Rare cancers in The Netherlands: a population-based study

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The conventional definition for rare disease is based on prevalence. Because of differences in prognosis, a definition on the basis of incidence was deemed to be more appropriate for rare cancers. Within the European RARECARE project, a definition was introduced that defines cancers as rare when the crude incidence rate is less than six per 100 000 per year. In this study, we applied the RARECARE definition for rare cancer to the Netherlands; this to identify the usefulness of the definition in a single country and to provide more insight into the burden of rare cancers in the Netherlands. Data for 2004 through 2008 were extracted from the Netherlands Cancer Registry and classified according to the RARECARE entities (tumour groupings). Crude and European standardized incidence rates were calculated. Out of the 260 entities, 223 (86%) were rare according to the definition, accounting for 14 000 cancers (17% of all). Considerable fluctuations in crude rates over years were observed for the major group of cancers. Rare tumours in the Netherlands constituted 17% of all newly diagnosed tumours, but were divided over 223 different entities, indicating the challenge that faces clinicians. To make the definition of rare cancers better applicable, it should be refined by taking into consideration the sex-specific incidence for sex-specific cancer sites. Moreover, a mean incidence over 5 years will provide more solid insight into the burden, eliminating large fluctuations in time of most of the cancers. *European Journal of Cancer Prevention* **27:384–390**

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Introduction

Clinicians consider patients with rare cancers in most cases as a challenge because they do not encounter a patient with this specific type of cancer regularly and are therefore less experienced with diagnostics, staging and treatment.

Until recently, only a definition for rare diseases on the basis of the prevalence rate existed. Diseases are defined as rare when the prevalence is less than 50 per 100 000 in the community (European Parliament and Council of the European Communities, 2003). Moreover, the American Orphan Drug Act defines rare diseases as those affecting fewer than 200 000 individuals in the USA (Developing Products for Rare Diseases & Conditions, 2011). For cancer, however, using prevalence as a measure of rarity may not be the most suitable. Some cancers with a low incidence but a good survival will have a high prevalence and would therefore not be considered rare. Still, the low incidence means limited opportunities to become acquainted with the specifics of diagnosis and treatment. Therefore, in the RARECARE project, a new definition was developed defining rare cancers, which was based on a wide consensus among organizations representing medical professionals (surgeons, pathologists and medical oncologists). Cancer should be considered rare when the crude incidence rate is less than six per 100 000 per year (Gatta *et al.*, 2010, 2011).

The RARECARE project provided a list of rare cancers for Europe and not for the separate European countries (Gatta *et al.*, 2010). Applying the definition to a single country will provide information on the usefulness of the definition on a national level. Furthermore, knowledge of the burden of rare cancers for a specific country could give an impulse in awareness and might lead to the development of (inter)national guidelines supporting the clinicians in diagnoses and treatment decision making. Moreover, the discussion on (virtual) centralizing the care for these patients within a country or even between countries could be supported; concentration of knowledge by increasing volume will identify caveats and tackle gaps of knowledge related to the management of patients with rare forms of cancer. It can also give an impulse to research focusing on diagnosis and treatment for this diverse group of patients in relation to outcome.

In this paper, we applied the RARECARE definition for rare cancer to the Netherlands for 2004 to 2008 to identify the usefulness of and to quantify rare cancers on a national level to provide more insight into the burden of rare cancers in the Netherlands.

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Table 1 Incidence of rare first-layer entities in the Netherlands, 2004–2008

