9 were found in Germany thoughout follow-up time after some fatal cancers (for <1 year follow-up after three fatal cancers, for 1-4 year follow-up after six fatal cancers, and for ≥5 years follow-up after one fatal cancer), while decreased SIRs at levels of 0.8 were found in Sweden for <1 year follow-up only after both breast cancer and melanoma (Table 4).

Additionally, sensitivity analyses restricted to eight (out of 12 in total) German cancer registries with full follow-up period 1997-2010 did not essentially change our results (Appendix Tables 2-4), we therefore reported data based on 12 German cancer registries to ensure larger sample size.

DISCUSSION

At the onset of investigations on the SPCs rates in two populations, some basic demographic and epidemiological data should be known. Firstly, overall, life expectancy is a relevant parameter. Life expectancy in 2010 for men generally was 77.5 years in Germany versus 79.2 years in Sweden, while

for women it reached 82.8 years in Germany versus 83.5 years in Sweden (19). Thus, life expectancy was similar in the two populations. Secondly, incidence rate of first primary cancer may influence SPCs rates in the two populations. Age-standardized incidence rate (European standard) in 2012 for men was higher (483 per 100,000) in Germany than in Sweden (428 per 100,000), while for women it was similar (344 in Germany versus 346 per 100,000 in Sweden) (11). Smoking-related cancers could largely explain higher incidence rate for German men compared to Swedish men. Thirdly, survival rate of first primary cancer may influence the SPCs rates in the two populations because survival rate in 1995-1999 period for most cancers is commonly lower in Germany compared to Sweden, e.g., for all malignant neoplasms, age-standardized 5-year relative survival in 1995-1999 reached 52 % in Germany and 58% in Sweden, while for multiple myeloma, it reached 30 % in Germany and 40% in Sweden (20). Nevertheless, age-standardized 5-year relative survival rate increased recently, reaching 61% for German men in 2010 versus 70% for Swedish men for 2009-2012 period, while it was 67% for women in both countries in the related periods (12). The male difference was largely contributed by the high prevalence of lung cancer in Germany, e.g., the percentage of first primary lung cancer was 10.6% in Germany, while it was 7.4% in Sweden (Appendix Table 1).

We found elevated overall risks after 23 cancers (out of 29 cancers in total) in Germany and after 24 cancers in Sweden, which is principally consistent with previous reports on the risk of a second primary cancer after a concordant or discordant cancer in a single country (21-23). Our findings of similar distribution of all SDPCs after any specific first cancer and of elevated risks after 19 cancers in both populations may suggest common etiology of SDPCs after most of first primary cancers and similar registration practices for those cancers in the two populations. Our finding of elevated higher risk of SDPCs after urinary bladder cancer (2.1 versus 1.3) and upper aerodigestive tract cancer (2.0 versus 1.2) in Germany compared to Sweden is in line with higher incidence rate of smoking-related cancers (upper aerodigestive tract and urinary bladder cancers) for German men compared to Swedish men.

We found decreased overall SIRs at levels ranging from 0.5 to 0.9 only in Germany after five fatal cancers (Table 2), which may be largely attributed to reporting practices in Germany as SIRs below 1.0 generally imply underreporting. Nevertheless, SIRs below 1.0 could also be a medical care problem because in the presence of a severe first primary cancer with poor prognosis, especially before 2000 in Germany (20, 24), no diagnostics for other SPCs could be made in fatal cancers in Germany. Furthermore, missed deaths data could also contribute to SIR<1.0. Additionally, we found the number of all SDPCs was small after nervous system tumors (0.3% of all SDPCs in Germany versus 2.0 % in Sweden; Table 1),which may appear to be underreporting of first primary nervous system tumors (Appendix Table 1) because those cancers may include benign tumors.

The etiology of an individual SPC is already very complex and has not been explicitly known because many risk factors could contribute, e.g., characteristics of cancer patients such as genetic predisposition to both first cancer and a SPC and shared lifestyle risk factors (e.g., smoking), as suggested by other studies (21, 22). Intensive medical surveillance after first primary cancer could be another reason, as suggested by our data for < 1-year follow-up (Table 4), i.e., elevated risk after 21 cancers in Germany and after 15 cancers in Sweden and decreased risk (SIR=0.8) after both breast cancer and melanoma in Sweden; consequently, we cautiously did not consider as a major finding. For all SDPCs combined, there could be even more complex etiology as more risk factors could contribute, i.e., accumulating different risk factors for a specific SPC after a specific first primary cancer. Since the risk of a SPC depends greatly on the specific type of first-second cancer pair regardless whether a SPC was the same type of first cancer and, there is substantial heterogeneity in the risk of an individual SPC after different type of first primary cancer (21, 22), further investigations on the SPC risk of a specific pair of first-second cancer (e.g., a specific SPC after multiple myeloma) in different populations for overall and by

characteristics of cancer patients (age at diagnosis of and follow-up time after first primary cancer) shall be warranted.

Our study has a number of strengths and limitations. Major strength is the design of population-based investigations on risk of all SPCs after first primary cancers in two different populations. Second strength is using very large databases (covering approximately 27 million Germans and 9 million Swedes) with high quality of data. All SIRs in the two populations were adjusted for three identical co-variables (age, sex, and calendar period) and additionally for a regional category (12 states in Germany and 4 categories in Sweden). A few of first primary cancers reported in early years of German cancer registry might be actually second primary cancers because German cancer registries included in this study were generally established in 1997 (except that four German registries even started data collection after 1997); nevertheless, for comparability and consistency, same criteria were also adopted for Swedish data, i.e., the definition of first and second primary cancers was recoded according to the study period 1997-2010. Additionally, because sensitivity analyses restricted to eight German cancer registries with full follow-up period 1997-2010 did not essentially change our results (Appendix Tables 2-4), we reported here with data from all 12 German cancer registries; nevertheless, we have taken into account this difference in data collection for person-year calculations in German dataset.

Conclusion

We found similar distribution of all SDPCs after any specific first cancer in the two populations and elevated overall risks after 23 cancers (out of 29 cancers in total) in Germany and after 24 cancers in Sweden. Among them, risks after 19 cancers were elevated in both populations, which may suggest common etiology of SDPCs after most of first primary cancers and similar registration practices for those cancers in the two populations. We found substantially higher risk of SDPCs after urinary bladder and upper aerodigestive tract cancers in Germany compared to Sweden, which is likely due to higher

incidence of smoking-related cancer for German men compared to Swedish men.While decreased overall SIRs found only in Germany after five fatal cancers may be attributed to reporting practices or missed death data in Germany. Consequently, our data validate their potential use in etiological studies. Nevertheless, further investigations on the SPC risk based on a specific pair of first-second cancers (e.g., a specific SPC after multiple myeloma) for overall and by characteristics of cancer patients in different populations are warranted, which may reveal the reasons behind different rate of second cancers that has clinical significance.

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Table 1. Distribution of all SDPCs after a specific first primary cancer in Germany and Sweden

Sites of first primary cancers	N		% of total		Rank *,#	
	Germany	Sweden	Germany	Sweden	Germany	Sweden
Prostate	13545	7316	16.9	22.5	1	1
Colorectum	11583	4022	14.4	12.4	2	2
Breast	8738	3849	10.9	11.8	3	3
Urinary bladder	7329	3353	9.1	10.3	4	4
Kidney	4780	1123	6.0	3.5	5	8
Upper aerodigestive tract	4684	950	5.8	2.9	6	11
Lung	4295	1063	5.4	3.3	7	9
Melanoma	3136	1672	3.9	5.1	8	5
Endometrium	2988	1348	3.7	4.1	9	6
Non-Hodgkin lymphoma	2686	1243	3.4	3.8	10	7
Stomach	2555	446	3.2	1.4	11	14
Leukemia	1743	1051	2.2	3.2	12	10
Ovary	1459	488	1.8	1.5	13	13
Esophagus	1116	151	1.4	0.5	14	22
Cervix uteri	1081	307	1.3	0.9	15	17
Liver and gallbladder	982	269	1.2	0.8	16	18
Thyroid glands	910	240	1.1	0.7	17	21
Connective tissue	786	258	1.0	0.8	18	19
Multiple myeloma	752	349	0.9	1.1	19	16
Pancreas	683	127	0.9	0.4	20	24
Unknown primary	667	418	0.8	1.3	21	15
Other female genital	611	146	0.8	0.4	22	23
Anus	365	111	0.5	0.3	23	25
Small intestine	357	241	0.4	0.7	24	20
Hodgkin lymphoma	324	106	0.4	0.3	25	28
Other male genital	232	104	0.3	0.3	26	29
Nervous system	230	644	0.3	2.0	27	12
Eye	229	107	0.3	0.3	28	27
Salivary glands	221	110	0.3	0.3	29	26
Total [a]	80162	32534	100	100		

SDPCs: second discordant primary cancers; Only cancer sites with a total number of all SDPCs ≥100 in both countries are presented; a Total number included the cancer sits not presented (all SDPCs <100); * Frequency rank; # There was no significant difference in rank between Germany and Sweden assessed by Wilcoxon two-sample test.

