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Analysis of the Methodology of skin cancer incidence registration in German cancer registries

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Abbreviations

BCC: Basal cell cancer

DCO: Death certificate only

DCI: Death certificate initiated

DCN: Death certificate Notified

GDR: German Democratic Republic

GEKID: Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V.

GLOBOCAN: Global Cancer Incidence, Mortality and Prevalence

IARC: International Agency for Research on cancer

IACR: International Association of Cancer Registries

ICD-O-3: International Classification of Diseases for Oncology 3rd revision

ICD: International Classification of Diseases

JCR: Joint Cancer Registry (Gemeinsames Krebsregister in German)

M/I index: Mortality/Incidence index

MM: Malignant melanoma

MCC: Merkel cell carcinoma

NMSC: Non- melanoma skin cancer

NNS: Number needed to screen

NORDCAN: Cancer statistics for the Nordic countries

NRW: North Rhine Westphalia

RKI: Robert Koch Institute

SCC: Squamous cell carcinoma

SCS: Skin cancer screening

SGB V: Fifth Social Code book (Sozialgesetzbuch)

TNM: Tumor, Node, Metastasis

UICC: UICC (International Union Against Cancer) classifies tumors based on prognostic groups (0 to IV). A higher stage indicates worse prognosis.

US: United States of America

UK: United Kingdom

Abstract

Background: Skin cancer is one of the most common cancers in the world and yet non-melanoma skin cancer (NMSC) has been included for the first time in the world cancer Atlas (GLOBOCAN 2018). The reason for this delay is the non-uniform data collection system for skin cancer across the countries. Germany is one of the 10 countries with the highest incidence of skin cancer reported in the world. This rate is estimated based on data collected by the 16 population-based cancer registries in Germany. While Malignant melanoma (MM) is being reported since the 1960s in Germany, NMSC data always faced completion issues because of out-patient based treatment and an extremely large number of cases. The purpose of this study is to analyze the methodology of skin cancer incidence registration followed by the German cancer registries and to assess the quality of data of skin cancer and suggest improvements.

Methodology: The information was extracted from annual reports of all the German cancer registries, from the website of Robert Koch Institute, the Manual of cancer registration, through a questionnaire sent via email to all the registries and relevant articles searched on PubMed. Comparison of the methodology with that of Nordic countries was done to suggest improvements.

Results: Legislative laws for remuneration to NMSC notifications, changes in ICD coding, and not counting the multiple tumors, all affect the registration process of skin cancer and hence its reported incidence rate. Use of Mortality/ Incidence ratio as an assessment of completeness, implementation of national screening project, and the incomplete TNM staging information, directly or indirectly determine the quality of skin cancer data. This data is more complete for MM as compared to NMSC. All registries replied back to the survey and confirmed these findings. On the other hand, Nordic countries report BCC in a separate file and count multiple skin tumors.

Conclusion: There is undoubtedly a huge gap in incidence reporting of skin cancer by the German cancer registries especially for NMSC, and the estimates are not reliable. Looking at the rising incidence of skin cancer and improving survival, more efforts are needed to improve the completion of data like recording the tumor stage and site specifications. Upcoming clinical cancer registries would complement the epidemiological registries and help improve the situation in the future. Influence of screening programs should be included in the incidence reporting and moreover its continuation justified.

Keywords: Skin cancer, incidence, methodology, German cancer registry, quality of data

I. Introduction

Cancer comprises one of the highest burdens of non-communicable diseases globally with the most recent estimates for the year 2018 being 18.1 million new cancer cases (17 million excluding non-melanoma skin cancer) and 9.6 million cancer deaths (9.5 million excluding non-melanoma skin cancer) across the world [1]. This statement spots the huge burden of non-melanoma of skin cancer, although it is lung cancer which contributes to maximum mortality among cancer patients [1]. This data is derived from the international epidemiological database GLOBOCAN, which in turn receives data from cancer registries of the respective countries. Cancer registries provide the most extensive epidemiological data related to incidence, prevalence, mortality and survival rates of all cancers in a particular country, evaluation of the screening programs and the expected disease trends for future too. The decisions on health care resource allocation are based on this data which means its quality is really important.

What is GLOBOCAN?

It is an online database which provides data on incidence and mortality of various cancers across the world, publishes regular reports and is accessible online on the website 'Cancer Today'. The most recent report was published in September 2018 and gives an estimate of 36 cancers in 185 countries [1]. These countries are categorized or graded as following based on the method used to estimate the incidence and mortality rates [2]:

- ⇒ *"**1** Observed national incidence rates projected to 2018 .*
- ⇒ ***2** The most recently observed incidence rates (national (**2a**) or regional (**2b**)) applied to the 2018 population.*
- ⇒ ***3a** Rates estimated from national mortality data by modeling, using mortality-to-incidence ratios derived from cancer registries in that country.*
- ⇒ ***3b** Rates estimated from national mortality estimates by modeling, using mortality-to-incidence ratios derived from cancer registries in neighboring countries.*
- ⇒ ***4** Age- and sex-specific national incidence rates for all cancers combined obtained by averaging overall rates from neighboring countries. These rates are then partitioned to obtain the national incidence for specific sites using available cancer-specific relative frequency data.*
- ⇒ ***9** Rates estimated as an average of those from selected neighboring countries".*

One of the countries included in 'category **1**' is Germany, which means that the estimates represent 'Observed national incidence rates projected to 2018' [3]. The data on these national incidence rates are collected by the German cancer registries. In Germany, at present there are 16 population-based epidemiological cancer registries (Hamburg; Berlin, Brandenburg, Mecklenburg, Saxony, Saxony-Anhalt, Thuringia-together called Joint cancer registry; Saarland; North Rhine Westphalia; Rhineland Palatinate; Schleswig-Holstein; Bavaria; Bremen; Lower Saxony; Hesse; and Baden-Wuerttemberg) functional across the country and provide highly valuable data [4]. Incidence rates (2008-12) from nine of these German cancer registries covering >50% of the population have been projected to 2018 in GLOBOCAN [3].

A *short history and legal issues of German cancer registries*

The first cancer registry was set up as early as in 1926 in Hamburg, but the data collection was not continuous and in fact, it was only after the 'Hamburg Cancer Registry Act' in 1985 that the registry became completely functional [5]. Saarland started collecting data in 1967 and together with Hamburg registry it soon reached 95% completion but due to data protection laws, the registration process had to be stopped in 1977-78 which was later resumed in 1979. It was the only registry providing good quality data until 1990 and the incidence rates for Saarland were extrapolated to the entire West German population [6]. East Germany had a much better central data collection system called 'National cancer registry of GDR-the German Democratic Republic' but after reunification of the two: East and West Germany in 1990s, the data collection by the National cancer registry of GDR suffered major setbacks because of changes in the health care system and legal issues with the establishment of new states. It was only after the Federal Cancer Registry Act 1995 was passed, that all the states were obliged to establish population-based cancer registries by the end of 1999. Later another law, the 'Federal Cancer registry Data Act' 2009 (Krebsregisterdatengesetz in German), established a legal basis for uniform, comprehensible data collection by all the registries and transmission of data to the Robert Koch Institute (the center of cancer registry data) [6].

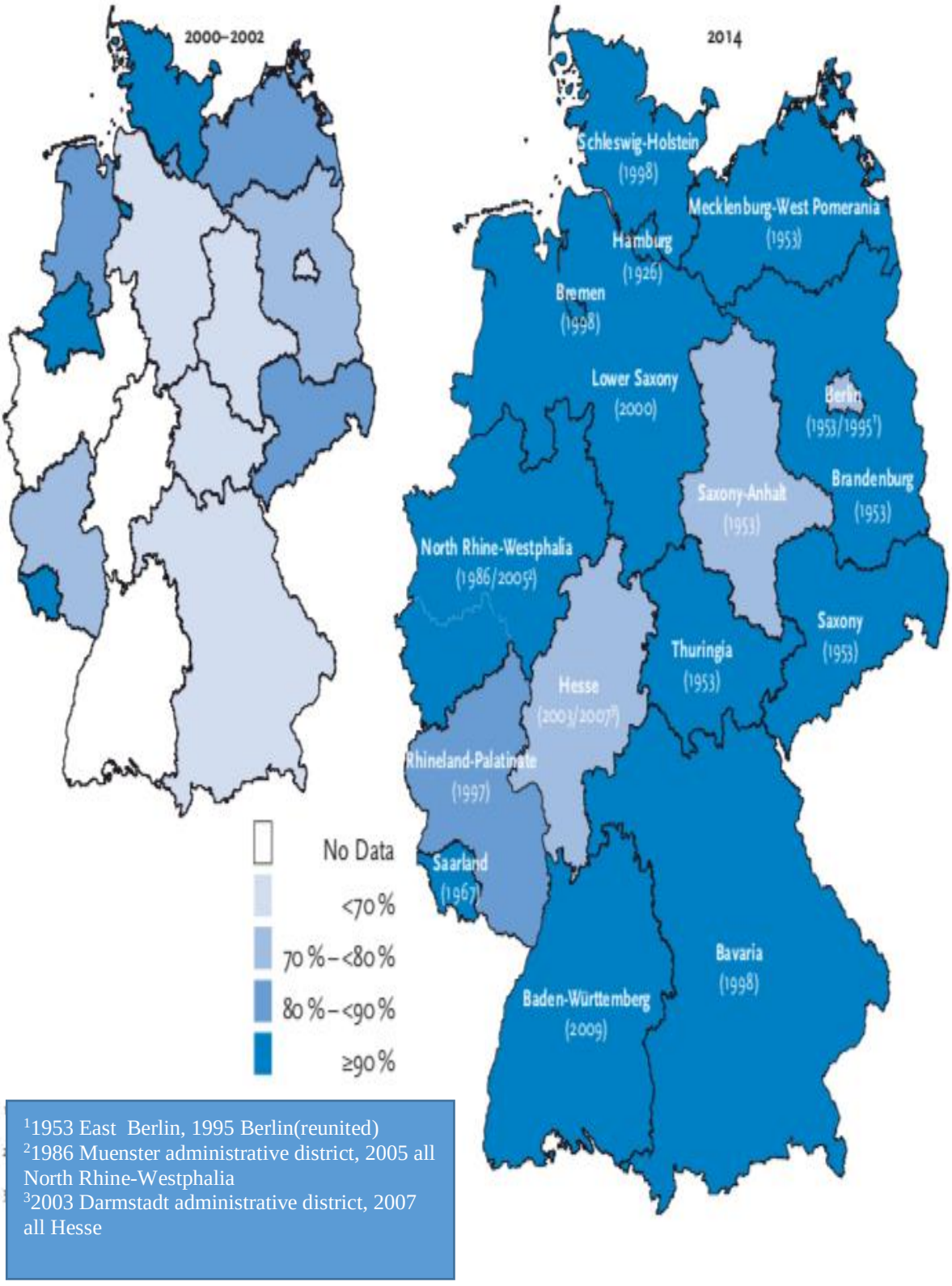

Figure 1: Map of Germany showing the various epidemiological registries (source Cancer report Germany 2013-14) [4]. The number in brackets represent the year of establishment of the respective registry and different colors represent completeness level of each registry.

As can be seen in the map (Fig. 1), the 16 registries were set up over decades in Germany with the last one established as late as in 2009 in Baden Wuerttemberg. The map points out well how the registries have made progress from 2000-2002 to 2014 and the regions like North Rhine-Westphalia (NRW) and Baden Wuerttemberg which reported no data in 2000-2002, or regions like Thuringia, Bavaria and Lower Saxony which had <70% completeness in 2000-2002, reached the ≥90% target in 2014. The registries established 5-15 years back are labeled as 'young registries' and include those in regions of Hesse, Baden Wuerttemberg and NRW [4]. Later another law §65c SGB V KFRG (Krebsfrüherkennungs- and -registergesetz in German) under 'The Cancer Awareness and Registration Act' in April 2013, directed the federal states to set up clinical cancer registries to improve the quality of oncological care [7]. The main task of clinical registries is to collect data for epidemiological cancer registries. The KFRG directs a collaboration between epidemiological and clinical cancer registration, but the logistical and organizational regulations in each federal state are in hands of the regional policymakers. This was necessary because of the pre-existing differences between federal states, for example in Bavaria and new Federal states, the epidemiological cancer registration was based entirely on data collection from clinical cancer registries, while in the northern German federal states and Saarland, there were already well- established epidemiological registers running for a long time [7]. According to the latest status of registries in January 2018 [7], the two forms of registries are integrated with each other in Schleswig-Holstein, Saarland, Rhineland Palatinate, NRW, Hesse, Hamburg, Bremen, Bavaria, and Baden Wuerttemberg but not in the Joint cancer registry area (6 registries).