	2004			2005			2006			2007			2008			2004–2008		
Rare first-layer entities	*N*	CR	ESR	*N*	CR	ESR	*N*	CR	ESR	*N*	CR	ESR	*N*	CR	ESR	Annual *N*	Annual CR	Annual ESR
Epithelial tumour of the nasal cavity and sinuses	99	0.6	0.5	107	0.7	0.6	112	0.7	0.6	117	0.7	0.6	123	0.7	0.6	112	0.7	0.6
Epithelial tumour of the nasopharynx	70	0.4	0.4	40	0.2	0.2	58	0.4	0.3	55	0.3	0.3	62	0.4	0.3	57	0.3	0.3
Epithelial tumour of major salivary glands and salivary gland type tumour	198	1.2	1.1	202	1.2	1.1	175	1.1	0.9	211	1.3	1.1	240	1.5	1.3	205	1.3	1.1
Epithelial tumour of the hypopharynx and larynx	868	5.4	4.9	945	5.8	5.3	898	5.5	4.9	821	5.0	4.4	897	5.5	4.7	886	5.4	4.8
Epithelial tumour of the oropharynx	477	2.9	2.7	438	2.7	2.5	449	2.8	2.5	471	2.9	2.5	545	3.3	2.9	476	2.9	2.6
Epithelial tumour of the oral cavity and lip	781	4.8	4.2	844	5.2	4.5	857	5.3	4.5	874	5.3	4.4	875	5.3	4.3	846	5.2	4.4
Epithelial tumour of the small intestine	89	0.5	0.5	118	0.7	0.6	126	0.8	0.6	130	0.8	0.6	135	0.8	0.6	120	0.7	0.6
Epithelial tumour of the anal canal	105	0.6	0.5	126	0.8	0.7	148	0.9	0.8	135	0.8	0.7	157	1.0	0.8	134	0.8	0.7
Epithelial tumour of liver and intrahepatic bile tract	318	2.0	1.7	327	2.0	1.8	333	2.0	1.7	390	2.4	2.0	421	2.6	2.1	358	2.2	1.9
Epithelial tumour of gallbladder and extrahepatic biliary duct	534	3.3	2.7	553	3.4	2.6	565	3.5	2.7	652	4.0	3.0	577	3.5	2.7	576	3.5	2.7
Epithelial tumour of the trachea	10	0.1	0.1	9	0.1	0.1	15	0.1	0.1	8	0.0	0.0	11	0.1	0.1	11	0.1	0.1
Epithelial tumour of the thymus	38	0.2	0.2	40	0.2	0.2	30	0.2	0.2	41	0.3	0.2	47	0.3	0.2	39	0.2	0.2
Mixed epithelial and mesenchymal tumour of the uterus	38	0.5	0.4	32	0.4	0.3	29	0.4	0.3	47	0.6	0.4	48	0.6	0.4	39	0.5	0.4
Nonepithelial tumour of the ovary	65	0.8	0.7	62	0.8	0.7	58	0.7	0.6	44	0.5	0.5	67	0.8	0.7	59	0.7	0.6
Epithelial tumour of the vulva and vagina	285	3.5	2.5	304	3.7	2.6	309	3.7	2.6	349	4.2	3.1	332	4.0	2.8	316	3.8	2.7
Trophoblastic tumour of the placenta	4	0.0	0.0	4	0.0	0.0	8	0.1	0.1	10	0.1	0.1	12	0.1	0.2	8	0.1	0.1
Epithelial tumour of the penis	113	1.4	1.3	106	1.3	1.2	117	1.4	1.3	108	1.3	1.2	123	1.5	1.3	113	1.4	1.3
Epithelial tumour of the pelvic ureter and urethra	311	1.9	1.7	351	2.2	1.8	354	2.2	1.8	389	2.4	1.9	417	2.5	2.0	364	2.2	1.8
Epithelial tumour of the eye and adnexa	12	0.1	0.1	13	0.1	0.1	8	0.0	0.0	9	0.1	0.0	13	0.1	0.1	11	0.1	0.1
Epithelial tumour of the middle ear	4	0.0	0.0	4	0.0	0.0	5	0.0	0.0	6	0.0	0.0	9	0.1	0.0	6	0.0	0.0
Malignant mesothelioma	447	2.8	2.5	501	3.1	2.8	491	3.0	2.6	460	2.8	2.4	497	3.0	2.5	479	2.9	2.6
Malignant melanoma of the mucosa	152	0.9	0.8	167	1.0	0.9	174	1.1	0.9	187	1.1	1.0	194	1.2	1.0	175	1.1	0.9
Malignant melanoma of the uvea	183	1.1	1.0	160	1.0	0.9	179	1.1	1.0	170	1.0	0.9	184	1.1	1.0	175	1.1	1.0
Adnexal carcinoma of the skin	92	0.6	0.5	88	0.5	0.4	96	0.6	0.5	115	0.7	0.6	95	0.6	0.4	97	0.6	0.5
Embryonal neoplasms	53	0.3	0.4	69	0.4	0.5	69	0.4	0.5	56	0.3	0.5	61	0.4	0.5	62	0.4	0.5
Extragonadic germ cell tumour	37	0.2	0.2	31	0.2	0.2	31	0.2	0.2	27	0.2	0.2	23	0.1	0.2	30	0.2	0.2
Soft tissue sarcoma	824	5.1	4.6	825	5.1	4.5	831	5.1	4.6	848	5.2	4.6	797	4.8	4.2	825	5.1	4.5
Bone sarcoma	172	1.1	1.0	167	1.0	1.0	208	1.3	1.2	222	1.4	1.3	210	1.3	1.3	196	1.2	1.2
Gastrointestinal stromal sarcoma	142	0.9	0.7	150	0.9	0.8	152	0.9	0.8	146	0.9	0.7	161	1.0	0.8	150	0.9	0.8
Kaposi sarcoma	49	0.3	0.3	53	0.3	0.3	52	0.3	0.3	39	0.2	0.2	57	0.3	0.3	50	0.3	0.3
Neuroendocrine tumours	659	4.0	3.5	733	4.5	3.8	777	4.8	4.0	805	4.9	4.1	803	4.9	4.0	755	4.6	3.9
Carcinoma of endocrine organs	436	2.7	2.4	474	2.9	2.6	443	2.7	2.4	457	2.8	2.5	494	3.0	2.7	461	2.8	2.5
Glial tumour of the CNS and pineal gland	856	5.3	4.9	897	5.5	5.0	886	5.4	5.0	903	5.5	5.0	930	5.7	5.1	894	5.5	5.0
Nonglial tumour of the CNS and pineal gland	38	0.2	0.3	44	0.3	0.3	33	0.2	0.2	51	0.3	0.4	48	0.3	0.3	43	0.3	0.3
Malignant meningiomas	14	0.1	0.1	8	0.0	0.0	8	0.0	0.0	9	0.1	0.1	6	0.0	0.0	9	0.0	0.0
Glial tumour of the autonomic nervous system and paraganglioma	3	0.0	0.0	1	0.0	0.0	–	–	–	2	0.0	0.0	–	–	–	1	0.0	0.0
Nonglial tumour of the autonomic nervous system and paraganglioma	18	0.1	0.1	16	0.1	0.1	17	0.1	0.1	16	0.1	0.1	13	0.1	0.1	16	0.1	0.1
Acute myeloyd leukaemia and related precursor neoplasms	646	4.0	3.5	595	3.7	3.2	617	3.8	3.3	576	3.5	3.0	635	3.9	3.2	614	3.8	3.2
Myeloproliferative neoplasms	429	2.6	2.3	558	3.4	2.9	565	3.5	2.9	578	3.5	2.9	553	3.4	2.8	537	3.3	2.8
Myelodysplastic syndrome	409	2.5	2.1	452	2.8	2.2	457	2.8	2.2	538	3.3	2.6	510	3.1	2.4	473	2.9	2.3
Myelodysplastic myeloproliferative	89	0.5	0.5	79	0.5	0.4	86	0.5	0.4	82	0.5	0.4	97	0.6	0.5	87	0.5	0.4
Histiocytic and dendritic cell neoplasms	8	0.0	0.1	12	0.1	0.1	2	0.0	0.0	7	0.0	0.0	8	0.0	0.1	7	0.0	0.1