Table 2. Standardized incidence ratios (SIRs) of all SDPCs after a specific first primary cancer in Germany and Sweden; for overall and by sex

Sites of first primary cancers	Germany									Sweden								
	Men			Women			Overall			Men			Women			Overall		
	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI
Upper aerodigestive tract	3927	**2.0**	(1.9-2.1)	757	**2.0**	(1.9-2.2)	4684	**2.0**	(1.9-2.1)	705	**1.2**	(1.1-1.3)	245	**1.2**	(1.0-1.3)	950	**1.2**	(1.1-1.3)
Salivary gland	140	**1.6**	(1.3-1.9)	81	**1.6**	(1.3-2.0)	221	**1.6**	(1.4-1.8)	62	**1.4**	(1.1-1.8)	48	1.2	(0.9-1.7)	110	**1.3**	(1.1-1.6)
Esophagus	920	**1.8**	(1.7-1.9)	196	**2.0**	(1.8-2.3)	1116	**1.9**	(1.7-2.0)	114	**1.5**	(1.2-1.8)	37	**1.9**	(1.4-2.7)	151	**1.6**	(1.3-1.8)
Stomach	1695	**1.1**	(1.1-1.2)	860	**1.2**	(1.1-1.3)	2555	**1.1**	(1.1-1.2)	278	**1.2**	(1.0-1.3)	168	**1.2**	(1.0-1.4)	446	**1.2**	(1.1-1.3)
Small intestine	196	**1.7**	(1.4-1.9)	161	**2.2**	(1.9-2.6)	357	**1.9**	(1.7-2.1)	145	**1.5**	(1.2-1.7)	96	**1.8**	(1.4-2.2)	241	**1.6**	(1.4-1.8)
Colorectum	7203	**1.1**	(1.0-1.1)	4380	**1.2**	(1.1-1.2)	11583	**1.1**	(1.1-1.1)	2392	**1.1**	(1.1-1.2)	1630	**1.1**	(1.1-1.2)	4022	**1.1**	(1.1-1.2)
Anus	146	**1.8**	(1.5-2.1)	219	**1.8**	(1.5-2.0)	365	**1.8**	(1.6-2.0)	43	1.1	(0.8-1.4)	68	0.9	(0.7-1.1)	111	1.0	(0.8-1.1)
Liver and gallbladder	597	0.9	(0.8-1.0)	385	1.1	(1.0-1.2)	982	1.0	(0.9-1.0)	157	**1.5**	(1.3-1.8)	112	**1.4**	(1.2-1.7)	269	**1.5**	(1.3-1.7)
Pancreas	389	0.7	(0.6-0.8)	294	0.8	(0.7-0.9)	683	0.7	(0.7-0.8)	61	0.9	(0.7-1.2)	66	1.3	(1.0-1.6)	127	1.1	(0.9-1.3)
Lung	3311	0.9	(0.9-0.9)	984	**1.1**	(1.0-1.2)	4295	0.9	(0.9-1.0)	640	**1.2**	(1.2-1.3)	423	**1.4**	(1.2-1.5)	1063	**1.3**	(1.2-1.4)
Breast	134	1.1	(0.9-1.3)	8604	**1.2**	(1.1-1.2)	8738	**1.2**	(1.1-1.2)	52	1.1	(0.8-1.5)	3797	**1.1**	(1.0-1.1)	3849	**1.1**	(1.0-1.1)
Cervix uteri	0			1081	**1.8**	(1.7-1.9)	1081	**1.8**	(1.7-1.9)	0			307	**1.3**	(1.1-1.4)	307	**1.3**	(1.1-1.4)
Endometrium	0			2988	**1.5**	(1.4-1.5)	2988	**1.5**	(1.4-1.5)	0			1348	**1.2**	(1.1-1.3)	1348	**1.2**	(1.1-1.3)
Ovary	0			1459	**1.6**	(1.6-1.7)	1459	**1.6**	(1.6-1.7)	0			488	**1.3**	(1.2-1.4)	488	**1.3**	(1.2-1.4)
Other female genital	0			611	**1.4**	(1.3-1.6)	611	**1.4**	(1.3-1.6)	0			146	1.2	(1.0-1.4)	146	1.2	(1.0-1.4)
Prostate	13545	**1.1**	(1.0-1.1)	0			13545	**1.1**	(1.0-1.1)	7316	**1.1**	(1.1-1.1)	0			7316	**1.1**	(1.1-1.1)
Other male genital	232	**1.4**	(1.2-1.6)	0			232	**1.4**	(1.2-1.6)	104	**1.3**	(1.1-1.6)	0			104	**1.3**	(1.1-1.6)
Kidney	3402	**1.5**	(1.5-1.6)	1378	**1.4**	(1.3-1.4)	4780	**1.5**	(1.4-1.5)	724	**1.4**	(1.3-1.5)	399	**1.4**	(1.2-1.5)	1123	**1.4**	(1.3-1.5)
Urinary bladder	6483	**2.3**	(2.2-2.3)	846	**1.3**	(1.2-1.4)	7329	**2.1**	(2.0-2.1)	2767	**1.4**	(1.3-1.4)	586	**1.2**	(1.1-1.3)	3353	**1.3**	(1.3-1.4)
Melanoma	1823	**1.2**	(1.1-1.2)	1313	**1.3**	(1.2-1.3)	3136	**1.2**	(1.2-1.3)	967	**1.1**	(1.0-1.2)	705	1.1	(1.0-1.1)	1672	**1.1**	(1.0-1.1)
Eye	131	**1.3**	(1.1-1.6)	98	**1.5**	(1.3-1.9)	229	**1.4**	(1.2-1.6)	53	1.1	(0.8-1.4)	54	**1.3**	(1.0-1.7)	107	1.2	(1.0-1.4)
Nervous system	138	0.5	(0.4-0.6)	92	0.5	(0.4-0.7)	230	0.5	(0.4-0.6)	281	1.1	(1.0-1.2)	363	1.1	(1.0-1.2)	644	**1.1**	(1.0-1.2)
Thyroid gland	301	**1.4**	(1.2-1.6)	609	**1.5**	(1.4-1.6)	910	**1.5**	(1.4-1.6)	83	1.2	(1.0-1.5)	157	**1.3**	(1.1-1.5)	240	**1.2**	(1.1-1.4)
Connective tissue	474	**1.2**	(1.1-1.3)	312	**1.7**	(1.5-1.8)	786	**1.3**	(1.2-1.4)	166	**1.3**	(1.1-1.5)	92	1.1	(0.9-1.4)	258	**1.2**	(1.1-1.4)
Non-Hodgkin lymphoma	1626	**1.2**	(1.1-1.3)	1060	**1.2**	(1.1-1.3)	2686	**1.2**	(1.2-1.2)	743	**1.2**	(1.1-1.2)	500	**1.1**	(1.0-1.2)	1243	**1.1**	(1.1-1.2)
Hodgkin lymphoma	193	**1.6**	(1.4-1.8)	131	**1.9**	(1.6-2.2)	324	**1.7**	(1.5-1.9)	58	1.0	(0.8-1.3)	48	1.1	(0.8-1.4)	106	1.0	(0.8-1.2)
Multiple myeloma	470	0.9	(0.8-1.0)	282	0.9	(0.8-1.0)	752	0.9	(0.8-0.9)	208	**1.3**	(1.1-1.5)	141	**1.3**	(1.1-1.5)	349	**1.3**	(1.2-1.4)
Leukemia	1206	**1.1**	(1.1-1.2)	537	1.0	(0.9-1.1)	1743	**1.1**	(1.0-1.1)	627	**1.2**	(1.1-1.3)	424	1.1	(1.0-1.2)	1051	**1.1**	(1.1-1.2)
Unknown primary	394	0.9	(0.8-1.0)	273	0.9	(0.8-1.0)	667	0.9	(0.8-1.0)	200	**1.3**	(1.1-1.4)	218	**1.4**	(1.2-1.5)	418	**1.3**	(1.2-1.4)

SDPCs: second discordant primary cancers; CI: confidence interval; only cancer sites shown in Table 1 are presented; Bold type (elevated risk) and underscored type (decreased risk): 95% CIs did not include 1.00.