Cancer burden in Germany

Looking at the cancer burden in Germany, according to the GLOBOCAN report 2018, breast, prostate and lung cancers have the highest age-standardized incidence rates (ASR) [3]. But what is important to notice is that Non-melanoma skin cancer (NMSC) and Malignant melanoma of the skin (MM) are ranked 4th and 5th respectively. A critical observation in Table 1 is that though the ASR of NMSC incidence is lower, the absolute incidence exceeds even that of the breast cancer (77 272 vs 71 888) which has the highest ASR and yet Basal cell carcinoma has not been included in these NMSC rates.

Table 1: Incidence rates for common cancers in Germany (source Cancer Today)[3]

	Absolute incidence	*ASR* per 100,000*	*Crude rate per 100,000*
Breast	71 888	85.4	172.2
Prostate	62 641	63.2	154.5
Lung	66 749	33.7	81.1
NMSC (excluding BCC)	77 272	27.5	93.9
MM	31 432	21.6	38.2
Colon	36 956	15.7	44.9
*standardized to world population			

After studying more details of this high crude rate of skin cancer, it was found that Germany is one of the 10 countries with the highest incidence of skin cancer reported in the world according to GLOBOCAN [3]. Though the incidence and the prevalence rates for NMSC and MM are high, NMSC (excluding basal cell carcinoma) contributes to only 0.3% of overall mortality due to cancer in the country and MM to 1.6% of cancer-related deaths [3]. Many studies from Germany have proven the rise in incidence of skin cancer over years. A study by Rudolph et al., 2015 [8] evaluated the NMSC incidence trends in 14 federal states of Germany from 1998 to 2010 and found that the rates increased from 3.1 to 105.2 cases per 100 000. Leiter et al., 2017 [9] analyzed the increase in age-standardized (European standard) and crude incidence rates of NMSC based on data obtained from the registries of Schleswig-Holstein from 1999 to 2012 and Saarland federal state from 1970 to 2012. The study showed an increase in ASR of NMSC incidence by 10-fold in Saarland and 1.5-fold in Schleswig-Holstein. According to the Cancer Report 2013/14 [4], the estimated incidence rate of MM in Germany for 2014 in both the genders increased five times since the 1970s. Looking at the data in GEK*ID* (Association of Population-based Cancer Registries in Germany) atlas [10], which provides age-standardized incidence rate estimates of MM and NMSC respectively from 1995 to 2015, it is apparent from both Tables 2 and 3 that data from many German cancer registries was missing until 2002 due to the simple fact of their late establishment (as seen in Fig.1) [4] or other legal issues mentioned earlier. It is also clear that the incidence rate of NMSC is much higher as compared to MM and both have shown an increasing trend over the years.

Table 2: Age-standardized estimate of MM incidence rate per 100,000 in various regions from 1997-2013 (source GEKID atlas)[10]

Year	1997		1998		1999		2000		2001		2002		2003		2004		2005	
Gender	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Region																		
Baden-Württemberg																		
Bavaria											15.54	13.99	14.71	13.8	16.18	14.93	16.31	15.61
Berlin	7.2	4.7	8.9	6.4	8.8	7.4	10.4	7.4	8.6	9.1	9.2	8.3	10.14	8.59	11.09	8.15	12.99	8.62
Brandenburg	8.9	7.7	9.7	8.6	9.5	9.5	9.7	9.9	12.3	9.9	10.5	9.2	11.13	10.21	10.25	9.68	11.83	9.82
Bremen							9.6	13.7	9.4	11.7	12.7	10.8	13.82	11.69	14.14	8.35	17.36	11.89
Hamburg	11.8	12.3	12.1	13.9	11.3	12.0	15.7	13.5	14.5	16.8	17.2	16.9	16.53	15.69	14.36	15.24	17.57	17.55
Hessen																		
Mecklenburg-Vorpommern	8.3	9.8	7.0	7.0	11.4	11.6	9.7	7.6	8.6	9.4	9.4	11.9	10.68	8.77	11.29	8.88	10.95	12.26
Lower Saxony													15.81	19.08	16.48	16.63	17.3	17.72
NRW																		
Rheinland-Palatinate			10.5	8.7	11.2	9.2	13.4	12.5	13.1	15.2	15.6	15.6	15.87	16.28	14.41	16.54	18.3	19.21
Saarland	0.6	0.7	9.6	8.4	9.8	8.8	10.8	9.2	9.2	10.9	12.5	11.3	12.07	10.18	11.93	11.71	10.55	10.55
Saxony	11.3	9.1	10.4	9.6	12.8	9.4	14.0	11.4	12.5	11.2	11.5	11.9	12.38	10.88	12.53	9.87	11.23	9.56
Saxony-Anhalt	8.4	8.7	8.6	10.2	9.5	9.3	8.8	9.6	10.7	10.1	10.2	8.1	9.59	9.29	10.47	11.04	10.28	11.52
Schleswig-Holstein			15.3	17.8	16.6	19.6	21.1	19.0	18.9	22.2	17.1	19.0	18.45	24.29	20.7	22.33	17.46	17.24
Thuringia	11.3	9.9	10.1	9.1	9.4	9.0	11.3	9.9	11.9	9.9	10.5	11.2	13.75	12.37	13.7	11.92	15.38	11.63
Germany													13.68	14.44	14.52	13.91	14.92	14.5

M=Male; F=Female

Table 2 continued……

Year	2006		2007		2008		2009		2010		2011		2012		2013	
Gender	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Region																
Baden-Württemberg															19.91	16.19
Bavaria	16.43	15.06	16.94	15.5	20.16	17.08	20.86	17.32	21.9	19.18	22.04	19.63	21.44	19.55	21.76	18.66
Berlin	12.18	9.22	10.27	7.29	9.85	7.88	10.5	7.27	12.83	10.82	11.23	10.51	11.57	10.8	12.13	10.56
Brandenburg	9.93	10.09	11.43	10.64	13.27	11.87	16.55	11.43	14.05	13.14	14.77	12.19	15.5	14.49	14.88	12.82
Bremen	12.76	10.07	15.47	15.27	25.38	21.7	14.64	15.52	17.62	20.4	17.29	12.82	15.2	8.06	13.48	14.17
Hamburg	13.8	13.27	14.46	14.57	16.42	16.28	18.21	16.43	17.67	15.42	16.03	14	14.7	12.15	14.88	11.49
Hessen					22	20.39	20.92	20.26	20.5	19.33	21.52	19.38	21.6	22.11	21.73	19.62
Mecklenburg-Vorpommern	13.15	13.32	12.45	11.25	12.7	14.68	14.26	14.35	13.32	15.87	15.21	14.83	14.78	15.09	14.75	15.64
Lower Saxony	15.65	17.86	16.83	19.15	22.27	22.65	21.55	22.93	21.08	24.36	22.62	23.93	21.48	22.43	22.38	22.89
NRW					19.11	20.83	20.96	23.87	20.42	22.34	23.02	24.16	22.91	25.04	21.22	24.28
Rheinland-Palatinate	17.71	18.61	17.21	20.39	23.75	20	24.07	20.99	21.46	21.74	21.47	23.43	22.97	23.83	21.39	22.27
Saarland	12.02	12.41	11.87	12.72	20.22	16.67	16.53	15.05	15.24	10.72	16.46	15.55	15.36	13.17	17.64	17.84
Saxony	12.7	10.71	13	12	15.99	12.54	16.46	13	16.03	13.36	14.71	12.7	15.71	14.35	15.09	10.82
Saxony-Anhalt	13.47	12.13	12.1	12.19	13.74	15.77	12.9	15.41	15.85	15.18	16.31	15.13	14.06	12.95	12.02	13.4
Schleswig-Holstein	16.38	16.01	15.89	16.7	17.39	19.64	18.9	19.29	17.64	19.29	18.95	20.42	20.37	19.62	20.44	18.56
Thuringia	12.87	12.51	12.83	15.25	17.18	17.73	16.29	15.79	12.36	14.18	18.12	15.7	12.96	13.9	16.43	13.3
Germany	14.53	14.24	15.08	15.25	18.59	17.49	19.04	17.76	18.77	18.64	19.65	18.58	18.86	18.28	19.27	17.51

M=Male; F=Female

Table 3:Age-standardized estimate of NMSC incidence rate per 100,000 in various regions from 1997-2013(source GEKID atlas)[10]

Year	1997		1998		1999		2000		2001		2002		2003		2004		2005	
Gender	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Region																		
Baden-Württemberg																		
Bavaria											27.9	14.1	31.9	18.4	37.7	22.2	38.6	22
Berlin	16.1	9.2	22.6	13.4	24.9	14.7	23.7	13.8	20.8	12.5	21.1	13	25.2	17.1	27	19	35.5	24
Brandenburg	41.9	26.7	48	27.4	52.5	35.6	59.3	40.1	55.8	41.3	60.9	44.3	67.1	47.1	74	52.5	81.8	55.9
Bremen							45.7	33.8	98.5	76.8	139	90.3	128.1	87	131.9	96.1	141.1	87.5
Hamburg	59	39	72.6	45	74.8	52.6	78.8	53.7	81.6	56.4	92	60.2	87.7	63	92.2	68.2	91.3	66
Hessen																		
Mecklenburg-Vorpommern	19.8	14.8	32.7	24.3	43.9	28.6	48.5	39.2	62.9	44.9	78.9	59.2	78.3	63.1	75	57.8	96.8	76.4
Lower Saxony													96.9	69	109	78.2	116.1	82.4
NRW																		
Rheinland-Palatinate			68.8	41.9	72.7	44.6	95.1	62.3	108.8	68.2	116.7	77.4	121.9	85	126.1	89.5	152.7	106.3
Saarland	93.8	66.8	79.3	57	86.7	57.2	80.3	51.4	88.4	49.8	79.7	56.5	83.2	62.3	87.9	59.3	92	61.5
Saxony	35.5	21.2	47.3	27.6	53.6	32	63.1	35.8	64.7	39.8	75.4	43.3	72.8	48.8	74.1	50.6	78	49.9
Saxony-Anhalt	35.6	23.3	32.7	22.6	39.1	24	51.4	30.4	57.8	39.5	58	36.8	55.6	37.3	56.3	38.6	58.1	39
Schleswig-Holstein			125.2	82.4	125.7	91.8	123.4	92.3	137.7	93	136.9	95.6	146.6	111.8	159.4	117.7	159.2	122.1
Thuringia	17.4	11.9	19.7	11.6	18.6	10.5	21.7	11.8	25.4	15.3	28.7	16.3	41.7	26.6	54.1	31.7	46.7	29.5
Germany													70.9	49.1	78.2	53.7	81.9	56.4

M=Male; F=Female

Table 3 continued……

Year	2006		2007		2008		2009		2010		2011		2012		2013	
Gender	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Region																
Baden-Württemberg															64.1	42.7
Bavaria	41.6	24.9	45.3	27.7	55.8	34.3	61.5	37	61.1	37.9	57.9	38.3	54.3	36.1	47.1	30.5
Berlin	38.4	25.1	46	31	56.9	38.5	66.7	49.3	61.5	45.6	63.5	52.9	69.8	54.2	66	52.3
Brandenburg	79.9	55.3	85.4	60.8	90.5	62.6	97.6	68.8	97.5	65	102.8	76.1	108.2	76.8	109.1	77.5
Bremen	142.2	104.4	161.2	118.6	162.3	121.3	171.3	124.2	152.6	112.5	156.7	115.4	123.4	90	122.4	87.9
Hamburg	86.4	72.4	103	75.4	121.8	96.2	139	105.3	125.6	104.6	129.5	108.7	108.2	90.7	119	102.3
Hessen					180.4	123.1	189.5	135.2	175.6	126.4	174	123.1	175.3	129.8	171	127.9
Mecklenburg-Vorpommern	119.4	82.3	112.3	87.4	117.8	94.3	126.4	100.4	125	99	139.5	111.1	147	116.1	151.9	119.7
Lower Saxony	118.4	85	121.7	91.4	147.3	109.2	153.9	114.6	142.2	108.6	160.9	120.3	162.7	125.6	175.2	138.2
NRW					160.3	116.7	196	146.5	186.2	137.8	200	149.5	194.7	150.2	187.4	148.5
Rheinland-Palatinate	153.1	108.8	159.8	114.9	182.1	128.2	184.5	134	180.6	134.5	185.7	141.4	183.9	135	174.2	136.6
Saarland	88.8	68.1	92.4	67.6	119.5	83.5	125.2	98.7	137.5	95.7	146.5	114.2	135.3	106.9	141.2	115
Saxony	89.2	56.2	93.9	63.4	110.4	73	115.8	81	122	78.2	124.7	88.4	132.1	84	123.6	86
Saxony-Anhalt	54.2	35.8	61.8	43.5	69.4	46.6	65.1	44.3	62.5	39.6	51.7	32.5	54.8	33.9	50.5	37.9
Schleswig-Holstein	150.8	120.7	151.8	118.4	159.2	131.6	169.5	135.6	163.1	131.5	176.6	134.6	172.6	136.8	166.8	132.1
Thuringia	55.4	31.3	66.9	38.8	79.2	49.9	92.8	64.4	87.2	58.3	92.6	61.6	96.1	62.1	98.9	62.9
Germany	86.4	59.9	90.9	64.2	104.9	75.4	113.9	81.3	109.6	78.6	116.1	84.8	115.4	84.1	114.8	85.8

M=Male; F=Female

General overview of skin cancer

Disease burden in world: Skin cancer is one of the malignancies with rapidly rising incidence. As reported by WHO, one out of every three cancers which are diagnosed across the world is a skin cancer and according to the Skin Cancer Foundation Statistics, it is estimated that one in every five Americans will suffer from skin cancer [11]. Analysis of registry data from 1982 to 2011 from six populations (US Whites, United Kingdom, Sweden, Norway, Australia, New Zealand) has shown that melanoma rates in the US, UK, Sweden, and Norway have increased by >3% annually [12].