CNS, central nervous system; CR, Cancer Registry; ESR, European standardized rate.

Table 2 Incidence of rare second-layer entities that are included in nonrare first-layer entities, the Netherlands 2004–2008

	2004			2005			2006			2007			2008			2004–2008		
Rare second layer entities included in nonrare first layer entities	*N*	CR	ESR	*N*	CR	ESR	*N*	CR	ESR	*N*	CR	ESR	*N*	CR	ESR	Annual *N*	Annual CR	Annual ESR
Epithelial tumour of the oesophagus																		
Squamous cell carcinoma and variants of the oesophagus	543	3.3	2.9	499	3.1	2.6	534	3.3	2.7	527	3.2	2.7	604	3.7	3.0	541	3.3	2.8
Salivary gland type tumour of the oesophagus	0	0.0	0.0	0.0	0.0	0.0	0	0.0	0.0	1	0.0	0.0	0	0.0	0.0	0	0.0	0.0
Undifferentiated carcinoma of the oesophagus	5	0.0	0.0	3	0.0	0.0	2	0.0	0.0	3	0.0	0.0	3	0.0	0.0	3	0.0	0.0
Epithelial tumour of the stomach																		
Squamous cell carcinoma and variants of the stomach	5	0.0	0.0	5	0.0	0.0	9	0.1	0.0	5	0.0	0.0	3	0.0	0.0	5	0.0	0.0
Undifferentiated carcinoma of the stomach	4	0.0	0.0	4	0.0	0.0	1	0.0	0.0	3	0.0	0.0	0	0	0	2	0.0	0.0
Epithelial tumour of the colon																		
Squamous cell carcinoma and variants of the colon	0	0	0	2	0.0	0.0	3	0.0	0.0	1	0.0	0.0	1	0.0	0.0	1	0.0	0.0
Epithelial tumour of the rectum																		
Squamous cell carcinoma and variants of the rectum	3	0.0	0.0	2	0.0	0.0	4	0.0	0.0	7	0.0	0.0	1	0.0	0.0	3	0.0	0.0
Epithelial tumour of the pancreas																		
Squamous cell carcinoma and variants of the pancreas	3	0.0	0.0	3	0.0	0.0	2	0.0	0.0	0	0.0	0.0	1	0.0	0.0	2	0.0	0.0
Acinar cell carcinoma of the pancreas	2	0.0	0.0	5	0.0	0.0	3	0.0	0.0	6	0.0	0.0	6	0.0	0.0	4	0.0	0.0
Mucinous cyst adenocarcinoma of the pancreas	2	0.0	0.0	3	0.0	0.0	4	0.0	0.0	1	0.0	0.0	4	0.0	0.0	3	0.0	0.0
Intraductal papillary mucinous carcinoma invasion of the pancreas	4	0.0	0.0	2	0.0	0.0	1	0.0	0.0	7	0.0	0.0	7	0.0	0.0	4	0.0	0.0
Solid pseudopapillary carcinoma of the pancreas	0	0.0	0	0	0.0	0.0	0	0.0	0.0	1	0.0	0.0	1	0.0	0.0	0	0.0	0.0
Carcinoma with osteoclast-like giant cells of the pancreas	0	0	0	1	0.0	0.0	1	0.0	0.0	1	0.0	0.0	1	0.0	0.0	1	0.0	0.0
Epithelial tumour of the lung																		
Well differentiated endocrine carcinoma of the lung	112	0.7	0.6	112	0.7	0.6	107	0.7	0.6	109	0.7	0.6	134	0.8	0.7	115	1.2	0.6
Bronchioloalveolar carcinoma of the lung	159	1.0	0.9	172	1.1	0.9	171	1.0	0.9	207	1.3	1.1	214	1.3	1.1	185	1.1	1.0
Salivary gland type tumour of the lung	5	0.0	0.0	3	0.0	0.0	8	0.0	0.0	8	0.0	0.0	10	0.1	0.1	7	0.0	0.0
Sarcomatoid carcinoma of the lung	38	0.2	0.2	31	0.2	0.2	40	0.2	0.2	42	0.3	0.2	38	0.2	0.2	38	0.2	0.2
Undifferentiated carcinoma of the lung	29	0.2	0.1	30	0.2	0.2	35	0.2	0.2	18	0.1	0.1	4	0.0	0.0	23	0.1	0.1
Epithelial tumour of the breast																		