Table 3. Standardized incidence ratios (SIRs) of all SDPCs after a specific first primary cancer by age at diagnosis of first cancer in Germany and Sweden

Sites of first primary cancers	Germany									Sweden								
	<65 years			65-74 years			≥75 years			<65 years			65-74 years			≥75 years		
	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI
Upper aerodigestive tract	2748	**2.6**	(2.5-2.7)	1493	**1.7**	(1.6-1.8)	443	1.1	(1.0-1.2)	400	**1.2**	(1.1-1.4)	275	**1.2**	(1.0-1.3)	275	**1.2**	(1.0-1.3)
Salivary gland	100	**2.3**	(1.9-2.8)	71	**1.5**	(1.2-2.0)	50	1.0	(0.7-1.3)	41	**1.4**	(1.0-2.0)	34	1.2	(0.8-1.7)	35	1.3	(0.9-1.8)
Esophagus	581	**2.9**	(2.7-3.2)	391	**1.5**	(1.4-1.7)	144	1.0	(0.8-1.2)	51	**1.8**	(1.3-2.3)	63	**1.7**	(1.3-2.2)	37	1.2	(0.8-1.6)
Stomach	741	**1.5**	(1.4-1.6)	1008	**1.2**	(1.1-1.2)	806	0.9	(0.8-0.9)	100	**1.3**	(1.0-1.6)	159	**1.2**	(1.0-1.4)	187	1.1	(1.0-1.3)
Small intestine	142	**2.4**	(2.0-2.8)	137	**1.8**	(1.5-2.1)	78	**1.4**	(1.1-1.8)	76	**1.5**	(1.2-1.9)	69	**1.6**	(1.2-2.0)	96	**1.6**	(1.3-2.0)
Colorectum	3125	**1.3**	(1.2-1.3)	4753	**1.1**	(1.1-1.1)	3705	1.0	(0.9-1.0)	829	**1.2**	(1.1-1.2)	1349	**1.1**	(1.1-1.2)	1844	**1.1**	(1.1-1.2)
Anus	164	**2.4**	(2.0-2.7)	110	**1.6**	(1.3-1.9)	91	**1.4**	(1.1-1.7)	49	0.9	(0.7-1.3)	28	1.0	(0.6-1.4)	34	0.9	(0.7-1.3)
Liver and gallbladder	311	**1.5**	(1.4-1.7)	389	0.9	(0.8-1.0)	282	0.7	(0.6-0.8)	74	**1.6**	(1.3-2.1)	85	**1.5**	(1.2-1.8)	110	**1.4**	(1.1-1.7)
Pancreas	265	**1.3**	(1.2-1.5)	266	0.7	(0.6-0.8)	152	0.4	(0.4-0.5)	38	1.3	(0.9-1.8)	41	1.0	(0.7-1.3)	48	1.0	(0.8-1.4)
Lung	1555	**1.3**	(1.3-1.4)	1892	0.9	(0.9-1.0)	848	0.6	(0.6-0.7)	301	**1.3**	(1.2-1.5)	404	**1.2**	(1.1-1.4)	358	**1.3**	(1.2-1.4)
Breast	3698	**1.3**	(1.3-1.3)	2868	**1.2**	(1.1-1.2)	2172	1.0	(1.0-1.0)	1732	**1.1**	(1.1-1.2)	1196	1.0	(1.0-1.1)	922	1.1	(1.0-1.1)
Cervix uteri	659	**1.9**	(1.8-2.1)	250	**1.7**	(1.5-1.9)	172	**1.4**	(1.2-1.6)	167	**1.3**	(1.1-1.5)	65	1.1	(0.9-1.5)	75	**1.3**	(1.1-1.7)
Endometrium	1086	**1.7**	(1.6-1.8)	1184	**1.6**	(1.5-1.6)	718	**1.2**	(1.1-1.3)	476	**1.3**	(1.2-1.4)	474	**1.1**	(1.0-1.2)	398	**1.2**	(1.1-1.3)
Ovary	755	**2.2**	(2.0-2.3)	418	**1.4**	(1.2-1.5)	286	**1.2**	(1.1-1.3)	257	**1.5**	(1.4-1.7)	134	1.1	(0.9-1.3)	97	1.1	(0.9-1.3)
Other female genital	208	**2.0**	(1.8-2.3)	192	**1.4**	(1.2-1.6)	211	1.1	(1.0-1.3)	47	1.3	(1.0-1.8)	33	1.1	(0.8-1.6)	66	1.1	(0.9-1.4)
Prostate	2763	**1.1**	(1.0-1.1)	6866	**1.1**	(1.0-1.1)	3916	**1.1**	(1.0-1.1)	1323	**1.1**	(1.0-1.1)	3014	**1.1**	(1.0-1.1)	2980	**1.1**	(1.1-1.1)
Other male genital	78	**1.5**	(1.2-1.9)	106	**1.6**	(1.3-1.9)	48	0.9	(0.7-1.2)	35	**1.5**	(1.0-2.0)	33	1.1	(0.8-1.6)	36	1.4	(1.0-1.9)
Kidney	1757	**1.6**	(1.6-1.7)	1990	**1.4**	(1.4-1.5)	1033	**1.3**	(1.2-1.4)	312	**1.4**	(1.3-1.6)	454	**1.4**	(1.3-1.5)	357	**1.4**	(1.2-1.5)
Urinary bladder	1739	**2.6**	(2.5-2.7)	3322	**2.3**	(2.2-2.4)	2268	**1.6**	(1.6-1.7)	729	**1.5**	(1.4-1.6)	1303	**1.4**	(1.3-1.4)	1321	**1.3**	(1.2-1.3)
Melanoma	1293	**1.3**	(1.2-1.4)	1130	**1.2**	(1.2-1.3)	713	1.1	(1.0-1.2)	665	**1.1**	(1.0-1.2)	513	1.0	(1.0-1.1)	495	1.1	(1.0-1.2)
Eye	86	**1.7**	(1.4-2.1)	94	**1.5**	(1.2-1.8)	49	1.0	(0.8-1.4)	38	1.1	(0.8-1.5)	35	1.1	(0.8-1.6)	34	1.4	(0.9-1.9)
Nervous system	131	0.7	(0.6-0.9)	68	0.4	(0.3-0.5)	31	0.3	(0.2-0.5)	355	**1.1**	(1.0-1.3)	168	1.0	(0.8-1.2)	121	1.1	(0.9-1.3)
Thyroid gland	517	**1.5**	(1.4-1.7)	271	**1.4**	(1.3-1.6)	122	**1.3**	(1.1-1.5)	142	**1.3**	(1.1-1.6)	54	1.0	(0.7-1.3)	44	1.3	(0.9-1.7)
Connective tissue	344	**2.1**	(1.9-2.3)	253	**1.1**	(1.0-1.2)	189	1.0	(0.9-1.1)	92	**1.2**	(1.0-1.5)	89	**1.4**	(1.1-1.7)	77	1.0	(0.8-1.3)
Non-Hodgkin lymphoma	1006	**1.4**	(1.3-1.5)	1017	**1.2**	(1.1-1.3)	663	1.0	(0.9-1.0)	401	**1.2**	(1.1-1.3)	429	**1.1**	(1.0-1.2)	414	**1.2**	(1.0-1.3)
Hodgkin lymphoma	204	**2.1**	(1.8-2.4)	78	**1.3**	(1.1-1.7)	42	1.3	(0.9-1.7)	57	1.1	(0.8-1.4)	32	0.9	(0.6-1.2)	17	1.2	(0.7-1.9)
Multiple myeloma	245	1.1	(1.0-1.2)	305	0.9	(0.8-1.0)	202	0.7	(0.6-0.8)	87	1.2	(1.0-1.5)	124	**1.4**	(1.2-1.7)	138	**1.2**	(1.0-1.5)
Leukemia	598	**1.3**	(1.2-1.4)	710	**1.1**	(1.0-1.2)	435	0.9	(0.8-1.0)	318	**1.2**	(1.1-1.3)	368	1.1	(1.0-1.2)	365	**1.1**	(1.0-1.3)
Unknown primary	311	**1.8**	(1.6-2.0)	236	0.9	(0.8-1.0)	120	0.4	(0.3-0.5)	159	**1.8**	(1.5-2.1)	121	1.2	(1.0-1.4)	138	1.1	(0.9-1.3)