Disease characteristics: Skin cancers are divided into two broad categories malignant melanoma (MM) and non-melanoma skin cancers (NMSC) which further includes basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) and other less common types like Merkel cell carcinoma, Kaposi sarcoma, cutaneous lymphomas etc. [13]. The basis for this categorization is the cell of origin of these cancers. MM arises from the *melanocytes* while NMSC such as BCC and SCC originate from the *keratinocytes*. MM is an invasive tumor with a very high risk of metastasis. Various etiological factors responsible include UV radiation, either due to excessive sun exposure or indoor tanning, fair skin, family history, multiple moles (dysplastic naevus syndrome), and immuno-suppression [14]. MM is best treated if detected in early stages and treatment is mainly directed by the thickness of skin involved (Breslow's thickness). It includes surgery and/or chemotherapy depending upon the state of metastasis [15]. BCC or commonly also known as 'rodent ulcer', on the other hand, is a locally invasive tumor with very rare metastasis. The major risk factor being UV exposure, these cancers are mostly seen on the sun-exposed areas such as the nose, face, shoulders, and back [14]. Treatment mainly includes surgery in the form of local excision [15]. SCC is another locally invasive skin cancer most commonly seen in sun-exposed areas with the main etiological factors being UV exposure and immunosuppression. The risk of metastasis is much higher than BCC. Treatment includes surgical excision with clear margins (Mohs micrographic surgery) and radiation therapy if indicated [14,15]. Merkel cell carcinoma (MCC) is a rare but aggressive skin tumor and originates from *neuroendocrine cells*. The risk factors predisposing to MCC include whites with European ancestry, history of PUVA irradiation like in psoriasis patients, UV radiation, immunosuppression etc. The prognosis and treatment of MCC depend on the stage of the disease [13].

A distinct finding in the GLOBOCAN report is that, in spite of the rising incidence, NMSC (still excluding BCC) rates have been included for the first time in the report. Ferlay et al., 2018 [2] warned that the estimates in GLOBOCAN for NMSC should be interpreted very cautiously as they are based on data from national cancer registries which show widespread differences in the completion of NMSC registration. The same fact gets confirmed for Germany from the study by Rudolph al., 2015 [8] mentioned earlier which was one of the first studies to assess NMSC incidence in the country. In this study, data could be obtained for the entire period of 1998- 2010 from eleven cancer registries (Berlin, Brandenburg, Bremen, Hamburg, Mecklenburg-Western Pomerania, Rhineland-Palatinate, Saarland, Saxony, Saxony-Anhalt, Schleswig-Holstein, and Thuringia). Lower Saxony provided data from 2003 to 2010 while two other registries had data only for some selected regions (Bavaria for Oberpfalz and Mittelfranken and North Rhine-Westphalia for Muenster) from 2006 to 2010. Two newly established registries (Hesse and Baden-Wuerttemberg) could not provide any data at all. In the study by Leiter et al., 2017 [9], Saarland was the only registry which provided data since 1970 for NMSC. So both the studies prove the lack of uniformity in NMSC data collection across German registries.

Why this non uniformity in NMSC data collection?

The reason is that incident cases were either not registered by the local registries or even if registered were not reported as the data was considered to be incomplete [4]. One of the explanations for this incompleteness is the characteristic feature of NMSC i.e. treatment is mostly out-patient based and then there are practical problems in collecting data on such a huge number of cases (211 600 incident cases of NMSC after including BCC in Germany in 2013 compared to 21 410 cases of MM according to Cancer report 2016) [16]. Also, the case fatality rate of NMSC is very low leading to its ignorance while MM mortality is still high especially if diagnosed in advanced stages. But it is rather important to look at the cost of resources imposed by NMSC even with such low mortality rates. According to a 2003 study [17], the hospitalization costs for NMSC in Germany ranged from 105 to 130 million Euros which was almost double as that for MM. The difference between registration of MM and NMSC in Germany gets highlighted from the fact that the incidence of MM has been registered separately since the late 60s in Saarland registry and a Central Malignant Melanoma registry (CMMR) was established in Berlin for registering MM cases in 1983 by the German Dermatological society [18].

In spite of the incomplete data on skin cancer, Germany was the first country to introduce skin cancer screening at a national level. It started in mid-2008 according to which men and women ≥35 yrs. with compulsory health insurance undergo skin examination every 2 years by a physician, either by a dermatologist or general practitioner [19]. The influence of this screening program also needs to be taken into consideration to understand whether the rise in incidence is due to actual increase in the number of cases or due to better registration procedures and early detection of cancer.

So, taking into account the above arguments, it can be inferred that many factors, for example, the history of registries, nature of the disease, screening programs can influence the estimation of the skin cancer incidence rates, and affect the quality and reliability of this data. The extreme numbers for skin cancer mentioned like in the Cancer report 2016 [16] can have a direct impact on a governments' decisions over the use of resources and therefore it is necessary to get accurate estimates. Also evident is the lack of registration of NMSC in Germany. So it is important to understand the elements which make the true estimation of NMSC incidence rates more difficult and different from MM and overall challenges faced with skin cancer registration. And, in order to understand NMSC registration issues, that of MM would also need to be studied in detail.

II. Objective

The purpose of this study is

a. To understand the methodology of skin cancer incidence registration followed by the German cancer registries and its effect on incidence estimation.
b. To study the differences in the registration of malignant melanoma and non-melanoma skin cancer.
c. To study the differences in the quality of data for malignant melanoma and non-melanoma skin cancer.
d. To suggest improvements.

III. Methodology

All the German cancer registries publish regular annual reports on the incidence, mortality and survival rates of various cancers. The information on the registration methodology used by the registries and data quality assessment for MM and NMSC (SCC and BCC only as other skin cancers are very rare) was collected from the latest annual reports available on the website of each cancer registry till October 2018 [20-30]. General facts about the methodology of cancer incidence estimation and evaluation of data quality of the registries is available on the Robert Koch Institute website [31], in its report Cancer in Germany for the years 2013/14 [4] and 2016 [16] and also in the 'Manual of cancer registration' [7] available on GEK*ID* website. The skin cancer incidence trends from 1995 to 2015 were obtained from GEK*ID* atlas [10]. A questionnaire (attached in Appendix) was developed based on the queries arising from these annual reports and a contact list for all the registries was prepared from the information available on the GEK*ID* website (https://www.gekid.de/members). The questionnaire was sent to all the registries in August 2018 and a reminder was sent to the respective person if no reply was received within 2 weeks. The registries which did not respond after 2 reminders were approached telephonically. In the survey itself, the name of a person was asked who could be contacted further to answer any more queries and follow up questions were sent via email. In order to suggest improvements, the methodology used by the German cancer registries was compared with that of cancer registries in Nordic countries which claim to have complete data for last 60 years [32]. The information on methodology followed by the registries of Denmark, Norway, and Sweden was extracted from the NORDCAN database [32] and the main reference article Pukkala et al., 2017 [33]. These three registries were also contacted with information requests via email to understand their system of registration and data quality measurement tools for skin cancer in particular used by them. Relevant articles were looked for in PubMed, and in the references of the annual reports, in the Manual of cancer registration 2018, and further articles and research materials as suggested in the survey by the registries. Tables and graphs were prepared using MS Excel ver. 2016.

IV. Results

Epidemiological and clinical cancer registration in Germany has different historical development and legal bases as mentioned already in the introduction. Although clinical cancer registries have started operating in all federal states, not all of them are fully functional and are still in developing stages. Therefore the data from clinical cancer registries are neither yet well-structured nor of comparable quality [7]. The results in this study are hence mainly based on epidemiological registries.

Common registration procedure followed by registries for all cancers

This information was collected from the Manual of cancer registration [7] which explains in detail each step of the registration process and the European Network of Cancer Registries (ENCR) report on NRW [34] which is issued by the ENCR experts after conducting reviews of registries such as for NRW in 2010 and for Bremen in 2003 [35]. The procedure mentioned here is similar in all registries with very few differences. A registry collects data passively and receives notifications from various sources including hospitals, oncologists, dermatologists, radiological and pathological institutes. All notifications are electronic (paper form in case of upcoming registries in certain regions) and any incomplete information can be traced back by the registries by contacting the provider. Since it is not allowed to disclose the identity of the patient, all the data is first converted into codes, the process is called ‘pseudonymization’. A patient’s details are forwarded from the physician’s server to the pseudonymization server and the pseudonyms are further sent to the registry. Then it goes through a ‘linkage process’ to identify potential matches to the incoming notification and a certain proportion of these linkages (20% in case of NRW registry) have to be handled manually to look into the uncertainties. After this manual processing of the notifications, to identify whether they are for the same person or for the same tumor, finally the ‘best- of- tumor’ is chosen and in case of any changes, these are informed back to the coding registrar. Regular monthly meetings are held to discuss such discrepancies. The data is then uploaded into a database and the common variables recorded include gender, month and year of birth, postal code and place of residence at the time of diagnosis, nationality, month and year of diagnosis, occasion of cancer diagnosis (e.g. screening), tumor diagnosis (coded as per ICD-10), histology and site of cancer, history of previous cancer, stage, histological confirmation of diagnosis,

type of primary therapy, month and year of death, causes of death (coded as per ICD-10), autopsy findings [34].

Results specific to skin cancer

The annual reports and feedback to the surveys from the registries showed many factors on which the skin cancer incidence rates and the data quality are dependent. The information collected reflects the differences between the registries in MM and NMSC incidence registration and also between the two types within a registry itself. An important fact was highlighted by the cancer registry of Bavaria that though GEK*ID* atlas mentions the incidence of NMSC for all federal states but these are just "estimates" and not the actual "counted" incidence, as in the state of Bavaria itself, NMSC data is collected only in three (Middle Franconia, Upper Palatinate, and Lower Bavaria) out of seven administrative regions but in GEK*ID*, these regional estimates have been projected to the whole of Bavaria and hence might not reflect the true incidence. In fact the national estimates for NMSC in Germany are still based on data from only "those German cancer registries which showed a deviation of <25% of age-standardized incidence rates from the federal state with highest reported incidence in the past two years (Schleswig-Holstein, Lower Saxony, North Rhine-Westphalia, Hesse, Mecklenburg-Western Pomerania and the Rhineland Palatinate)" [4]. Also all the registries filled in the survey and the details are described later in 'response evaluation of survey' section. The findings from German cancer registries are elaborated below under the headings of factors influencing the registration, quality of the data and response evaluation of the survey followed by the comparison with Nordic countries.

Factors influencing skin cancer registration and incidence rate

1. Legislative laws governing the skin cancer data collection

§ 65c Social Code Book V for the Clinical cancer Registries lays down the rules for payment by the Statutory insurance for tumor notifications [36]. In the Code Book Paragraph 4, it is stated that if a clinical cancer registry meets the following criteria of eligibility (point 2 and 3 in paragraph 2 of the Code Book),

> *Paragraph 2 Point 2) "The minimum requirements for the level of coverage and completeness of the different categories of data referred to in paragraph 1 point 1, as well as the necessary data validation procedures";*

Paragraph1 Point 1) "The personal data collection of all inpatient and outpatient care in a regionally defined catchment area on the occurrence, treatment and course of malignant neoplasms including their early stages as well as benign tumors of the central nervous system according to Chapter II of the International Statistical Classification of Diseases (ICD) and related health problems with the exception of data from cases of illness to be reported to the German Childhood Cancer Registry".