Mammary Paget's disease of the breast	41	0.2	0.2	36	0.2	0.2	45	0.3	0.2	56	0.3	0.3	46	0.3	0.2	45	0.3	0.2
Special types of adenocarcinoma of the breast	337	2.0	1.7	317	1.9	1.5	342	2.1	1.6	372	2.2	1.7	386	2.3	1.8	351	2.1	1.7
Metaplastic carcinoma of the breast	38	0.2	0.2	44	0.3	0.2	39	0.2	0.2	51	0.3	0.3	31	0.2	0.2	41	0.2	0.2
Salivary gland type tumour of the breast	11	0.1	0.1	19	0.1	0.1	8	0.0	0.0	14	0.1	0.1	16	0.1	0.1	14	0.1	0.1
Epithelial tumour of the male breast	88	0.5	1.0	93	0.6	1.1	70	0.4	0.8	88	0.5	0.9	92	0.6	1.0	86	0.5	1.0
Epithelial tumour of the corpus uteri																		
Squamous cell carcinoma and variants of the corpus uteri	3	0.0	0.0	5	0.1	0.1	4	0.0	0.0	4	0.0	0.0	1	0.0	0.0	3	0.0	0.0
Transitional cell carcinoma of the corpus uteri	0	0.0	0.0	1	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0-	0.0	0.0	0	0.0	0.0
Epithelial tumour of the cervix uteri																		
Adenocarcinoma and variants of the cervix uteri	129	1.6	1.4	138	1.7	1.5	126	1.5	1.4	144	1.7	1.6	126	1.5	1.4	133	1.6	1.5
Undifferentiated carcinoma of the cervix uteri	0	0.0	0.0	2	0.0	0.0	2	0.0	0.0	3	0.0	0.0	2	0.0	0.0	2	0.0	0.0
Epithelial tumour of the ovary and fallopian tube																		
Mucinous adenocarcinoma of the ovary	106	1.3	1.1	103	1.2	1.1	91	1.1	1.0	87	1.1	0.9	91	1.1	1.0	96	1.2	1.0
Clear cell adenocarcinoma of the ovary	50	0.6	0.6	55	0.7	0.6	62	0.8	0.7	58	0.7	0.6	58	0.7	0.6	57	0.7	0.6
Adenocarcinoma and variants of the fallopian tube	47	0.6	0.5	37	0.4	0.4	32	0.4	0.3	29	0.4	0.3	23	0.3	0.2	34	0.4	0.3
Epithelial tumour of the prostate																		
Squamous cell carcinoma and variants of the prostate	2	0.0	0.0	1	0.0	0.0	2	0.0	0.0	0	0.0	0.0	3	0.0	0.0	2	0.0	0.0
Infiltrating duct carcinoma of the prostate	17	0.2	0.2	13	0.2	0.1	69	0.9	0.8	75	0.9	0.8	44	0.5	0.4	44	0.5	0.5
Transitional cell carcinoma of the prostate	3	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	1	0.0	0.0
Salivary gland type tumour of the prostate	0	0.0	0.0	0	0.0	0.0	1	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0
Tumour of the testis and paratestis																		
Adenocarcinoma and variants of the paratestis	1	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0.0	0.0	0.0	1	0.0	0.0	0	0.0	0.0
Malignant immature teratomas of the testis	167	2.1	2.2	179	2.2	2.3	173	2.1	2.2	172	2.1	2.3	187	2.3	2.4	176	2.2	2.3
Germ cell tumour seminomatous of the testis	304	3.8	3.5	270	3.3	3.2	328	4.1	3.9	334	4.1	4.0	364	4.5	4.4	320	4.0	3.8
Germ cell tumour nonseminomatous of the testis	95	1.2	1.2	126	1.6	1.6	103	1.3	1.3	89	1.1	1.2	119	1.5	1.6	106	1.3	1.4
Trophoblastic tumour of the testis	1	0.0	0.0	0.0	0.0	0.0	4	0.0	0.0	0	0.0	0.0	2	0.0	0.0	1	0.0	0.0
Sex cord tumour of the testis	1	0.0	0.0	1	0.0	0.0	2	0.0	0.0	3	0.0	0.0	4	0.0	0.0	2	0.0	0.0