SDPCs: second discordant primary cancers; CI: confidence interval; Only cancer sites shown in Table 1 are presented; Bold type (elevated risk) and underscored type (decreased risk): 95% CIs did not include 1.00.

Table 4. Standardized incidence ratios (SIRs) of all SDPCs after a specific first primary cancer by follow-up time after first cancer in Germany and Sweden

Sites of first primary cancers	Germany									Sweden								
	<1 year			1-4 yers			≥5 years			<1 year			1-4 yers			≥5 years		
	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI
Upper aerodigestive tract	1157	**2.1**	(2.0-2.3)	2382	**2.0**	(1.9-2.1)	1145	**1.9**	(1.8-2.0)	178	1.1	(1.0-1.3)	489	**1.2**	(1.1-1.3)	283	**1.2**	(1.1-1.4)
Salivary gland	59	**1.9**	(1.4-2.4)	113	**1.6**	(1.3-1.9)	49	**1.4**	(1.0-1.8)	29	**2.0**	(1.3-2.8)	47	1.3	(0.9-1.7)	34	1.1	(0.7-1.5)
Esophagus	581	**2.4**	(2.2-2.6)	434	**1.5**	(1.4-1.7)	101	**1.4**	(1.1-1.7)	63	**1.5**	(1.2-1.9)	66	**1.6**	(1.2-2.0)	22	**1.6**	(1.0-2.4)
Stomach	1055	**1.4**	(1.3-1.5)	1037	1.0	(0.9-1.0)	463	1.1	(1.0-1.2)	171	**1.4**	(1.2-1.6)	167	1.0	(0.9-1.2)	108	1.1	(0.9-1.4)
Small intestine	186	**3.7**	(3.2-4.2)	130	**1.3**	(1.1-1.6)	41	0.9	(0.7-1.3)	107	**2.5**	(2.0-3.0)	84	1.2	(1.0-1.5)	50	1.2	(0.9-1.6)
Colorectum	3184	**1.3**	(1.3-1.3)	5575	**1.0**	(1.0-1.1)	2824	**1.1**	(1.0-1.1)	954	**1.2**	(1.1-1.3)	1920	**1.1**	(1.1-1.2)	1148	**1.1**	(1.0-1.2)
Anus	137	**2.9**	(2.4-3.4)	156	**1.5**	(1.3-1.8)	72	**1.3**	(1.0-1.7)	20	1.1	(0.7-1.7)	48	1.0	(0.8-1.4)	43	0.8	(0.6-1.1)
Liver and gallbladder	483	1.0	(0.9-1.1)	393	0.9	(0.8-1.0)	106	0.9	(0.8-1.1)	143	**1.7**	(1.4-2.0)	92	**1.3**	(1.0-1.6)	34	1.3	(0.9-1.9)
Pancreas	404	0.8	(0.7-0.9)	228	0.6	(0.6-0.7)	51	0.9	(0.6-1.1)	69	1.0	(0.8-1.3)	40	1.1	(0.8-1.5)	18	1.2	(0.7-1.9)
Lung	1866	1.0	(0.9-1.0)	1837	0.9	(0.9-0.9)	592	1.0	(1.0-1.1)	432	**1.4**	(1.3-1.5)	442	**1.2**	(1.1-1.4)	189	**1.2**	(1.0-1.3)
Breast	1489	**1.1**	(1.1-1.2)	4326	**1.2**	(1.1-1.2)	2923	**1.2**	(1.2-1.2)	430	0.8	(0.7-0.9)	1883	**1.1**	(1.0-1.1)	1537	**1.1**	(1.1-1.2)
Cervix uteri	343	**3.0**	(2.7-3.3)	443	**1.6**	(1.4-1.7)	295	**1.4**	(1.2-1.5)	77	**1.7**	(1.4-2.1)	127	1.1	(1.0-1.4)	103	1.2	(1.0-1.4)
Endometrium	935	**2.5**	(2.4-2.7)	1286	**1.3**	(1.2-1.3)	767	**1.1**	(1.0-1.2)	349	**1.7**	(1.6-1.9)	576	**1.1**	(1.0-1.2)	423	1.1	(1.0-1.2)
Ovary	727	**3.1**	(2.9-3.3)	497	**1.1**	(1.0-1.2)	235	1.1	(1.0-1.3)	159	**2.0**	(1.7-2.3)	183	1.0	(0.9-1.2)	146	**1.3**	(1.1-1.5)
Other female genital	215	**2.1**	(1.8-2.3)	286	**1.3**	(1.2-1.5)	110	1.1	(0.9-1.3)	40	**1.5**	(1.1-2.0)	65	1.0	(0.8-1.3)	41	1.3	(0.9-1.8)
Prostate	2994	**1.2**	(1.2-1.3)	7141	**1.0**	(1.0-1.1)	3410	1.0	(1.0-1.0)	1281	1.0	(0.9-1.0)	3878	**1.1**	(1.0-1.1)	2158	**1.2**	(1.1-1.2)
Other male genital	70	**1.9**	(1.4-2.3)	105	1.2	(1.0-1.4)	57	1.3	(1.0-1.7)	25	**1.6**	(1.0-2.4)	53	1.2	(0.9-1.6)	26	1.2	(0.8-1.8)
Kidney	1295	**2.0**	(1.9-2.1)	2240	**1.4**	(1.3-1.5)	1245	**1.2**	(1.2-1.3)	334	**1.6**	(1.5-1.8)	536	**1.4**	(1.3-1.5)	253	**1.2**	(1.0-1.3)
Urinary bladder	3419	**4.0**	(3.9-4.2)	2775	**1.6**	(1.5-1.6)	1135	**1.3**	(1.2-1.3)	1013	**1.7**	(1.6-1.8)	1554	**1.3**	(1.2-1.3)	786	**1.1**	(1.1-1.2)
Melanoma	558	**1.2**	(1.1-1.3)	1670	**1.3**	(1.2-1.3)	908	**1.1**	(1.1-1.2)	216	0.8	(0.7-0.9)	862	**1.1**	(1.0-1.2)	595	**1.2**	(1.1-1.3)
Eye	39	1.2	(0.9-1.7)	131	**1.5**	(1.3-1.8)	59	**1.4**	(1.1-1.8)	14	0.8	(0.5-1.4)	64	**1.5**	(1.1-1.9)	29	1.0	(0.7-1.4)
Nervous system	86	0.4	(0.3-0.5)	93	0.5	(0.4-0.6)	51	0.8	(0.6-1.1)	88	0.9	(0.7-1.1)	296	1.1	(0.9-1.2)	260	**1.2**	(1.1-1.4)
Thyroid gland	148	**1.4**	(1.2-1.6)	433	**1.5**	(1.3-1.6)	329	**1.5**	(1.3-1.6)	50	**1.6**	(1.2-2.1)	102	1.2	(1.0-1.4)	88	1.2	(0.9-1.4)
Connective tissue	338	**1.9**	(1.7-2.1)	330	**1.1**	(1.0-1.3)	118	1.0	(0.8-1.2)	43	1.0	(0.7-1.4)	141	**1.4**	(1.1-1.6)	74	1.1	(0.9-1.4)
Non-Hodgkin lymphoma	604	**1.2**	(1.1-1.2)	1339	**1.2**	(1.1-1.2)	743	**1.3**	(1.2-1.4)	231	1.1	(0.9-1.2)	625	**1.1**	(1.0-1.2)	388	**1.2**	(1.1-1.4)
Hodgkin lymphoma	74	**2.1**	(1.6-2.6)	139	**1.5**	(1.3-1.8)	111	**1.8**	(1.4-2.1)	19	1.4	(0.9-2.2)	38	0.9	(0.6-1.2)	49	1.1	(0.8-1.4)
Multiple myeloma	198	0.8	(0.7-1.0)	402	0.9	(0.8-1.0)	152	1.0	(0.8-1.2)	88	1.1	(0.9-1.4)	199	**1.4**	(1.2-1.6)	62	**1.3**	(1.0-1.7)
Leukemia	403	1.0	(0.9-1.1)	878	**1.1**	(1.0-1.2)	462	**1.2**	(1.1-1.4)	174	0.9	(0.8-1.0)	578	**1.2**	(1.1-1.3)	299	**1.2**	(1.1-1.4)
Unknown primary	357	1.0	(0.9-1.1)	229	0.8	(0.7-0.9)	81	0.8	(0.6-1.0)	161	1.1	(0.9-1.3)	189	**1.6**	(1.4-1.8)	68	1.2	(0.9-1.5)