Paragraph 2 Point 3) "A uniform procedure for the feedback of the evaluation results to the service providers",

then the health insurance pays 119 Euros to the registry for each new tumor reported to the registry **except for NMSC and its early stages.**

Paragraph 6 states that for each notification of the clinical data made to the cancer registry which meets all the criteria mentioned above, a reporting fee has to be paid to the service providers by the respective cancer registry for all cancers **except for the NMSC and early stages** [36].

As mentioned earlier, the § 65c SGB V is for clinical cancer registries which are still developing and not uniformly running across all federal states and so are the rules governing these registries. According to the recommendations for epidemiological registries on the GEK*ID* website last updated in 2011, the third recommendation [37] states that "all epidemiological registries should comprehensively register other skin tumors (C44)" which by definition includes NMSC.

So although registration is recommended for NMSC by GEK*ID*, no reimbursement for NMSC notification by clinical registries can result in underreporting of these cancers by service providers especially in those regions where clinical registries are the only source of data collection and hence lead to underestimation of the incidence rates.

2. Source of data

It is important to cover maximum sources of data which means wherever a cancer patient may visit so that no case is missed. Mostly this information can be obtained from hospitals but for cancers like skin cancers which do not always require patients to be hospitalized, this source is not sufficient. Similarly the pathology reports may be missed from path labs because some of dermatologists or specialists conduct their own histopathology examinations, therefore inclusion of dermatologists was essential [34]. In many cases when

the cancer is diagnosed in end stage or in very old age like SCC, the cases may not be referred by the general practitioners to hospitals or oncologists. So missing those practitioners can also result in underestimation of incidence.

A method used by the registries to fill in the gap of the cases missed during routine registration is the inclusion of the 'Death Certificate Notified' (DCN) cases [7]. DCN cases are patients who are diagnosed with cancer only after death. A traceback is run on DCN cases and if the follow up does not reveal any further information, they are then recorded by the registries as new incident cases from the time of death as 'Death certificate only' (DCO) cases. If the cases are successfully investigated, then they are referred to as 'Death certificate initiated' (DCI) cases. The traceback for DCN cases is not regularly run by all the cancer registries as was confirmed in the survey too (Table 6). Also in the context of skin cancer, it is important to take into consideration the very low case fatality rate of skin cancer especially NMSC (approx. 3000 per year of which >80% is contributed by MM) [19] and therefore, DCN cases might not serve the purpose of finding the cases missed during routine registration of skin cancer. There is another drawback that the year of death in DCO cases does not correspond to the actual year of diagnosis [7]. Moreover the death certificates do not differentiate between the type of NMSC which makes it even more difficult to classify these cases [4] and hence again affecting the estimated incidence.

3. Coding of skin cancer

The registries use both ICD-10-GM (International classification of diseases German modification) and ICD-O-3.1 code (International classification of diseases for Oncology-3.1 revision updated in 2011) for coding the tumors [38]. Using the same coding system implies uniformity in case-definition across registries and reassures comparability with international data. While ICD-10 system was only based on the topography i.e. site of the tumor, ICD-O-3.1 combines information on topography and morphology of the tumors. The topographical ICD code definitions of MM and NMSC are described below:

Malignant Melanoma (MM) of skin [39]

For melanoma, the ICD code is C43 and according to the specific location (subsite) of the tumor such as lip, eyelid including canthus, ear and auditory canal, other unspecified parts of face, scalp and neck, trunk, upper limb, lower limb etc., a 4th character (0 to 9) is added to the code and it ranges from C43.0 to C43.9. The definition excludes-

1. Melanoma in situ (D03)
2. Malignant melanoma of skin of genital organs (C51-52)

3. Merkel Cell ca. (C4A)

Non-melanoma skin cancer (NMSC) [40]

NMSC is coded as C44 and similar to MM, the code varies from C44.0 to C44.9 depending upon the site involved. The definition includes-

1. Malignant neoplasm of sebaceous glands
2. Malignant neoplasm of sweat glands

and excludes-

1. Kaposi's sarcoma of skin
2. Malignant neoplasm of skin of genital organs
3. Merkel cell carcinoma

It is important to notice that only a few sites of the face have specific codes while the rest get included in the code for unspecified parts of the face. This might not influence the overall incidence rate of skin cancer but becomes significant for calculating the frequency of tumors of specific sites [41].

In the ICD-O-3 system, the topography code is same as the ICD-10 code, morphology code which represents the histology (e.g. basal cell or squamous cell carcinoma) is indicated by the first four digits in the code, behavior of tumor (whether malignant or benign or carcinoma in situ) is indicated by the fifth digit separated from the histology key by a slash and histological grading/differentiation of the tumor is indicated by a sixth digit [42]. The ICD-O-3 codes for MM and NMSC are extensive and are briefly described here:

MM: 8720-8790

BCC: 8090-8098

SCC: 8050-8078, 8083-8084

Unspecified carcinoma: 8010-8035

It is obvious that registries earlier followed the ICD-10 principles, and then adopted ICD-O from 2000 onwards and the further revisions over time, which contributed to the difficulty in the classification of some tumors affecting the registration of cases [38]. A coding manual for the interconversion between the two coding systems is mentioned on the RKI website, still in some cases this conversion can be difficult especially if it requires more information to be collected to convert the codes and this backdate information might not be always available [43]. An important distinction between the two coding systems in relation to skin cancer is that C43 is no longer a part of ICD-O-3, so the topography code for MM

is also C44._(same as NMSC) [42]. The differences between the registries, and difficulties faced due to changing coding system get reflected from the fact that on the Saarland cancer registry website (http://www.krebsregister.saarland.de/datenbank/ datenbank.html), the tumors are still coded according to ICD- 9, which has been retained as per the latest annual report of Saarland 2006 to include the tumors registered before the coding system was changed in 1997 [22] while rest of the registries report as per ICD-10 system. Furthermore, there is another coding system ICD-11 soon to be introduced [4].

4. Coding rules for multiple tumors

German cancer registries follow "International Rules for Multiple Primary Cancers (ICD-O Third Edition)" IARC report 2004 to code multiple tumors [7]. This is particularly important for skin cancers because of a high probability of developing new cancers in patients already treated for NMSC (67.8% according to an Australian study) and even more so in patients with multiple NMSC at initial diagnosis (51.8% from the same study) [44].

According to IARC [45]

a) "*Cancers which occur in any 4th character subcategory of skin (C44) should be registered as multiple primary cancers".*
b) *"Only one tumor is counted even in case of multiple tumors if they involve the same organ or tissue".*
c) *"Multifocal tumors which mean masses not in continuity with each other and arising in the same primary site or tissue are to be counted only once*".

Skin is a single organ, so multiple primaries in it are counted only once. All German cancer registries confirmed in the survey that they counted only the first tumor of MM and NMSC of one histological type (Table 6). While the criteria state to count any different 4th character subcategory as separate tumor but in the coding system (ICD) many sites just get designated as unspecified tumors which therefore will not be counted as a second primary. So this is another important factor which can lead to underestimation of skin cancer incidence rates especially for NMSC.

5. Skin cancer screening program

Skin cancer screening (SCS) program was introduced nationwide in 2008 across Germany. Before the application of national program, a pilot project was run in 2003-04 in Schleswig -Holstein and due to screening, many skin cancers other than MM were detected and the

reported cases exceeded the number of expected cases (176% in 2006, 164% in 2007 and 146% in 2008 for other skin cancers). On the other hand, the registered number of cases of MM and completeness fell from 110% in 2006 to 95% in 2008 [46]. Fig. 2 and 3 show the incidence rate trends of MM and NMSC respectively in Germany from 2007 to 2014. The charts are based on estimated rates mentioned in GEK*ID* atlas [10].

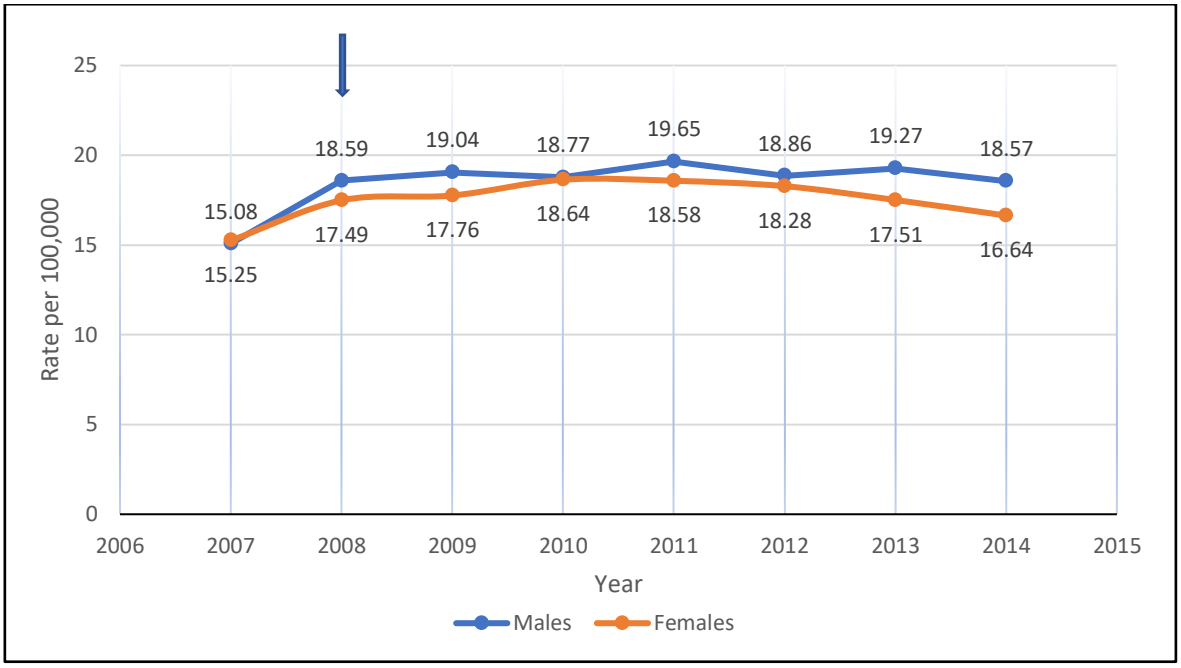

Figure 2: Age-standardized incidence rate estimate of MM per 100,000 in Germany from 2007-2014 (source GEK*ID atlas)*

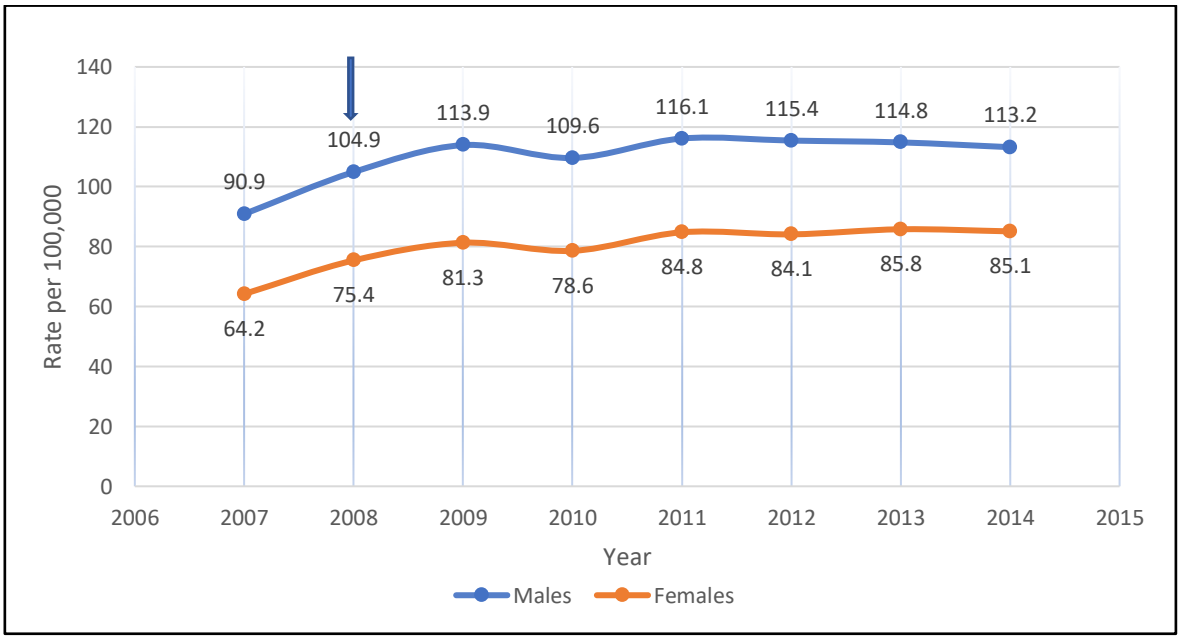

Figure 3: Age-standardized incidence rate estimate of NMSC per 100,000 in Germany from 2007-2014 (source GEKID atlas)

It is clear that there was a discrete increase in national incidence estimates in 2009 as compared to 2007 and after that the rate has stabilized. This sudden increase can only be explained by the introduction of SCS in 2008 but the influence of screening on incidence rate is not routinely mentioned in any of the annual reports of the registries. Though the impact of screening on incidence estimates is quite evident, no study so far has been able to prove if this is an actual increase in incidence rate of skin cancer or just detection of the already existing ones.