Epithelial tumour of the kidney																								
Squamous cell carcinoma spindle cell type of the kidney	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	1	0.0	0.0	1	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0
Squamous cell carcinoma and variants of the kidney	2	0.0	0.0	1	0.0	0.0	1	0.0	0.0	0	0.0	0.0	3	0.0	0.0	1	0.0	0.0	1	0.0	0.0	1	0.0	0.0
Epithelial tumour of the bladder																								
Squamous cell carcinoma and variants of the bladder	48	0.3	0.3	67	0.4	0.3	73	0.4	0.4	60	0.4	0.3	58	0.4	0.3	61	0.4	0.3	61	0.4	0.3	61	0.4	0.3
Adenocarcinoma and variants of the bladder	31	0.2	0.2	20	0.1	0.1	26	0.2	0.1	34	0.2	0.2	29	0.2	0.1	28	0.2	0.1	28	0.2	0.1	28	0.2	0.1
Salivary gland type tumour of the bladder	1	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0
Lymphoid diseases																								
Classical Hodgkin lymphoma	362	2.2	2.2	363	2.2	2.2	374	2.3	2.3	383	2.3	2.3	406	2.5	2.4	378	2.3	2.3	378	2.3	2.3	378	2.3	2.3
Hodgkin lymphoma nodular lymphocyte predominant	29	0.2	0.2	26	0.1	0.2	20	0.2	0.1	28	0.2	0.2	37	0.2	0.2	28	0.2	0.2	28	0.2	0.2	28	0.2	0.2
Composite Hodgkin NHL	1	0.0	0.0	0	0.0	0.0	0	0.0	0.0	1	0.0	0.0	4	0.0	0.0	1	0.0	0.0	1	0.0	0.0	1	0.0	0.0
Precursor BT lymphoblastic leukemia lymphoblastic lymphoma	184	1.1	1.2	220	1.3	1.5	230	1.4	1.5	228	1.4	1.5	224	1.4	1.5	217	1.3	1.4	217	1.3	1.4	217	1.3	1.4
Non-Hodgkin mature T-cell and NK-cell neoplasms	233	1.4	1.3	261	1.6	1.4	238	1.5	1.3	246	1.5	1.3	231	1.4	1.2	242	1.5	1.3	242	1.5	1.3	242	1.5	1.3

BT, B cell and T cell; CR, Cancer Registry; ESR, European standardized rate; NHL, non-Hodgkin's lymphoma; NK, natural killer.