SDPCs: second discordant primary cancers; CI: confidence interval; Only cancer sites shown in Table 1 are presented; Bold type (elevated risk) and underscored type (decreased risk): 95% CIs did not include 1.00.

Appendix Table 1. Distribution of first primary cancer (except non-melanoma skin cancer) diagnosed at ≥15 years in Germany and Sweden

Sites of first primary cancers	Germany			Sweden		
	N	%	Rank*	N	%	Rank*
Breast	234863	15.28	1	87448	14.87	2
Colorectum	219468	14.28	2	69774	11.86	3
Prostate	202961	13.20	3	114088	19.40	1
Lung	163537	10.64	4	43502	7.40	4
Stomach	59835	3.89	5	12666	2.15	13
Urinary bladder	58779	3.82	6	28710	4.88	5
Kidney	57156	3.72	7	12696	2.16	12
Upper aerodigestive tract	54550	3.55	8	11966	2.03	14
Melanoma	53605	3.49	9	26500	4.51	6
Non-Hodgkin lymphoma	47242	3.07	10	19772	3.36	8
Endometrium	41103	2.67	11	17406	2.96	9
Pancreas	40514	2.64	12	11748	2.00	15
Liver and gallbladder	36811	2.39	13	11536	1.96	16
Leukemia	35711	2.32	14	17096	2.91	10
Unknown primary	28418	1.85	15	20287	3.45	7
Ovary	28265	1.84	16	10591	1.80	17
Cervix uteri	21232	1.38	17	6123	1.04	20
Nervous system	20872	1.36	18	16371	2.78	11
Esophagus	19534	1.27	19	5121	0.87	21
Multiple myeloma	18735	1.22	20	7560	1.29	19
Thyroid glands	16314	1.06	21	4215	0.72	22
Testis	16148	1.05	22	3827	0.65	23
Connective tissue	14825	0.96	23	3737	0.64	24
Other female genital	11095	0.72	24	2727	0.46	26
Hodgkin lymphoma	7233	0.47	25	2303	0.39	27
Anus	4801	0.31	26	1614	0.27	28
Small intestine	4449	0.29	27	2752	0.47	25
Any other cancers	3536	0.23	28	550	0.09	35
Eye	2916	0.19	29	1483	0.25	30
Salivary gland	2837	0.18	30	1204	0.20	31
Other male genital	2623	0.17	31	1100	0.19	32
Bone	2516	0.16	32	814	0.14	34
Nose	2447	0.16	33	842	0.14	33
Other uterus	1223	0.08	34	1572	0.27	29
Non-thyroid endocrine glands	850	0.06	35	8402	1.43	18
Total	1537004	100		588103	100	

*Frequency rank.

Appendix Table 2. Standardized incidence ratios (SIRs) of all SDPCs after a specific first primary cancer for overall and by sex in Germany (exclude 4 cancer registries started data collection later than 1997) and Sweden