Overall Interpretation: The factors affecting the registration process and incidence estimates definitely disfavor NMSC more than MM.

Quality of skin cancer data

The data is assessed for its completeness, validity, and comparability [7]. Overall completeness and quality of the data in a cancer registry are assessed regularly by the RKI [31] based on the following criteria:

1. The proportion of histologically confirmed cases
2. The share of Death Certificates Only (DCO) cases
3. The proportion of cases with unknown primary tumor
4. The proportion of cases with an inaccurate indication of the diagnostic category
5. Mortality/Incidence (M/I) index
6. The proportion of missing information

The information on the above factors related to MM and NMSC collected from the annual reports of each registry including the diagnosis year of incidence calculation is recapitulated in Table 4 and 5 respectively and all the criteria are explained in detail afterward. The tables highlight the existing differences in the quality of data of MM and NMSC between the registries. Information for NMSC data quality could be traced back in annual reports of only four registries and for Bavaria, it was obtained by information sent via email and should be interpreted cautiously given that it is based on data from only 3 administrative regions of Bavaria while the data for MM on the respective parameters were available from all registries.

Table 4: Quality of MM data across German cancer registries [20-30]

Region		Diagnosis year	Unknown primary site	Missing/ Incomplete 'T' stage	Histological confirmation	M/I index	Completeness & Quality of data	DCO rate
Hamburg [20]		2013-15	-	40%	99.2 % (M) & 99.6%(F)	0.22 (M) & 0.44 (F)	77 % (M) & 73% (F)	2.7 % (M) & 1.9%(F)
Joint cancer registry [21]	Berlin	2009-12	2.5 % ICD-O-3 C80	40.4%	95.4% (M) & 95.1% (F)	0.23(M) & 0.16(F)	<80%	4.3%(M) & 4.5% (F)
	Brandenburg		1.3%ICD-O-3 C80	20.5%	98.1%(M) & 98.7% (F)	0.21(M) & 0.11(F)	80-85%	1.9%(M) & 1.3% (F)
	Mecklenburg		1% ICD-O-3 C80	28.4%	98.9%(M) & 97.6% (F)	0.19(M) & 0.11(F)	80-85%	0.9%(M) & 2.3%(F)
	Saxony		2.1% ICD-O-3 C80	9.1%	99.2%(M) & 98.9% (F)	0.19(M) & 0.12(F)	80-85%	0.6%(M) & 0.8%(F)
	Saxony-Anhalt		1.4% ICD-O-3 C80	43.7%	97.9%(M) & 98% (F)	0.18(M) & 0.10(F)	85-90%	2.1%(M) & 2%(F)
	Thuringia		1.1% ICD-O-3 C80	18.2%	98.7%(M) & 98.2 %(F)	0.16(M) & 0.10(F)	85-90%	1.2%(M) & 1.7%(F)
Saarland [22]		2004 - 2006	-	-	98.4%(M) & 98.9% (F)	0.23 (M) & 0.19 (F)	97.5% (M) & 99.3% (F)	1.2%(M) & 1% (F)

M=Male; F=Female; DCO= Death certified only; M/I=Mortality/Incidence index; ICD-O-3 C80=unknown primary site

Table 4 continued…

Region	Diagnosis year	Unknown primary site	Missing/ Incomplete 'T' stage	Histological confirmation	M/I index	Completeness & Quality of data	DCO rate
North Rhine-Westphalia [23]	**2013**	-	approx. 20%	86.3% (M) & 86.4%(F)	0.15 (M) & 0.1(F)	>95% (M&F)	1.5% (M&F)
Rhineland - Palatinate [24]	**2013**	-	28%(M) & 27% (F)	99.6% (M) & 100%(F)	0.2(M) & 0.1(F)	>95% (M&F)	3% (M) & 1.8 %(F)
Schleswig-Holstein [25]	**2012-14**	-	62.4.6% (M) & 60.9% (F) without UICC staging	94.3% (M) & 93.9% (F)	0.13 (M&F)	>95% (M&F)	5.4% (M&F)
Bavaria [26]	**2011-12**	-	10%	email reply 97%	-	>95% (M&F)	email reply 2%
Bremen [27]	**2009-11**	-	52.6% (M) & 52.2 %(F)	98.4% (M) & 98.5%(F)	0.29 (M) & 0.18 (F)	90% (M) & 87%(F) *	1.1% (M) & 1.05%(F)
Lower Saxony [28]	**2015**	-	9.8% (M) & 8.1% (F)	99% (M) & 99.6%(F)	0.2 (M) & 0.1(F)	93.2% (M) & 95%(F)	2.1%(M) & 1.9%(F)
Hesse [29]	**2013**	-	25.9% with unknown T stage & UICC stage missing in 78.9%.	99.8 %	0.16 (M) & 0.1(F)	80% (2008)	5.1% (M) & 4.6% (F)
Baden-Wuerttemberg [30]	**2012-13**	-	39% with missing T stage & UICC stage missing in 40%	-	-	99.7 %	-

M=Male; F=Female; DCO= Death certified only; M/I=Mortality/Incidence index;

**It is 76% for the diagnosis year 2013 according to the most recent report.*

Table 5: Quality of NMSC data across German cancer registries [20-30]

	Region	Diagnosis year	Unknown primary site	Missing/ Incomplete 'T' stage	Histological confirmation	M/I index	Completeness & Quality of data	DCO rate
	Hamburg [20]	2013	-	85 %	98.8% (M&F)	0.1	-	0.3% (M&F)
Joint Cancer registry [21]	Berlin	2009-12	-	-	-	-	-	-
	Brandenburg		-	-	-	-	-	-
	Mecklenburg		-	-	-	-	-	-
	Saxony		-	-	-	-	-	-
	Saxony-Anhalt		-	-	-	-	-	-
	Thuringia		-	-	-	-	-	-
	Saarland [22]	2004--2006	-	-	-	-	-	-

M=Male; F= Female; DCO= Death certified only; M/I=Mortality/Incidence index

Table 5 continued…

Region	Diagnosis year	Unknown primary site	Missing/ Incomplete "T" stage	Histological confirmation	M/I index	Completeness & Quality of data	DCO rate
North Rhine-Westphalia [23]	**2013**	-	-	92.7% (M) & 92.5% (F)	0	-	0.0%(M) & 0.1% (F)
Rhineland - Palatinate [24]	**2013**	-	-	-	-	>95%**	-
Schleswig-Holstein [25]	**2012-14**	-	84.2% (M) & 84.1%(F) without information on UICC stage	99.4%(M) & 99.3% (F)	-	-	0.3%(M) & 0.4% (F)
Bavaria*[26]	**2011-12**	-	-	99%	-	-	0%
Bremen [27]	**2009-11**	-	80.8% (M) & 77.3%(F)	99.6% (M&F)	0	-	0.3% (M& F)
Lower Saxony [28]	**2015**	-	-	-	-	-	-
Hesse [29]	**2013**	-	-	-	-	-	-
Baden-Wuerttemberg [30]	**2012-13**	-	-	-	-	-	-

M=Male; F= Female; DCO= Death certified only; M/I=Mortality/Incidence index

*The estimates for NMSC are based on data from only three out of seven administrative regions in Bavaria: Middle Franconia. Upper Palatinate. and Lower Bavaria

**Based on Saarland cancer registry

Completeness of data

The completeness of data has increased over the years- 12 Federal states achieved 90% completion and 7 Federal states achieved 95% completion by 2014 which was only 65% ten years back [4]. But a high rate of capture (>90%) for a registry doesn't necessarily implicate high coverage of each cancer site, for instance, though the overall completeness of Hamburg cancer registry is >90%, for MM it is as low as 73-77% [20]. The information on the completeness of NMSC could not be found in any of the registries (explained later under Mortality/Incidence index section). Some reasons detected for the deficit in the overall completeness were the absence of laws regulating the transmission of data for patients who move out of the state of residence for treatment and also because of the late beginning of data collection by some of the registries (already mentioned in the introduction). This is reflected in the low completeness of registry in Hesse region (80% for the year 2008) and the explanation mentioned in its annual report was that 7% of Hesse patients get treated in Baden-Wuerttemberg hospitals [29].

Based on the completeness of the registries there are defined 'reference regions '. As per the definition of the RKI, a registry is labeled a reference region if it satisfies the following criteria [4]:

a) *"A minimum of 10 years of State-wide coverage duration (currently, since 1999)*
b) *Overall completeness (according to the previous method) of >90% since 1999 and >80% for each year*
c) *Average DCO% under 15% for cancer overall since 1999 or since the 6th year after the registry was established".*

At present 10 regions (Saarland, Hamburg, Bremen, Schleswig-Holstein, Lower Saxony, Bavaria, Brandenburg, Mecklenburg-Western Pomerania, Saxony, Thuringia and the administrative district of Muenster in NRW), with stable time trends and low DCO rates qualify as reference regions and are together called "reference pool" [4].

The parameters used to evaluate the completeness of a registry are discussed as follows:

1. <u>The share of DCO rate for MM and NMSC</u>

For the complete German registries, DCO rates are included from the 6th year of registration while for the incomplete registries and for first five years of statewide registration, the DCO rates are defined on basis of reference regions [4]. A very high DCO rate indicates an inefficient system of collecting data and on the other hand, a rate lower

than 1% indicates that not all death certificates are reaching the registry [7]. For all registries, DCO rates are declining with time indicating improvement in the data collection system. The recommended value by IARC for an epidemiological registry is less than 5% [7]. As seen in Table 4, for MM, DCO rate varies from 0.6% to 5.4% across the registries with the highest in Schleswig-Holstein although Schleswig-Holstein has also shown a declining trend when the previous annual reports are compared [25]. Also, as seen in the annual reports of the registries and the replies to the survey, the traceback procedure for DCO cases is not uniform across all registries (Table 6) may be a contributing factor to the differences in DCO rate among registries. Ideally, the DCO rates are not to be included during the completeness assessment [4]. Apart from JCR which mentioned clearly the inclusion of DCO rate in the completeness estimate, none of the other registries specified whether they did or did not include the DCO though, the high rates despite the registration gaps for MM point towards its inclusion.

For NMSC, the rate is reported by only 5 registries and it is even lower than MM, approaching almost 0%. Such low DCO rate does not directly imply a proficient registration system, rather reflects the few death certificates received because of the very low mortality rate of NMSC. The reason being that NMSC is common in >70-year age group [4] and death in this age group is more likely to be due to other diseases common in old age rather than due to oncological complications. So, on one hand, there is a risk of missing these cases by death registries and at the same time, when recorded on death certificates it can create a false picture of high cancer-related mortality rate.

Inference:

DCO cases are not a reliable source to detect the missed skin cancer cases or to assess the quality of data for skin cancer.

2. Mortality/Incidence index (M/I)

M/I quotient is used to assess the completeness of the registry. This is based on the presumption that the ratio of mortality and incidence for particular cancer, age group, and gender distribution, and diagnosis years remains constant across various regions in Germany and no major regional differences exist between the survival rate for a particular cancer [7]. For cancers with high case fatality rate like lung cancer, the ratio would be near to 1 and on the contrary, for cancers with a good prognosis like breast cancer, the ratio will be much less than 1. As seen in Table 4, the quotient for MM in all registries ranges from 0.1 to 0.44, indicating towards the low case fatality rate of MM (index<1) but not a

constant quotient across all regions. For NMSC, M/I index is approximate ‘0’ reported by most of the registries again suggesting an extremely low mortality rate (Table 5).

All registries can calculate the M/I index for each cancer site based on the incidence cases and age and gender-specific mortality rates and compare them with the expected ratios provided by the International Association of Cancer Registries (IACR) specific for region, gender and cancer sites or with the reference register in Germany [7]. For all diagnoses except for thyroid cancer and the MM, registries with a degree of capture of at least 90% are considered as complete. Due to strong instabilities in M/I ratio, the standard for the MM has been lowered to 80% [4]. For NMSC as the M/I index is almost zero, the information on the completeness of registry is missing for NMSC from all the annual reports except Rhineland Palatinate (also seen in Table 5) because this method is not suitable for evaluating the completeness of NMSC. Rhineland’s estimate is based on Saarland cancer registry [24] but the method used has not been clarified in the annual report.