Methods

Study population

In this study, data from the population-based Netherlands Cancer Registry (NCR) were included. The NCR covers the complete Dutch population and receives lists of newly diagnosed cancer cases from the nationwide Automated Pathology System (PALGA) on a weekly basis (Casparie *et al.*, 2007). In addition, lists of discharged cancer patients from the national registry of hospital discharge diagnosis are obtained to capture cancer cases with only a clinical diagnosis (About Cancer Registry, 2011). Completeness checks showed a national coverage of about 95% of incident cancers (Goldbohm *et al.*, 1994).

A high level of data quality is secured by the specially trained registry clerks who abstract patient, tumour and treatment characteristics directly from the patient files. International standards set by the International Association for Cancer Registries and the European Network of Cancer Registries are used (Curado *et al.*, 2007). The International Classification of Disease for Oncology, 3rd ed. (ICD-O-3) developed by the WHO is used. To study fluctuations in incidence over several years, we selected data over the period 2004–2008, covering a 5-year period. The period 2004–2008 was selected as this period had the most complete data at the time of data inclusion.

Tumour grouping

The RARECARE project performed a data selection using the EUROCARE 4 database. The RARECARE data collection was carried out following the EUROCARE protocol and using the RARECARE inclusion criteria; this enables the working group to standardize and obtain data checks for analyses (De Angelis *et al.*, 2009; Gatta *et al.*, 2011). The RARECARE project linked their newly developed definition to a predefined list of cancers that follows a three-layer structure of cancer type groupings (entities), including all existing ICD-O-3 topography and malignant morphology codes (Fritz *et al.*, 2000). Layer one entities are considered family of cancers relevant for healthcare organizations, created by grouping layer two entities. Layer two entities are defined in a clinically sound manner (perceived by clinicians as single diseases and relevant for clinical decision making and research) and are based on the third layer that corresponds to the WHO names of individual cancer entities and their corresponding ICD-O-3 codes. The definition for rare and common cancer entities only applies to the first two levels, with a total of 260 cancer types in Europe (59 first layers/201 second layers).

For this study, we classified all cancers according to the RARECARE list (*http://www.rarecare.eu*) (Gatta *et al.*, 2010).

Methods of analysis

The number of newly diagnosed cancers was counted per year per entity for the selected period. Annual incidence rates were calculated per 100 000 person years using the annual mid-year population size obtained from Statistics Netherlands (CBS).

Furthermore, the European standardized rate (ESR) was computed by correcting the crude incidence rate for sex and age using the European standardized population. For the sex-specific cancer entities, we calculated the crude incidence and ESR using the sex-specific population at risk. For all rates, the mean for the 5-year period was determined. All outcomes were compared with the RARECARE results as presented on their website (*http://www.rarecare.eu*).

Results

In the Netherlands, 86% of the RARECARE-defined entities and 17% ($N \approx 14\,000$) of all newly diagnosed cancers should be considered rare according to the RARECARE definition.

Out of the total 260 entities defined by RARECARE, we identified 223 entities (86%) with a crude incidence rate of less than 6.0 per 100 000 per year in the Netherlands over 5 years (Appendix). 'Squamous cell of the cervix uteri' and the 'tumours of the testis and paratestis' were considered rare in Europe, but common in the Netherlands, whereas 'Tumours of the liver and intrahepatic bile tract' and the 'epithelial tumours of the hypopharynx and larynx' were rare cancers in the Netherlands, but common in Europe. The 223 rare entities included 42 rare first-layer cancer entities (Table 1) and 181 second layer entities. Of these second layer entities, 54 (incidence rate < 6.0 per 100 000 person years per year) were included in 15 nonrare first-layer entities (incidence rate ≥ 6.0 per 100 000 per year) (Table 2). An example is the rare second-layer entity 'epithelial tumour of the male breast', which is included in the not rare first-layer entity 'epithelial tumour of the breast'.