Sites of first primary cancers	Germany									Sweden								
	Men			Women			Overall			Men			Women			Overall		
	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI
Upper aerodigestive tract	2949	**2.0**	(2.0-2.1)	531	**2.0**	(1.8-2.2)	3480	**2.0**	(2.0-2.1)	705	**1.2**	(1.1-1.3)	245	**1.2**	(1.0-1.3)	950	**1.2**	(1.1-1.3)
Salivary gland	103	**1.6**	(1.3-2.0)	64	**1.7**	(1.3-2.2)	167	**1.7**	(1.4-1.9)	62	**1.4**	(1.1-1.8)	48	1.2	(0.9-1.7)	110	**1.3**	(1.1-1.6)
Esophagus	690	**2.0**	(1.9-2.2)	142	**2.3**	(2.0-2.8)	832	**2.1**	(1.9-2.2)	114	**1.5**	(1.2-1.8)	37	**1.9**	(1.4-2.7)	151	**1.6**	(1.3-1.8)
Stomach	1321	**1.1**	(1.1-1.2)	645	**1.2**	(1.1-1.3)	1966	**1.2**	(1.1-1.2)	278	**1.2**	(1.0-1.3)	168	**1.2**	(1.0-1.4)	446	**1.2**	(1.1-1.3)
Small intestine	157	**1.9**	(1.6-2.2)	120	**2.5**	(2.0-2.9)	277	**2.1**	(1.9-2.4)	145	**1.5**	(1.2-1.7)	96	**1.8**	(1.4-2.2)	241	**1.6**	(1.4-1.8)
Colorectum	5299	0.9	(0.9-1.0)	3148	1.0	(0.9-1.0)	8447	0.9	(0.9-1.0)	2392	**1.1**	(1.1-1.2)	1630	**1.1**	(1.1-1.2)	4022	**1.1**	(1.1-1.2)
Anus	110	**2.0**	(1.6-2.4)	159	**1.8**	(1.5-2.1)	269	**1.9**	(1.6-2.1)	43	1.1	(0.8-1.4)	68	0.9	(0.7-1.1)	111	1.0	(0.8-1.1)
Liver and gallbladder	477	1.0	(0.9-1.1)	330	**1.2**	(1.1-1.3)	807	**1.1**	(1.0-1.2)	157	**1.5**	(1.3-1.8)	112	**1.4**	(1.2-1.7)	269	**1.5**	(1.3-1.7)
Pancreas	309	0.8	(0.7-0.9)	232	0.9	(0.8-1.0)	541	0.8	(0.8-0.9)	61	0.9	(0.7-1.2)	66	1.3	(1.0-1.6)	127	1.1	(0.9-1.3)
Lung	2532	1.0	(0.9-1.0)	726	**1.2**	(1.1-1.3)	3258	1.0	(1.0-1.0)	640	**1.2**	(1.2-1.3)	423	**1.4**	(1.2-1.5)	1063	**1.3**	(1.2-1.4)
Breast	104	1.1	(0.9-1.4)	6219	**1.2**	(1.2-1.2)	6323	**1.2**	(1.2-1.2)	52	1.1	(0.8-1.5)	3797	**1.1**	(1.0-1.1)	3849	**1.1**	(1.0-1.1)
Cervix uteri	0			849	**1.8**	(1.7-1.9)	849	**1.8**	(1.7-1.9)	0			307	**1.3**	(1.1-1.4)	307	**1.3**	(1.1-1.4)
Endometrium	0			2306	**1.5**	(1.5-1.6)	2306	**1.5**	(1.5-1.6)	0			1348	**1.2**	(1.1-1.3)	1348	**1.2**	(1.1-1.3)
Ovary	0			1119	**1.8**	(1.7-1.9)	1119	**1.8**	(1.7-1.9)	0			488	**1.3**	(1.2-1.4)	488	**1.3**	(1.2-1.4)
Other female genital	0			451	**1.5**	(1.4-1.6)	451	**1.5**	(1.4-1.6)	0			146	1.2	(1.0-1.4)	146	1.2	(1.0-1.4)
Prostate	9506	**1.1**	(1.1-1.1)	0			9506	**1.1**	(1.1-1.1)	7316	**1.1**	(1.1-1.1)	0			7316	**1.1**	(1.1-1.1)
Other male genital	178	**1.4**	(1.2-1.7)	0			178	**1.4**	(1.2-1.7)	104	**1.3**	(1.1-1.6)	0			104	**1.3**	(1.1-1.6)
Kidney	2766	**1.6**	(1.5-1.6)	1111	**1.4**	(1.3-1.5)	3877	**1.5**	(1.5-1.6)	724	**1.4**	(1.3-1.5)	399	**1.4**	(1.2-1.5)	1123	**1.4**	(1.3-1.5)
Urinary bladder	4922	**2.3**	(2.2-2.3)	653	**1.3**	(1.2-1.4)	5575	**2.1**	(2.0-2.1)	2767	**1.4**	(1.3-1.4)	586	**1.2**	(1.1-1.3)	3353	**1.3**	(1.3-1.4)
Melanoma	1280	**1.2**	(1.1-1.3)	892	**1.3**	(1.2-1.4)	2172	**1.2**	(1.2-1.3)	967	**1.1**	(1.0-1.2)	705	1.1	(1.0-1.1)	1672	**1.1**	(1.0-1.1)
Eye	100	**1.4**	(1.1-1.7)	80	**1.7**	(1.4-2.1)	180	**1.5**	(1.3-1.7)	53	1.1	(0.8-1.4)	54	**1.3**	(1.0-1.7)	107	1.2	(1.0-1.4)
Nervous system	104	0.5	(0.4-0.6)	68	0.6	(0.4-0.7)	172	0.5	(0.4-0.6)	281	1.1	(1.0-1.2)	363	1.1	(1.0-1.2)	644	**1.1**	(1.0-1.2)
Thyroid gland	232	**1.4**	(1.2-1.6)	486	**1.6**	(1.4-1.7)	718	**1.5**	(1.4-1.6)	83	1.2	(1.0-1.5)	157	**1.3**	(1.1-1.5)	240	**1.2**	(1.1-1.4)
Connective tissue	356	**1.3**	(1.2-1.5)	244	**1.8**	(1.6-2.1)	600	**1.5**	(1.4-1.6)	166	**1.3**	(1.1-1.5)	92	1.1	(0.9-1.4)	258	**1.2**	(1.1-1.4)
Non-Hodgkin lymphoma	1157	**1.3**	(1.2-1.3)	759	**1.2**	(1.1-1.3)	1916	**1.2**	(1.2-1.3)	743	**1.2**	(1.1-1.2)	500	**1.1**	(1.0-1.2)	1243	**1.1**	(1.1-1.2)
Hodgkin lymphoma	145	**1.7**	(1.4-2.0)	94	**1.9**	(1.5-2.3)	239	**1.8**	(1.5-2.0)	58	1.0	(0.8-1.3)	48	1.1	(0.8-1.4)	106	1.0	(0.8-1.2)
Multiple myeloma	334	0.9	(0.8-1.0)	198	0.9	(0.8-1.0)	532	0.9	(0.8-1.0)	208	**1.3**	(1.1-1.5)	141	**1.3**	(1.1-1.5)	349	**1.3**	(1.2-1.4)
Leukemia	929	**1.2**	(1.1-1.3)	415	1.1	(1.0-1.2)	1344	**1.2**	(1.1-1.2)	627	**1.2**	(1.1-1.3)	424	1.1	(1.0-1.2)	1051	**1.1**	(1.1-1.2)
Unknown primary	312	1.0	(0.9-1.1)	208	1.0	(0.8-1.1)	520	1.0	(0.9-1.1)	200	**1.3**	(1.1-1.4)	218	**1.4**	(1.2-1.5)	418	**1.3**	(1.2-1.4)

SDPCs: second discordant primary cancers; CI: confidence interval; Only cancer sites shown in Table 1 are presented; Bold type (elevated risk) and underscored type (decreased risk): 95% CIs did not include 1.00.

Appendix Table 3. Standardized incidence ratios (SIRs) of all SDPCs after a specific first primary cancer by age at diagnosis of first cancer in Germany (exclude 4 cancer registries started data collection later than 1997) and Sweden