Differences in stage distributions of a cancer across various regions can cause variability in the average survival rates too and thus question the assumption of constancy of M/I index across all regions [7]. As a lot of information was missing on stages in the annual reports (Table 4 and 5), so it is not possible to comment on the differences in the distribution of tumor stages of MM or NMSC among the federal states. Even with regional variations in the proportion of incidence of a particular site in a single diagnosis group like the incidence of involvement of different sites of skin in skin cancer can in turn affect the chances of survival and hence result in regional deviations in the "true" M / I quotients [7]. All these disparities can be further heightened because of screening programs like the national SCS in Germany.

Drawbacks: A reference index is needed. Comparison with expected values does not lead to a direct assessment of completeness. The method would fail in the absence of uniformity in the coding principles and definition of cases, and quality of care followed across different regions [7]. Another presumption is that the mortality rate among the registered and the unregistered cases is same which might not be the actual case since the unregistered cases are mostly those in advanced stages and have a poorer prognosis and thus higher chances of dying.

Inference:

Regional variations in the M / I ratio have a greater impact on the estimates of low-mortality cancers like skin cancer than for those with a high mortality rate or poor prognosis. This regional variability and low M/I ratio for MM and even lower ones for NMSC make it an unreliable method to assess the completeness of skin cancer data.

3. Log-linear model for completeness assessment

This approach is at present considered the best way to assess the completeness of a registry. It is also based on the principle of mortality and incidence relation as in M/I index and on the same presumptions but, in this approach, the age- and gender-specific polynomial trends are adjusted to the logarithmic quotients of incidence and mortality for each type of cancer [7]. The incidence/mortality data from the reference pool registries are fitted using the model to estimate age-specific incidence/ mortality ratios (I/M) and this is then multiplied with the fitted local age-specific mortality rates (modeled to age, population, and diagnosis year) to derive the expected number of cases [47,48]. Expected values are calculated for 18 diagnosis groups, 5 age groups, both sexes and each diagnosis year [7]. Then the expected incidence is compared with that observed in the local region. In the case of very low mortality (<5 deaths per year), the modeled incidence from the reference region is used for the respective age and diagnosis group as the expected number of cases instead of using I/M quotient for calculation [4]. Haberland et al. [5] applied this method to the completeness estimation of the individual state registers in Germany. GEK*ID* estimated the completeness of all registers using this method in 2002 based on the data of the state cancer registries for the diagnostic years 1997-1999 [7]. Since the calculations are extensive, they can be carried out only centrally at the Robert Koch Institute in Berlin. The complex modeling and smoothing procedure lead to stable estimates by taking into account the cancer-specific fluctuations which means the disparities which effect the M/I index might be taken care of by using this model. Still this approach is not considered suitable for NMSC.

Drawbacks: No regional expectations can be derived and is applicable to only selected cancers. Because of the cost and extensive calculations involved, it can be carried out only at a central institute like the RKI [7]. The reference register should also have long term completeness.

Inference: Log-linear model is appropriate for MM data completeness assessment but not for NMSC because the data for NMSC is still not considered reliable [4].

4. Completeness of information on diagnosis and tumor classification

This is defined as the percentage of cases for which tumor classification such as TNM (Tumor Node Metastasis) staging or histopathological grading is defined. The recommended standard of completeness for TNM staging and histological grading of a cancer registry is defined as at least 80% [7]. This information is extremely valuable for assessing the survival rates, evaluating stage-specific therapy or screening programs [7].

As seen in Table 4, the proportion of cases with missing or incomplete TNM stage or UICC stage (Union for International Cancer Control staging based on prognoses) varies across the registries from 8-9% in Saxony and Lower Saxony to around >60% in Schleswig-Holstein for MM. For NMSC, the rate of this missing information is almost double that of MM and ranges from 77-85% across the registries (Table 5).

Inference:

There is a huge gap in the completeness of information on tumor classification for both MM and NMSC.

5. Completeness of therapy information

The standard for completeness of therapy information has been not been defined so far [7]. This was not included in the tables because the data is available from only one registry: Schleswig-Holstein. The annual report of this registry mentions the proportion of cases undergoing various treatments for example surgery, chemotherapy, immunotherapy or no treatment at all for both MM and NMSC [25].

Comparability

According to Bray and Parkin [49], comparability is defined as "the extent to which coding and classification procedures at a registry, together with the definitions of recording and reporting specific data items, agree with international guidelines". Comparability is evaluated based on four main criteria:

a) "the system used for classification and coding of neoplasms;

b) the definition of incidence, i.e. what is defined as a case, and what is the definition of the incidence date;

c) the difference between a new case and an extension, recurrence or metastasis of

an existing one;

d) the recoding of cancers detected in asymptomatic individuals".

All these factors with respect to skin cancer, their influence on skin cancer incidence and differences between registries have already been discussed in the 'coding of skin cancer' and 'coding rules for multiple tumors' section. The principle of coding tumors and case definitions are similar across all regions. Though international standards are followed by German registries, yet there are practical problems associated with coding conversion and registration of multiple tumors. It is to maintain international comparability, that NMSC is not included in the reported incidences of 'all cancer sites'[4] and multiple tumors are not counted. As far as the 4th criteria i.e. coding and recoding of tumors detected in asymptomatic individuals or in other words by screening is concerned, none of the annual reports explained the screening principles.

Validity

The validity of a cancer register is assessed based on two factors: Proportion of unknown /unspecific primary tumor and Proportion of histologically confirmed cases.

1. The proportion of cases with inaccurate/unspecific primary tumors

A high proportion of such cases indicates a low quality of data. It should be <10% for an epidemiological cancer registry [7]. ICD-10 codes for such tumors are C26.0, C26.9, C39.0, C39.9, C76, and C80.9. This parameter is not specific to any particular cancer but rather an indicator of the overall quality of a cancer registry.

The annual report of Joint Cancer Registry specifies the proportion of such cases for MM coded as ICD-O-3 C80 ranging from 1% to 2.5% across the 6 cancer registries included under JCR, thus implying a high-quality data [21]. But the controversial point is that ICD-O-3 C80 represents the tumors for which the primary site could not be identified, and it does not make sense to provide such data for each cancer type. When the cases (as in the annual report of JCR) specify the diagnosis as MM, then the primary site is automatically skin. Even in case, the definite site of skin involvement was not clear in these cases, it still does not justify the use of code C80 because such tumors are coded as C43.9 or C44.9. For NMSC, no such data could be extracted from the annual reports.

Inference

The data is debatable, and no final conclusion can be drawn.

2. The proportion of Histologically confirmed cases

Also known as microscopically verified (MV%) cases, these are the cases for which the diagnosis has been confirmed histologically on biopsy/ excision samples by the pathology laboratories and indicates the validity of diagnoses. It is an indicator of the good quality of the registration procedure and care. The standard value of HV share is >85% for all cancers [7]. It is >90% in case of both MM and NMSC in all the registries except for NRW which has MV% of approx. 86% for MM (Table 4 and 5). Though high MV% indicates good quality data but a proportion as high as 100% also points out towards only histology reports being the source of notification and lack of clinical reports [7]. So the results should be interpreted with caution.

Inference

In case of NMSC, where the MV% is as high as 98-99% while the TNM stage is lacking in almost 80% cases, this might be an indicator of pathological reports being the sole source of notification and scarcity of clinical reports.

Overall Interpretation: The data quality for both NMSC and MM is poor but for NMSC even the appropriate quality assessment tools are lacking.

Handling missing data

As explained in the Manual of cancer registration [7], missing values cannot be completely avoided. For example, in MM patients who have not undergone surgery, information like tumor thickness cannot be obtained and hence the tumor staging based on this criterion is missing. To deal with this problem of missing data, one of the methods followed is Imputation- multiple imputations are proven better than simple imputation. No information on the use of imputation for skin cancer could be found in the annual reports but the registries do always report the missing data to assess the potential bias.

Response evaluation of survey

All the German cancer registries except for the Joint cancer registry group had replied back to the survey by October 2018. The last survey was received from Berlin in February 2019. The survey from Berlin was considered as representative of all the six registries included

in Joint cancer registry (as per confirmation via email by Berlin cancer registry). The responses of each registry to the questions of the survey are summarized in Table 6.

Table 6: Response to the online survey sent to the German cancer registries

Region	Imputation of Missing T stage	Effect of screening included	Multiple tumor counting	M/I index used to calculate incidence	Traceback done for DCN cases
Hamburg	No	No	No	No	**Yes**
Berlin	No	No	No	No	**Yes**
Brandenburg	No	No	No	No	**Yes**
Mecklenburg	No	No	No	No	**Yes**
Saxony	No	No	No	No	**Yes**
Saxony-Anhalt	No	No	No	No	**Yes**
Thuringia	No	No	No	No	**Yes**
Saarland	No	No	No	No	**Yes**
NRW	No	No	No	No	**No**
Rhineland	No	No	No	No	**No**
Schleswig-Holstein	No	No	No	No	**done once in 2010**
Bavaria	No	No	No	No	**Yes, since 2017**
Bremen	No	No	No	No	**Yes**
Lower Saxony	No	No	No	No	**Yes**
Hesse	No	No	No	No	**No**
Baden-Wuerttemberg	No	No	No	No	**No**

11 out of the 16 registries do run a regular traceback on DCN cases (although in Bavaria since 2017 only). Four (NRW, Rhineland, Hesse, Baden Wuerttemberg) of the rest five registries do not run any traceback while Schleswig-Holstein (the registry which has always been in the forefront for skin cancer) did it only once in 2010. This can contribute to differences among the registries and raises questions on the reliability of DCO rate as a quality indicator. To the question, if M/I index of the reference region is used to calculate the incidence of MM in a registry, all the registries replied back 'No'. For counting multiple tumors, all the registries confirmed to follow IARC rules 2004. So no secondary tumors involving the same site or multifocal tumors are included in the incidence calculation. None of the registries include the effect of screening on the incidence rates. As was seen in the annual reports of all the registries that a high proportion of information on 'T' stage or UICC stage was missing for both MM and NMSC, it was inquired in the survey if the registries use an 'imputation method' to fill in the missing stage information during evaluation. All the registries responded back that they do not use the imputation method for skin cancer and report the various stages of cancer and missing information as such. It was further inquired about the method of completeness assessment by the registries and all of them confirmed that it is evaluated by the RKI annually using log-linear model for MM but not for NMSC. Thus the survey too highlighted the contributing factors to low-quality data of skin cancer.

Comparison with Nordic countries to suggest improvements

The Nordic countries have an extensive data collection system and more complete cancer registries as compared to Germany. The Nordic countries claim to have complete data for last 60 years [33]. The features of three of these Nordic country registries are described in Table 7. Denmark, Norway, and Sweden have even a higher ASR (world standardized) of skin cancer incidence than Germany [3] and yet the completeness of data for skin cancers is also >90% in all the three countries [32]. The methodology in the context of skin cancers in Nordic cancer registries was compared with German cancer registries to suggest improvements.

Table 7: Features of Danish, Norwegian, and Swedish cancer registries (source NORDCAN database) [32]

	Denmark	*Norway*	*Sweden*
Year of establishment	1942	1952	1958
Earliest/first complete year of cancer registration	1943/1943	1952/1953	1958
Percentage of DCO cases (NORDCAN data 2009–2013)	0.3%	1.1%	—
Percentage of microscopically verified (MV) cases (NORDCAN data 2009–2013)	95%	94%	98%

Differences in recording tumors

Nordic countries have a database for international comparison called NORDCAN [32]. As there are disparities between Nordic countries and other countries across the world in reporting BCC, therefore though the local registries collect data on BCC, for international comparison, these rates are not included in NORDCAN database and are also omitted from the national statistics [33]. There is also a controversy over the ICD-O-3 coding for BCC. The behavior code (to specify malignant/ benign/ in situ tumors) for BCC is 3 since it is a malignant tumor but most of the registries across the world either do not register it or have different policies for coding (e.g. not including it in malignant tumors), making the data less comparable. As a result, BCC is registered in Nordic countries in a separate file with much less extensive manual coding and efforts to ensure the quality of data as compared to other cancers in the main database [33]. The Danish cancer registry reported BCC with other non-melanoma skin cancers until 1978 after which BCC was reported separate from rest of the NMSCs. Sweden started reporting BCC in a separate file in 2004 while the Norwegian cancer registry started BCC registration in 1971 and store them in a separate file since 2008. Similar is the case for in situ tumors. Sweden has registered carcinoma in situ for all tumors from the beginning but did not include them in routine statistics until 2013 whereas the Norwegian registry has stopped recording in situ skin cancers. Denmark and Norway count pre-invasive and invasive lesions as separate entities if there is a time interval of 4 months between them [33]. This information on in situ tumors and consideration of time factor is not only significant to calculate the incidence rate but also important to study the progression of lesions from pre-invasive to invasive stage.