In the years 2004–2008 combined, more than 71 000 patients were newly diagnosed with a rare cancer type. On an average, the crude number resulted in 14 279 rare cancers (range 13 421–15 108) per year out of a total of 84 479 cancers (range 80 616–89 228) per year in the Netherlands (Table 3).

Table 4 shows that for the period 2004–2008, the group with an annual incidence rate of up to 0.5 per 100 000 comprised an estimated number of 881 cases per year, representing 6.2% of all rare cancers. This group of very rare cancers consists of a relatively large number of entities ($N = 85$). Of these, 54 entities were rare second-layer entities within nonrare first-layer entities, representing 23.9% of all rare tumours and 4.0% of all cancers. The annual crude incidence rate was generally very low for these entities, with the exception of squamous cell carcinoma and variants of the 'Oesophagus' and 'Germ cell seminomatous tumours of the testis' (crude incidence rate > 3 per 100 000 per year) (Table 2).

We observed fluctuations in incidence rates for many cancer types through the years 2004–2008 for some first-layer entities. The difference in crude rate was 0.9 per 100 000 (149 cases) for 'Myeloproliferative neoplasms' between 2004 and 2007 (Table 1). However, the largest difference in ESR between the highest and the lowest count was 0.9 per 100 000 per year for the 'Epithelial tumour of the hypopharynx and larynx', accounting for an absolute difference of 124 cancer cases between 2005 and 2007 (Table 1). Fluctuations in incidence over the years also showed that the cut-off of less than six per 100 000 per year could be crossed during the time period. An example is the entity 'Adenocarcinoma and variants of the oesophagus', for which a crude incidence rate of 5.4 per 100 000 per year was calculated in 2004, which increased steadily to 7.2 per 100 000 per year in 2008, crossing the limit of 6.0 per 100 000 per year in 2006.

Discussion

In this study, the recently developed European definition for rare cancers was applied to the Netherlands. In the Netherlands, 86% of the RARECARE-defined entities and 17% ($N \approx 14\,000$) of all newly diagnosed cancers should be considered rare according to this definition of a crude incidence rate of less than six cases per 10 000 per year. For the 5-year period 2004–2008, over 71 000 newly diagnosed rare cancers were observed. Under the assumption that there would be an even distribution over all hospitals, a crude incidence of six per 100 000 per year would account for a maximum of 11 newly diagnosed patients with a specific type of rare cancer per hospital per year or 1000 incident cases per year in the Netherlands on the basis of 16.7 million inhabitants and over 90 hospitals. Furthermore, these patients would probably be diagnosed and treated by different clinicians in each hospital. Of course, this assumption does not reflect daily practice. Some patients will be referred to, for instance, university hospitals, resulting in even fewer or no patients per year in a general hospital.

The percentage of rare cancer types among all cancer diagnoses was similar to the RARECARE findings (about 17%) and was divided over a similar number of entities.

We observed fluctuations of almost one per 100 000 per year in crude rates over the years. This may have consequences for the entities with a crude rate around six per 100 000 person years. These entities could be classified as rare one year and as nonrare the next year. We suggest using the average incidence rate over 5 years to limit random fluctuations affecting the classification as rare cancer or not. An example in our results is oesophageal

Table 3 Number of rare and all tumours for the years 2004–2008

	2004	2005	2006	2007	2008	2004–2008 Total	2004–2008 Average per year
N of rare tumours	13 421	13 980	14 218	14 668	15 108	71 395	14 279
N of all tumours[a]	80 616	81 632	84 119	86 800	89 228	422 395	84 479
Rare tumours (%)	16.6	17.1	16.9	16.9	16.9	16.9	16.9

[a]Source Netherlands Cancer Registry, available at: *http://www.cijfersoverkanker.nl*.

Table 4 Incidence per year on actual number of tumours for 2004–2008 and number of entities included

	N per year	Percentage of all rare	Percentage of all tumours	*N* of entities	Percentage of *N* entities
≤0.5	881	6.2	1.0	85	33
>0.5<1.0	816	5.7	1.0	25	9.6
≥1.0<2.0	1607	11	1.9	21	8.1
≥2.0<3.0	3865	27	4.6	28	11
≥3.0<4.0	2904	20	3.4	26	10
≥4.0<5.0	755	5.3	0.9	9	3.5
≥5.0<6.0	3451	24	4.1	29	11
Total	14 279	100.0	16.9	223	85.8

adenocarcinoma, which would be classified as rare in 2004 (not shown), but would be considered not rare in the following years because of increasing incidence. A European study also observed increasing incidence rates for oesophageal adenocarcinoma (Bosetti *et al.*, 2008).