Sites of first primary cancers	Gemany									Sweden								
	<65 years			65-74 years			≥75 years			<65 years			65-74 years			≥75 years		
	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI
Upper aerodigestive tract	2086	**2.6**	(2.5-2.7)	1089	**1.7**	(1.6-1.8)	305	**1.1**	(1.0-1.3)	400	**1.2**	(1.1-1.4)	275	**1.2**	(1.0-1.3)	275	**1.2**	(1.0-1.3)
Salivary gland	78	**2.3**	(1.8-2.9)	52	**1.6**	(1.2-2.1)	37	1.1	(0.8-1.5)	41	**1.4**	(1.0-2.0)	34	1.2	(0.8-1.7)	35	1.3	(0.9-1.8)
Esophagus	449	**3.3**	(3.0-3.6)	279	**1.6**	(1.4-1.8)	104	1.1	(0.9-1.3)	51	**1.8**	(1.3-2.3)	63	**1.7**	(1.3-2.2)	37	1.2	(0.8-1.6)
Stomach	595	**1.6**	(1.5-1.7)	770	**1.2**	(1.1-1.3)	601	0.9	(0.9-1.0)	100	**1.3**	(1.0-1.6)	159	**1.2**	(1.0-1.4)	187	1.1	(1.0-1.3)
Small intestine	117	**2.8**	(2.3-3.3)	100	**1.9**	(1.5-2.3)	60	**1.6**	(1.3-2.1)	76	**1.5**	(1.2-1.9)	69	**1.6**	(1.2-2.0)	96	**1.6**	(1.3-2.0)
Colorectum	2374	**1.3**	(1.2-1.3)	3516	**1.1**	(1.1-1.2)	2557	1.0	(1.0-1.0)	829	**1.2**	(1.1-1.2)	1349	**1.1**	(1.1-1.2)	1844	**1.1**	(1.1-1.2)
Anus	116	**2.4**	(2.0-2.9)	83	**1.6**	(1.3-2.0)	70	**1.5**	(1.2-1.9)	49	0.9	(0.7-1.3)	28	1.0	(0.6-1.4)	34	0.9	(0.7-1.3)
Liver and gallbladder	259	**1.7**	(1.5-1.9)	321	1.0	(0.9-1.1)	227	0.8	(0.7-0.9)	74	**1.6**	(1.3-2.1)	85	**1.5**	(1.2-1.8)	110	**1.4**	(1.1-1.7)
Pancreas	213	**1.5**	(1.3-1.7)	211	0.8	(0.7-0.9)	117	0.5	(0.4-0.6)	38	1.3	(0.9-1.8)	41	1.0	(0.7-1.3)	48	1.0	(0.8-1.4)
Lung	1189	**1.4**	(1.3-1.5)	1437	1.0	(0.9-1.0)	632	0.7	(0.6-0.8)	301	**1.3**	(1.2-1.5)	404	**1.2**	(1.1-1.4)	358	**1.3**	(1.2-1.4)
Breast	2694	**1.3**	(1.3-1.4)	2074	**1.2**	(1.1-1.2)	1555	1.0	(1.0-1.1)	1732	**1.1**	(1.1-1.2)	1196	1.0	(1.0-1.1)	922	1.1	(1.0-1.1)
Cervix uteri	518	**1.9**	(1.8-2.1)	196	**1.7**	(1.5-2.0)	135	**1.5**	(1.2-1.7)	167	**1.3**	(1.1-1.5)	65	1.1	(0.9-1.5)	75	**1.3**	(1.1-1.7)
Endometrium	869	**1.8**	(1.7-1.9)	889	**1.6**	(1.5-1.7)	548	**1.3**	(1.1-1.4)	476	**1.3**	(1.2-1.4)	474	**1.1**	(1.0-1.2)	398	**1.2**	(1.1-1.3)
Ovary	575	**2.3**	(2.1-2.5)	323	**1.5**	(1.3-1.7)	221	**1.3**	(1.2-1.5)	257	**1.5**	(1.4-1.7)	134	1.1	(0.9-1.3)	97	1.1	(0.9-1.3)
Other female genital	160	**2.2**	(1.9-2.6)	141	**1.4**	(1.2-1.7)	150	1.2	(1.0-1.4)	47	1.3	(1.0-1.8)	33	1.1	(0.8-1.6)	66	1.1	(0.9-1.4)
Prostate	2002	**1.1**	(1.0-1.1)	4879	**1.1**	(1.1-1.1)	2625	**1.1**	(1.1-1.1)	1323	**1.1**	(1.0-1.1)	3014	**1.1**	(1.0-1.1)	2980	**1.1**	(1.1-1.1)
Other male genital	59	**1.5**	(1.1-1.9)	89	**1.9**	(1.5-2.3)	30	0.8	(0.6-1.2)	35	**1.5**	(1.0-2.0)	33	1.1	(0.8-1.6)	36	1.4	(1.0-1.9)
Kidney	1466	**1.7**	(1.6-1.8)	1613	**1.5**	(1.4-1.6)	798	**1.4**	(1.3-1.5)	312	**1.4**	(1.3-1.6)	454	**1.4**	(1.3-1.5)	357	**1.4**	(1.2-1.5)
Urinary bladder	1340	**2.5**	(2.4-2.7)	2561	**2.3**	(2.2-2.4)	1674	**1.7**	(1.6-1.7)	729	**1.5**	(1.4-1.6)	1303	**1.4**	(1.3-1.4)	1321	**1.3**	(1.2-1.3)
Melanoma	938	**1.3**	(1.2-1.4)	742	**1.2**	(1.1-1.3)	492	**1.2**	(1.1-1.3)	665	**1.1**	(1.0-1.2)	513	1.0	(1.0-1.1)	495	1.1	(1.0-1.2)
Eye	72	**1.8**	(1.4-2.3)	73	**1.5**	(1.2-1.9)	35	1.1	(0.7-1.5)	38	1.1	(0.8-1.5)	35	1.1	(0.8-1.6)	34	1.4	(0.9-1.9)
Nervous system	100	0.7	(0.6-0.9)	45	0.4	(0.3-0.5)	27	0.4	(0.3-0.6)	355	**1.1**	(1.0-1.3)	168	1.0	(0.8-1.2)	121	1.1	(0.9-1.3)
Thyroid gland	413	**1.6**	(1.4-1.7)	220	**1.5**	(1.3-1.7)	85	**1.3**	(1.0-1.6)	142	**1.3**	(1.1-1.6)	54	1.0	(0.7-1.3)	44	1.3	(0.9-1.7)
Connective tissue	274	**2.3**	(2.0-2.6)	186	**1.2**	(1.0-1.3)	140	**1.1**	(1.0-1.3)	92	**1.2**	(1.0-1.5)	89	**1.4**	(1.1-1.7)	77	1.0	(0.8-1.3)
Non-Hodgkin lymphoma	731	**1.4**	(1.3-1.5)	735	**1.2**	(1.2-1.3)	450	**1.0**	(0.9-1.1)	401	**1.2**	(1.1-1.3)	429	**1.1**	(1.0-1.2)	414	**1.2**	(1.0-1.3)
Hodgkin lymphoma	150	**2.0**	(1.7-2.4)	56	**1.4**	(1.1-1.9)	33	**1.5**	(1.0-2.1)	57	1.1	(0.8-1.4)	32	0.9	(0.6-1.2)	17	1.2	(0.7-1.9)
Multiple myeloma	184	1.1	(1.0-1.3)	212	0.9	(0.7-1.0)	136	0.7	(0.6-0.9)	87	1.2	(1.0-1.5)	124	**1.4**	(1.2-1.7)	138	**1.2**	(1.0-1.5)
Leukemia	480	**1.3**	(1.2-1.5)	543	**1.2**	(1.1-1.3)	321	1.0	(0.9-1.1)	318	**1.2**	(1.1-1.3)	368	1.1	(1.0-1.2)	365	**1.1**	(1.0-1.3)
Unknown primary	252	**2.1**	(1.8-2.3)	179	1.0	(0.8-1.1)	89	0.4	(0.3-0.5)	159	**1.8**	(1.5-2.1)	121	1.2	(1.0-1.4)	138	1.1	(0.9-1.3)

SDPCs: second discordant primary cancers; CI: confidence interval;Only cancer sites shown in Table 1 are presented; Bold type (elevated risk) and underscored type (decreased risk): 95% CIs did not include 1.00.

Appendix Table 4. Standardized incidence ratios (SIRs) of all SDPCs after a specific first primary cancer by follow-up time after first cancer in Germany and Sweden