Different coding principles of multiple tumors [33]

In Denmark, if the same patient has second skin cancer, then the code is changed to C43.8 or C44.8 "multiple locations" to indicate it respectively for MM and NMSC. Sweden counts all multiple tumors occurring at the same time as separate entities even if they have the same morphology as multiple SCC and whether the tumor is a primary or a recurrence is decided clinically. Norway counts the first incidence of BCC and then all of the following tumors are coded as "second BCC" irrespective of the number, though for calculating the age-standardized rates (World), only first BCC is counted.

Quality assessment tool

The M/I index for MM and NMSC reported by NORDCAN in 2011-15 is shown in Fig.4 [32] and highlights the similar low mortality pattern as observed in Germany.

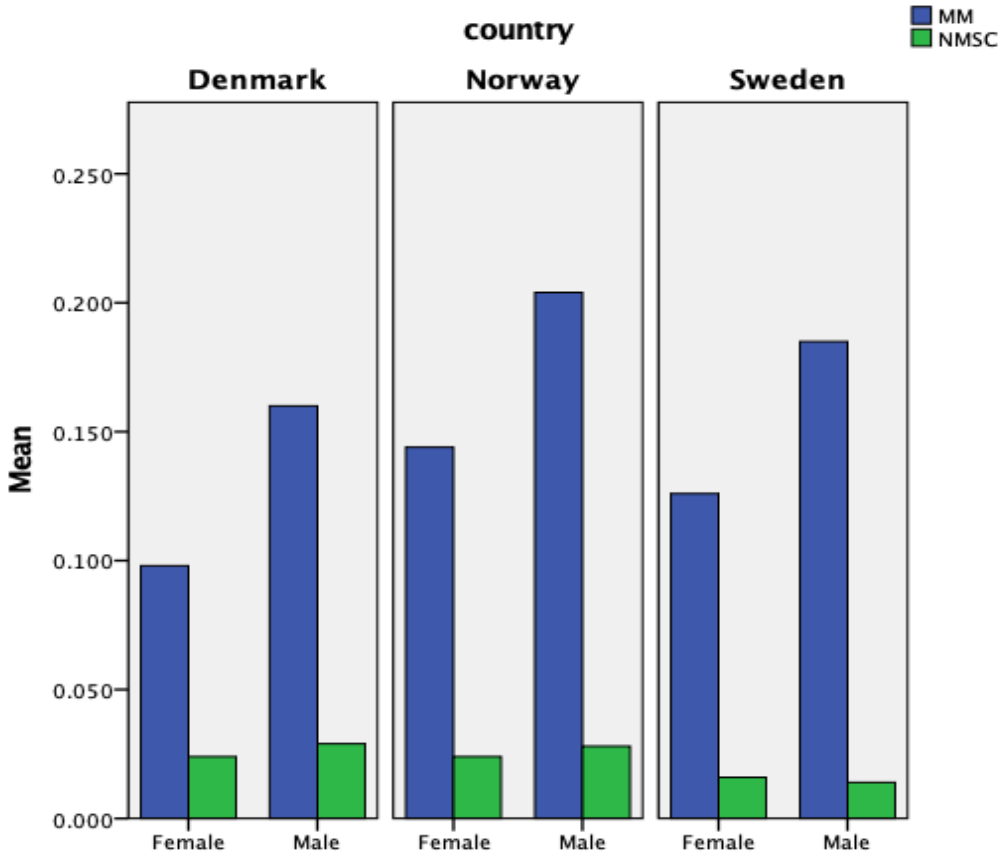

Figure 4: M/I index for MM and NMSC across the Nordic countries (source NORDCAN) [32]

Instead of M/I index, the Danish cancer registry evaluates data completeness by capture-recapture method and validity by the microscopically confirmed cases and multiple source

notifications [50]. Norwegian cancer registry uses quantitative methods- capture-recapture and flow method, and semi-quantitative methods- historical data method, M/I ratio compared with one minus five year relative survival and the number of sources/notifications per case, to check the completeness of the data [51] (all these methods are described in detail in discussion). The annual reports 2016 of Norwegian cancer registry have been published evaluating the completeness of data using the capture-recapture method. The Swedish cancer registry checks the completeness by comparing to the data of Population death register which is considered to have 98% completeness. Sweden registry does not use DCO cases but instead uses traceback to validate the diagnosis and then adds them as death certificate initiated (DCI) cases. Not using the DCO cases reduces the completeness of the registry especially for cancers diagnosed in late stages [52].

Inference

Though there are differences among Nordic countries too but reporting BCC in a separate file, counting multiple tumors, in situ lesions and maintaining a local registry data separate from an international database makes their data more reliable in terms of skin cancer than German cancer registries and if adopted into practice, would help improve the quality of skin cancer data in Germany. Considering the high survival rate of >100% for BCC [4], separating it from the rest of NMSC may reduce the burden on the main database and allow to attain a higher quality of data.

V. Discussion

In spite of 16 population-based registries running in the country, it is clear from the results that the data available for skin cancer in Germany is not complete, for NMSC more than MM. Several factors from the history of the registries and the legislative laws to frequently changing coding rules influence the incidence rates and can result in over- or under-estimation of true skin cancer incidence. Even the registries running since last 20 years in the country still don't have complete data on skin cancer making the young registries even lesser dependable. Keeping this in mind, it can be inferred that the data on which GLOBOCAN skin cancer incidence estimates are based is not complete itself.

Though NMSC recording gets ignored, the importance of epidemiological data for NMSC is highlighted from the example of the use of this data in a study by Stang et al., 2003 [41].

In this study, the age-standardized incidence rates of NMSC of the skin were compared based on the anatomic site involved and the data was derived from the Saarland Epidemiological Cancer Registry for the years 1995-1999. It was expected from the knowledge of risk factors responsible for skin cancer that sun-exposed skin areas would have higher incidence rates for NMSC as compared to the less exposed skin areas [7]. However, because of differences in the body surface areas of the different sites, for instance, approx. 0.5% for scalp vs 2.3% for face, the incidence rate of skin tumors on these sites are not directly comparable. The incidence, therefore had to be adjusted for the body surface area and it was found that BCCs have the highest incidence on the eyelids, face, and lips. Without this adjustment, it would have been concluded that the risks to BCCs are highest in the face, neck, and trunk.

This study also points out the importance of registration of various sites of tumors and coding principles. The reason why the author evaluated data post-1995 was that until 1994, the majority of NMSC cases were coded according to ICD-9 system or according to ICD-O as unspecified skin cancer or by a histology variable that categorized NMSC into BCC, SCC or other skin cancer [41]. This was because of the massive number of NMSC reports and the shortage of registry staff. Until 1995, the annual proportion of unspecified skin cancer was >10% in Saarland registry. The impact of changing coding rules over time from ICD-10 to ICD-O-3 on complete registration was also found in Nordic countries, for example in Finland, the precise evaluation of the incidence of many morphologies was only possible after 2007 because the conversion to ICD-O-3 morphology codes in 2007 was not considered 100% accurate [33].

A similar difficulty is with the principal of coding of multiple primary tumors which can impact the incidence rate and the reported cancer trends. For the reporting of multiple primary tumors, the European cancer registries follow the IARC report published in 2004 which has not been updated since then. Weir et al., 2016 [53] analyzed the differences in incidence rates of various cancers when coded according to SEER Program (Surveillance, Epidemiology, and End Results) followed in North America compared to that by using IARC rules. The calculations were based on data from 9 population-based registries covering 10% of the US population. When SEER rules were used, the incidence rate for melanoma was higher by 9% than that by using IARC rules. Rate ratios also increased with the age of diagnosis: for melanoma in specific by 13%. From 1975 to 2005-06, the incidence rate for melanoma increased annually by 5.7% according to SEER and by 2.7-2.9% according to IARC rules. Similarly, from 2005 to 2011, it increased by 1.3%

according to SEER but as per IARC, it remained stable. SEER counts each subsite of the skin as a separate entity and even the laterality of the tumors and the timing rules are taken into consideration [53]. The influence of multiple tumor counting was most evident on the incidence rates of urinary bladder tumors which have a tendency of multifocality. In this study, NMSC was not included but it can be anticipated that a similar increase in incidence rates would be observed for NMSC if multiple tumors are counted. Due to treatment improvements, as more patients are expected to survive and live longer, the chances of recurrences and new primaries would increase and since these will use up the resources of treatment too, it is important that we start registering them. The reporting of multiple tumors can also benefit further research on etiopathogenesis.

Looking at the quality of data, incomplete data on T stage or unspecified primary site of skin cancers can be explained by the lack of complete information provided by service providers. The reason for this could be no fee paid for the reporting (as was mentioned for NMSC in the §65c SGB V) or busy clinic schedule or lack of orientation among doctors towards the importance of this issue. Establishment of clinical cancer registries in Germany is a step in the right direction towards dealing with this problem. Lack of T stage information is also observed in Nordic countries where for example in Finland, only 50% TNM stage information was available until 2010 and in Iceland, metastasis of skin melanoma only got reported after 2010 [33]. But they are trying to improve the completeness of TNM information as this is valuable in survival studies.

As was seen in results, the two parameters- DCO rate and M/I index used to assess the completeness/quality of data, are not appropriate for cancers like NMSC and even MM which have a low mortality rate. The capture-recapture method is another approach used to assess completeness based on the comparison of the registry data with another independent source of data like with the Central Melanoma registry (CMMR). This is the method used by Denmark and Norway as seen in results. Brenner et al.,1994 [54] argued by calculating the completeness of Saarland registry that in spite of its limitations, capture-recapture is a better tool for assessing completeness than M/I index which is more dependent on the case fatality rate of particular cancer. Schouten et al., 1993 [55] carried out a study in the Netherlands in which he compared the database of the regional cancer registry located in Maastricht (IKL) with another independent source of data from General Physicians (RNFP) to assess the completeness of IKL registry and proved that using this approach, the registry had a high degree of completeness even without including DCO cases and in

addition comparable to other countries using the same approach. But a major pre-requirement for this approach to be considered reliable is the independence of the sources of data. This method may not be the best for cancers with a high mortality rate because then for obvious reasons more cases get registered through "DCO". For diseases like skin cancer, where the mortality rate is very low and M/I index method seems inappropriate, this could provide an alternative to assess the completeness of data based on 'clinical' and 'pathological reports' sources. But there are many disadvantages of this approach as highlighted in another study by Schouten et al.,1994 [56] in which he tried to assess the reliability of capture-recapture method using 'pathological' and 'discharge' reports assuming them to be independent sources. The completeness was lowest for skin cancer (excluding BCC) because most of the data came from 'pathological reports' only as patients with skin cancer usually get treated in outpatient clinics and hence were not notified by 'discharge reports '. He further emphasized that it was not possible to prove from his analysis whether both the sources were independent or not, but if they were correlated then the estimate made for the unknown number of missed cases would get significantly affected, thus affecting the completeness. He finally recommended not to use the capture-recapture method as a tool for completeness assessment of a cancer registry on a routine basis [56]. The major failure of this method is the practical absence of such independent data sources. As far as CMMR in Germany is concerned, a study has shown that it only records 35-50 % melanoma patients because of lack of participation by the clinical centers covered by this registry [57].

Hence the best approach for completeness evaluation of skin cancer still remains unclear. As mentioned in the results, the log-linear model might be the solution to assess the completeness of MM because the modeling does consider the instabilities in the regional incidence and mortality rates induced by screening or other factors, but even this method was not found suitable for NMSC. Apart from log-linear model, M/I quotient, and capture-recapture method, some other methods for completeness assessment discussed in the Manual of cancer registration [7] and advised by Parkin and Bray [58] are elaborated below:

M / I quotient and survival method

M/I quotient method in the context of skin cancer and its unacceptability for NMSC and inconsistency for MM was already discussed in detail in the result section. This method is suitable for comparison between different regions and within the same region for different

years. It provides a quick and simple quality assessment as compared to log-linear model. It also helps the registries to find the gaps in data in specific age- or diagnosis- group. But there is an alternative to it, which does not require any reference values: The M: I survival method [7]. The M: I quotient is compared with the complement of the relative survival i.e. 1-RS which denotes the case fatality. Both the parameters reflect the proportion of deaths due to cancer. The difference between M: I quotient and the 1-RS estimate is directly related to the level of completeness.
Drawback: This method requires a complete, multi-year follow up of vital status (survival, mortality, and incidence rates) and is therefore not suitable for young registries.

Counting the number of notifications or data sources

This method for completeness estimation was proposed by Parkin et al. [58] based on two criteria: the average number of data sources per case and the average number of notifications per case. It is based on the presumption that completeness improves with an increase in the number of data sources and reports per case. A good record linkage has to be reassured so that multiple notifications for a single case can be identified.
Drawback: Although the method is simple, no direct conclusions about the completeness can be drawn and even comparison of the same with an evidently complete register does not assure completeness [7]. It is a pre-requisite to have a clear definition of notifications and data sources.