Some sex-related cancers, such as 'Tumours of the testis and paratestis' and 'Squamous cell of the cervix uteri', were classified as nonrare in the Netherlands, but as rare in the RARECARE data set. This difference is the result of different methods used to calculate the crude incidence rate. In the RARECARE project, the total population without differentiating for sex was used, whereas in our study, we only used the population at risk for the sex-related tumours, which results in higher incidence rates. This same effect is detectable in all sex-related tumours, but does not result in differences in classification. Owing to the definition of the incidence rate, we suggest use of the sex-specific population at risk. However, we do agree that the limit should then also be changed to 12 per 100 000 for sex-specific cancers and that this limits the applicability of the new definition.

Four entities were not rare in Europe but rare in the Netherlands or vice versa. One of those entities concerns 'Epithelial tumours of the hypopharynx and larynx'. This difference was mainly because of the second-layer group 'Squamous cell carcinoma and variants of the larynx', and not 'Squamous cell carcinoma of the hypopharynx'. The remaining difference was found at the first-layer level, which includes unspecified and not otherwise specified codes. Because some cancers are classified as not otherwise specified, we expect an underestimation for the incidence rates in the second-layer entities. We observed this clearly in the data for 'Epithelial tumours of the pancreas', where a nonrare first layer crude incidence of 10.4 per 100 000 per year was observed, whereas the sum of all rare second-layer crude incidences equalled only 6.4 per 100 000 per year. This phenomenon was also observed within European RARECARE data, and will affect cancers that are mainly diagnosed clinically (without pathological confirmation) more strongly. The RARECARE project also reports this effect for the epithelial tumours of the oesophagus. Our findings suggest a better classification in the NCR because the sum of the incidence rates of all second-layer entities comes close to the incidence rate for the first nonrare layer entity. This indicates a more detailed pathologic diagnostic workup and coding in the Netherlands compared with overall RARECARE data. Differences in outcome between RARECARE and NCR data may partly be explained by the inclusion of different incidence years (1995–2002 for RARECARE and 2004–2008 for the Netherlands). Because tumour classification evolves continuously because of improved knowledge and better techniques, a yearly update of the analyses carried out by the RARECARE project, on the basis of the average for the most recent five incidence years for which data are available, should be carried out to provide an overview and monitor the current situation of rare cancers in Europe. To determine the differences in rare cancer between countries, we propose that each country develop a national list of rare cancers. Country-specific incidence rates would also provide insight into the experience level of countries with specific cancer entities. This knowledge may subsequently lead to further clinical and/or scientific collaboration.

Diagnosing and registering rare cancers, however, will always be more difficult than diagnosing and registering nonrare cancers because rare cancers (by definition) are encountered less regularly. Therefore, misclassifications may have occurred. Within the RARECARE project, a data quality check was carried out, which covered the years 1995–2002 and included three Dutch Cancer Registries, covering 44.5% of the total population of the Netherlands. These results were published on the RARECARE website; *http://www.rarecare.eu*. In summary, the quality check for the Netherlands included a review of 1018 cancers using the original patient files. Overall, for all cases reviewed, the majority was found to be registered correctly. For the selection of Dutch Cancer Registries, a percentage ranging from 4.1 to 5.3 unspecified morphology cases was found, which was one of the

lowest percentages for the participating Cancer Registries.

In conclusion, some improvements to the definition of rare cancers could be made. First, by determining the cut-off on the basis of an average annual rate of less than six per 100 000 over 5 years instead of 1 year, the influence of fluctuations on the classification can be obviated. Second, a sex-specific incidence limit should be introduced.

In the Netherlands, almost one in six cancer patients is affected by a cancer that is considered to be rare. Many of these rare tumour entities were very rare, with an incidence rate below 0.5, equalling ~100 cases per year, in the Netherlands, indicating the challenge that faces clinicians confronted with a patient with such a rare cancer. This also shows the need for (inter)national cooperation in caring for these patients. Furthermore, exploration of diagnostic, treatment and outcome, and referral patterns is needed and may help to identify caveats to research, which can help to enhance the care for patients with rare cancers.

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Conflicts of interest

There are no conflicts of interest.

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