Sites of first primary cancers	Germany									Sweden								
	<1 year			1-4 yers			≥5 years			< 1 year			1-4 years			≥5 years		
	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI
Upper aerodigestive tract	890	**2.5**	(2.3-2.6)	1680	**2.0**	(1.9-2.1)	910	**1.8**	(1.7-1.9)	178	1.1	(1.0-1.3)	489	**1.2**	(1.1-1.3)	283	**1.2**	(1.1-1.4)
Salivary gland	46	**2.1**	(1.6-2.9)	78	**1.6**	(1.3-2.0)	43	**1.4**	(1.0-2.0)	29	**2.0**	(1.3-2.8)	47	1.3	(0.9-1.7)	34	1.1	(0.7-1.5)
Esophagus	471	**3.0**	(2.7-3.2)	290	**1.6**	(1.4-1.8)	71	1.2	(1.0-1.6)	63	**1.5**	(1.2-1.9)	66	**1.6**	(1.2-2.0)	22	**1.6**	(1.0-2.4)
Stomach	823	**1.6**	(1.5-1.7)	753	1.0	(0.9-1.1)	390	1.1	(1.0-1.2)	171	**1.4**	(1.2-1.6)	167	1.0	(0.9-1.2)	108	1.1	(0.9-1.4)
Small intestine	157	**4.7**	(4.0-5.5)	85	**1.3**	(1.1-1.6)	35	1.0	(0.7-1.4)	107	**2.5**	(2.0-3.0)	84	1.2	(1.0-1.5)	50	1.2	(0.9-1.6)
Colorectum	2376	**1.5**	(1.4-1.5)	3855	**1.0**	(1.0-1.1)	2216	**1.0**	(1.0-1.1)	954	**1.2**	(1.1-1.3)	1920	**1.1**	(1.1-1.2)	1148	**1.1**	(1.0-1.2)
Anus	110	**3.5**	(2.9-4.2)	102	**1.5**	(1.2-1.8)	57	1.3	(1.0-1.7)	20	1.1	(0.7-1.7)	48	1.0	(0.8-1.4)	43	0.8	(0.6-1.1)
Liver and gallbladder	429	**1.2**	(1.1-1.4)	289	0.9	(0.8-1.0)	89	1.0	(0.8-1.2)	143	**1.7**	(1.4-2.0)	92	**1.3**	(1.0-1.6)	34	1.3	(0.9-1.9)
Pancreas	332	1.0	(0.9-1.1)	167	0.7	(0.6-0.8)	42	0.9	(0.6-1.2)	69	1.0	(0.8-1.3)	40	1.1	(0.8-1.5)	18	1.2	(0.7-1.9)
Lung	1472	**1.1**	(1.1-1.2)	1316	0.9	(0.9-1.0)	470	1.0	(0.9-1.1)	432	**1.4**	(1.3-1.5)	442	**1.2**	(1.1-1.4)	189	**1.2**	(1.0-1.3)
Breast	1074	**1.3**	(1.2-1.3)	2933	**1.2**	(1.1-1.2)	2316	**1.2**	(1.2-1.3)	430	0.8	(0.7-0.9)	1883	**1.1**	(1.0-1.1)	1537	**1.1**	(1.1-1.2)
Cervix uteri	276	**3.4**	(3.0-3.8)	325	**1.6**	(1.4-1.8)	248	**1.4**	(1.2-1.5)	77	**1.7**	(1.4-2.1)	127	1.1	(1.0-1.4)	103	1.2	(1.0-1.4)
Endometrium	752	**3.1**	(2.9-3.3)	905	**1.3**	(1.2-1.4)	649	**1.2**	(1.1-1.3)	349	**1.7**	(1.6-1.9)	576	**1.1**	(1.0-1.2)	423	1.1	(1.0-1.2)
Ovary	564	**3.6**	(3.3-3.9)	357	**1.2**	(1.1-1.3)	198	**1.2**	(1.0-1.3)	159	**2.0**	(1.7-2.3)	183	1.0	(0.9-1.2)	146	**1.3**	(1.1-1.5)
Other female genital	164	**2.4**	(2.0-2.8)	206	**1.4**	(1.2-1.6)	81	1.0	(0.8-1.2)	40	**1.5**	(1.1-2.0)	65	1.0	(0.8-1.3)	41	1.3	(0.9-1.8)
Prostate	2204	**1.4**	(1.3-1.5)	4723	**1.1**	(1.0-1.1)	2579	1.0	(0.9-1.0)	1281	1.0	(0.9-1.0)	3878	**1.1**	(1.0-1.1)	2158	**1.2**	(1.1-1.2)
Other male genital	56	**2.2**	(1.7-2.9)	75	1.2	(1.0-1.5)	47	1.3	(0.9-1.7)	25	**1.6**	(1.0-2.4)	53	1.2	(0.9-1.6)	26	1.2	(0.8-1.8)
Kidney	1074	**2.2**	(2.1-2.4)	1723	**1.4**	(1.4-1.5)	1080	**1.2**	(1.2-1.3)	334	**1.6**	(1.5-1.8)	536	**1.4**	(1.3-1.5)	253	**1.2**	(1.0-1.3)
Urinary bladder	2538	**4.2**	(4.1-4.4)	2060	**1.6**	(1.5-1.7)	977	**1.3**	(1.2-1.4)	1013	**1.7**	(1.6-1.8)	1554	**1.3**	(1.2-1.3)	786	**1.1**	(1.1-1.2)
Melanoma	377	**1.3**	(1.2-1.4)	1087	**1.3**	(1.2-1.4)	708	**1.2**	(1.1-1.2)	216	0.8	(0.7-0.9)	862	**1.1**	(1.0-1.2)	595	**1.2**	(1.1-1.3)
Eye	34	**1.6**	(1.1-2.2)	99	**1.6**	(1.3-2.0)	47	1.2	(0.9-1.7)	14	0.8	(0.5-1.4)	64	**1.5**	(1.1-1.9)	29	1.0	(0.7-1.4)
Nervous system	65	0.5	(0.4-0.6)	68	0.5	(0.4-0.6)	39	0.7	(0.5-1.0)	88	0.9	(0.7-1.1)	296	1.1	(0.9-1.2)	260	**1.2**	(1.1-1.4)
Thyroid gland	112	**1.5**	(1.2-1.8)	315	**1.5**	(1.3-1.7)	291	**1.5**	(1.3-1.7)	50	**1.6**	(1.2-2.1)	102	1.2	(1.0-1.4)	88	1.2	(0.9-1.4)
Connective tissue	271	**2.5**	(2.2-2.8)	221	**1.1**	(1.0-1.3)	108	1.1	(0.9-1.3)	43	1.0	(0.7-1.4)	141	**1.4**	(1.1-1.6)	74	1.1	(0.9-1.4)
Non-Hodgkin lymphoma	465	**1.4**	(1.2-1.5)	888	**1.2**	(1.1-1.3)	563	**1.2**	(1.1-1.4)	231	1.1	(0.9-1.2)	625	**1.1**	(1.0-1.2)	388	**1.2**	(1.1-1.4)
Hodgkin lymphoma	60	**2.5**	(1.9-3.3)	91	**1.5**	(1.2-1.8)	88	**1.7**	(1.4-2.2)	19	1.4	(0.9-2.2)	38	0.9	(0.6-1.2)	49	1.1	(0.8-1.4)
Multiple myeloma	156	1.0	(0.8-1.2)	259	0.8	(0.7-0.9)	117	1.0	(0.8-1.2)	88	1.1	(0.9-1.4)	199	**1.4**	(1.2-1.6)	62	**1.3**	(1.0-1.7)
Leukemia	317	**1.1**	(1.0-1.3)	637	**1.1**	(1.0-1.2)	390	**1.3**	(1.1-1.4)	174	0.9	(0.8-1.0)	578	**1.2**	(1.1-1.3)	299	**1.2**	(1.1-1.4)
Unknown primary	297	**1.2**	(1.0-1.3)	159	0.8	(0.7-0.9)	64	0.8	(0.6-1.0)	161	1.1	(0.9-1.3)	189	**1.6**	(1.4-1.8)	68	1.2	(0.9-1.5)

SDPCs: second discordant primary cancers; CI: confidence interval;Only cancer sites shown in Table 1 are presented; Bold type (elevated risk) and underscored type (decreased risk): 95% CIs did not include 1.00.

***Conflicts of Interest Statement**

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DEUTSCHES
KREBSFORSCHUNGSZENTRUM
IN DER HELMHOLTZ-GEMEINSCHAFT

50 Jahre – Forschen für
ein Leben ohne Krebs

Division
Molecular Genetic Epidemiology
C050

Dr. Tianhui Chen

Im Neuenheimer Feld 580
D-69120 Heidelberg
Phone +49.62 21.42-18 05
Telefax +49.62 21.42-18 10
www.dkfz.de
t.chen@dkfz.de

Heidelberg, June 10, 2015

Dear Prof Dr. Schwab,

We would like to submit our manuscript entitled “Distribution and risk of all second primary cancers combined after a specific first primary cancer in German and Swedish cancer registries” to ***Cancer Letters*** as an Original Article.

The corresponding author, on behalf of all coauthors, has declared no conflicts of interest.

Sincerely,

Tianhui Chen

Tianhui (Thomas) Chen, MD&PhD
Division of Molecular Genetic Epidemiology (C050)
German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ)
Im Neuenheimer Feld 580 (TP3)
D-69120, Heidelberg
Germany
Tel: +49 6221 42 1805
Fax: +49 6221 42 1810

Highlights for reviewers

1. Design of population-based investigations on risk of all second primary cancers after first primary cancers in two different populations.

2. We used very large databases (covering approximately 27 million Germans and 9 million Swedes) with high quality of data.

3. All standardized incidence ratios (SIRs) in the two populations were adjusted for three identical co-variables (age, sex, and calendar period) and additionally for a regional category (12 states in Germany and 4 categories in Sweden).

4. Our data provide new evidence on the risk of all SDPCs combined after a specific first primary cancer in Germany and Sweden, which offers insight into the epidemiology, etiology and registration practices of SDPCs in different populations and validates their potential use in etiological studies.

5. We found elevated overall risks after 23 cancers (out of 29 cancers in total) in Germany and after 24 cancers in Sweden and among them, risks after 19 cancers were elevated in both populations, which may suggest common etiology of SDPCs after most of first primary cancers and similar registration practices for those cancers in the two populations.

6. We found substantially higher risk of SDPCs after urinary bladder and upper aerodigestive tract cancers in Germany compared to Sweden, which is likely due to higher incidence of smoking-related cancer for German men compared to Swedish men.

7. Decreased overall risk found only in Germany after five fatal cancers may be attributed to reporting practices or missed death data in Germany.