Re-screening

This is the reevaluation of the same source of data to find out the number of cases missed during routine registration. As described by Parkin et al. [58], the audit of, for instance, a particular hospital can be carried out and the cancer cases reported in a specific time period can be compared with that of the registry. The unmatched cases are followed up and the proportion of such cases is calculated indicating the completeness of the hospital data.
Drawback: It has practical limitations i.e. it is an expensive method requiring an enormous amount of time and effort. This leads to its use being restricted to only one data source like a physician or hospital data over a particular duration of time. It is not possible to make an interpretation on complete registration of all cancers in a registry.

Historical data method [7]

With this method, the cancer registry derives the future estimates based on the observed trends in the past and the completeness is evaluated by comparing the expected and

observed number of cases. It is necessary that the respective registry has maintained complete data over the years. This method assures timely evaluation of completeness and any break found in the reporting activity can be dealt with quickly. Therefore, this method can be used as an additional approach for quality assurance in a cancer registry.
Drawback: Since no such trends are available in newly established registries, therefore this method is not suitable for such registries. Similarly, it is not appropriate for cancers with a small number of incident cases and strong random fluctuations. Various screening programs and risk factors, for instance, specific to skin cancer, the behavior patterns for sun exposure whether indoor artificial or outdoor tanning, can influence the trends and hence have an impact on the reliability of this method.

Flow method

This method for completeness estimation was presented by Bullard et al., 2000 [59] based on the database from Thames Cancer Registry, UK. In this study, the proportion of unregistered tumor patients was estimated using three time-dependent probability functions:

- *"the probability that a cancer patient has survived his disease after a time t;*
- *the probability that cancer was mentioned on the death certificate for the patient who died after time t;*
- *the probability that a cancer patient has survived his disease after a time t and still remained unregistered".*

Based on these probabilities, the missing and the lost (who are never registered with the registry, neither when they were alive nor by death certificates, after they die) number of cases are calculated and then the completeness of the registry is estimated. The major advantage is that there is no need of a reference index (as in M/I index method) or the independent data sources (like in capture-recapture method). In addition, contrary to other methods, this approach takes the 'lost' group into consideration and can be used for each cancer site, age group, and region. It is presumed that the registry receives all death certificates on which a cancer condition is noted. In this study, the data for MM was the least complete though the overall completeness of the registry was 92.1%, the reason being the high proportion of unregistered MM cases before death [59]. NMSC was not included in the assessment.

Drawback: Timely estimates of completeness are not possible, and the results are influenced by the lethality of the respective tumor (the same drawback as for M/I index) [7].

Larsen et al., 2009 [51] calculated the completeness of Norwegian cancer registry based on 2001-05 data using the methods mentioned above. Using the capture-recapture method, the completeness of NMSC was 99.78% and for MM was 99.76%. The average number of notifications per case for all sites together was 3.2, it was 2.3 for NMSC and 3.0 for MM. Other methods were also used taking into consideration the limitations of each method mentioned above and proved high overall completeness of the registry, but data specific to skin cancer could not be extracted. The study finally concluded in achieving "close-to-complete" data.

In addition to completeness, comparability, and validity, another factor listed for the first time by Bray and Parkin [49] as one of the most important quality characteristics of a cancer registry is 'timeliness'. At present, no international standards exist for it. Timeliness is defined as "*the time gap between the diagnosis and the publication of the data of that diagnostic year*" [49]. The reason for this gap between receipt of information and reporting is the time required for the process of transfer of information and various checks in the database in a registry. In addition, the traceback or follow up of the cases reported by death certificates also needs time. The time lapse is determined by many factors like the efficiency of the software used for documentation. In the SEER program, the North American Cancer Registry must report the incidence within 22 months of the end of a diagnostic year [7]. Norwegian cancer registry has decreased this time gap from 525 days in 2001 to 261 in 2005 [50]. The difference reported between the incidence rate for the diagnosis year 2005 in the report of 2006 and a later published report in 2007, was an increase by 1.3% for MM while a decrease by 0.5% for NMSC incidence. The report from the RKI 'Cancer in Germany 2013/14' also approves of the importance of timeliness by stating that the cancer estimates for the diagnosis year 2012 were 2.5% higher in the 2014 report than that estimated in the previous report for the same diagnosis year which was explained by the late registration of cases in the registries and the estimation method itself. For MM, this led to a 6.6% increase in incidence rate in men as compared to that reported two years back [4].

Another issue highlighted in the results which interferes with achieving good quality data is the missing information on stages and imputation is one of the methods to deal with it. A

study by Eisemann et al., 2011 [60] evaluated the accuracy of multiple imputations method to predict the missing UICC stage and TNM stage for breast cancer and MM. The results for MM were- 20% of the imputed values for UICC-stage were different from the observed values, but for T stage imputations, the difference was as high as 50%. So for MM, imputations provided more accurate results for UICC stage than for TNM stage. This was explained by the high percentage of missing values in MM cases. Whether to use imputation for MM on routine basis and for NMSC, which has even higher missing stage information than MM, is still a matter of debate and needs to be evaluated further.

As observed in the results, SCS can influence the incidence rates reported (Fig. 2 and 3) and also the M/I quotient. A study at Schleswig-Holstein [61], assessing the impact of skin cancer screening project of 2003-04 on the stage-specific incidence of MM, proves a shift towards the earlier stage and a decrease in the incidence rate of advanced stages. But as observed in the results (Table 4 and 5), the missing information on stage goes as high as >60% for MM and >80% for NMSC, so it is doubtful how much reliable this interpretation would be. Also, the Cancer report by RKI confirms to have found no such decrease in the advance stage incidence till 2014 [4]. So it is possible that the results observed in Schleswig-Holstein were temporary. A study by Eisemann et al, 2014 [62] comparing rise in the incidence of NMSC in Schleswig-Holstein with Saarland proved that the incidence increase reported in Saarland after the introduction of screening in 2008 was similar to that observed after the screen project of 2003/04 in Schleswig-Holstein. Thus the effect of SCS on incidence rates should be incorporated by the cancer registries to know the actual results of SCS, to prevent the overestimation of national incidence and to include its effect on the M/I ratio of reference regions which is used to evaluate the completeness of other registries.

The effectiveness of SCS is another controversial topic. SCS is not followed by the US and Australia which have a much higher incidence rate of skin cancer reported than Germany. According to the US Preventive Service Task Force recommendation [63], there is not enough evidence in favor of skin cancer screening and the benefits vs harms of screening test i.e. visual skin examination by a clinician, cannot be determined. Many studies have argued against the screening program and proved that the efficacy of general skin cancer screening in Germany is not clear. Looking at the performance of SCS program in Germany, Stang et al., 2018 [64] estimated that based on 2015 data, for people aged ≥35yrs., Number Needed to Screen for 50% relative risk reduction was 34 000 for MM and

191 000 for NMSC. This is extremely high when compared to other cancers such as for lung cancer, 320 heavy smokers aged 55–74 years would have to be screened by low-dose lung CT to prevent one extra death and for colorectal cancer, 402 people aged 55–64 years would have to undergo flexible sigmoidoscopy. A study by Breitbart et al., 2014 [65] analyzed the pros and cons of SCS program in Germany and mentioned a model-based calculation that proved approximately 27 000 people would need to be screened multiple times to prevent 2 MM related deaths and this, in turn, will require extensive amount of resources to train dermatologists and pathologists. Among the arguments against the use of screening for BCC and SCC, one was the age group in which both these cancers are common i.e. 75 yrs. and above, when people are more likely to die of diseases other than skin cancer. Also, the dropout rate from the screening program was observed to be very high in >75 yr. age group. The second factor was the very low mortality rate in BCC because of the nature of the disease itself i.e. slow progression and rare metastasis while in the case of SCC, cancer mostly occurs in exposed skin areas which makes it very apparent and patients usually go for treatment at very early stages. The author claimed that for the above reasons, the screening program was ineffective for BCC and SCC and therefore was mainly aimed at detecting MM cases which do contribute to the cancer deaths in Germany though still much less as compared to other cancers. Analyzing the Screen project for MM from Schleswig-Holstein done in 2003-04, it is still not proven whether there has been any substantial reduction in MM mortality as a result of SCS and moreover, if there are no harms related to SCS [65, 66].

Finally, it can be mentioned that many aspects need to be revised in the skin cancer registration process and its quality evaluation. Despite so many ambiguities, it is recommended to continue registration of MM and NMSC at the regional level and work towards assimilating comprehensive data.

VI. Limitations

The results are based on information collected from the annual reports of the registries, but the base year of data (diagnosis year) was different for all the registries reducing the comparability of the data. One of the oldest and most complete registries, Saarland had the latest annual report available only for the year 2006. The methodology undergoes very frequent changes, for instance, the soon to be introduced new ICD-11 code for

classification of tumors, changing legislative rules which regulate the registries and the upcoming clinical cancer registries, make this article valid for a limited duration. Even the remuneration rules are not practically the same for clinical cancer registries and epidemiological registries across all federal states, but this information could not be obtained in detail for each state. The M/I index of MM was not found constant across all the states, but it was not analyzed if there was a statistically significant difference. Although all the registries replied back to the survey, to the follow-up questions very few responded back and hence the doubts for each registry could not be clarified like why Berlin registry has included C80 code in MM cases. No conclusion on the best approach to assess the quality of data of skin cancer (in particular NMSC) could be reached in this study. Additionally, it was beyond the scope of this paper to analyze and compare the results of completeness or incidence estimates using alternative approaches.

VII. Conclusion

There is undoubtedly underreporting of skin cancer and the quality of existing data is poor, for NMSC more than MM. An important and distinct component of NMSC is Basal cell carcinoma with a very low mortality rate and the policy followed by Nordic countries to report the huge number of BCC cases in an independent database seems a more practical approach. Probably adopting this approach would reduce the disparity among the rest of skin cancers and reduce the burden on the main database and might even solve the problem of data quality assessment. The rules whether governing the compensation for notification or coding of multiple tumors need to be reformed. With upcoming clinical registries, the situation would expectantly improve in coming years and the quality and completeness of the data available in the cancer registry will definitely rise if both the forms of registries complement each other. More emphasis, efforts, and resources should be directed towards completing the information related to each case like the TNM staging and site specifications, and even treatment, which may require appropriate training of the service providers to orient them towards the importance this information.

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IX. Declaration of independent work

I hereby declare that I wrote this thesis without any assistance and used only the aids listed. Any material taken from other works, either as a quote or idea have been indicated under ‘Sources’.”

X. Appendix

The questionnaire

Germany is one of the countries with highest incidence of skin cancer in the world. Cancer registries in Germany collect data for both melanoma and non- melanoma skin cancer but there is huge disparity in its collecting and reporting.
Methodology of data collection and reporting varies with each registry which can influence the final incidence rate. Analysis of this methodology for skin cancer is the topic of my master thesis. This questionnaire includes queries that could not be answered by carefully reading the annual reports of the registries and will not take more than 15 minutes for completion. Please cross (X) the appropriate reply.

Q1. 'Death Certificate Only' cases are used to complete the cases of melanoma which have not been reported to the cancer registry. Does your registry run a traceback for DCO cases?

a) Yes ___
b) No ___

If Yes, how?

(e. g. every month / every year, contact to local registration office / contact to physicians and / or clinics, data exchange with other cancer registries, ...)

Q2a. M/I index is used in some cancer registries to calculate the incidence rate of melanoma in their federal state.

a) Yes ___ → Q2b. Some registries use M/I index from a reference registry. Does your registry use M/I index from another registry?
b) No ___

Q2b.
a) Yes ___ → Q2c. If yes, which registry serves as the reference registry?
b) No ___

Q2c.

Q3. Skin cancer screening was introduced in 2008 in Germany. Is the potential influence of this screening taken into account in the estimation of incidence of skin cancer in your region?

a) Yes ___
b) No ___

If Yes, where can more information be found (any website or reference article)?

Q4. For melanoma specifically, there are around 40% of cases in each registry with missing 'T' category or UICC stage. When reporting stage-specific skin cancer incidence, do you set up a model to replace the missing categories?

a) Yes ___
b) No, we report data as it is (that is, we report the incidence of tumors with T1-, T2-, T3-, T4- and with missing T-category). ___
c) No, we do not report stage-specific incidence. ___

If Yes, could you please explain the model used?

Q5. How are multiple / recurrent skin tumors included in the incidence rate by your registry?

Melanoma: *Non-Melanoma Skin Cancer:*

Q6. Is completeness of the data assessed in your registry?

a) Yes ___
b) No ___

If Yes, how?

Any further information that you would like to add:

Thank you for completing the survey!