European Journal of Cancer (2015) 51, 997–1017

Available at www.sciencedirect.com

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journal homepage: www.ejcancer.com

EUROCOURSE lessons learned from and for population-based cancer registries in Europe and their programme owners: Improving performance by research programming for public health and clinical evaluation ☆

Jan Willem Coebergh [a,b,1], Corina van den Hurk [a,c,1,*], Stefano Rosso [d,1,2], Harry Comber [e,1], Hans Storm [f,1,2], Roberto Zanetti [d,1], Lidia Sacchetto [d,g], Maryska Janssen-Heijnen [a,h], Melissa Thong [a,i], Sabine Siesling [c,j,1,2], Janny van den Eijnden-van Raaij [a]

[a] *Eindhoven Cancer Registry, Comprehensive Cancer Centre South (IKZ), PO Box 231, 5600 AE Eindhoven, The Netherlands*[3]
[b] *Dept. of Public Health, Erasmus University Medical Cancer Centre, PO Box 2040, 3000 CA Rotterdam, The Netherlands*
[c] *Dept. of Registration and Research, Netherlands Comprehensive Cancer Organization, PO Box 19079, 3501 DB Utrecht, The Netherlands*
[d] *Piedmont Cancer Registry – CPO, Centre for Cancer Prevention, Torino, Italy*
[e] *National Cancer Registry, Building 6800, Cork Airport Business Park, Cork, Ireland*
[f] *Dept. of Cancer Information, Danish Cancer Society (DCS), Copenhagen, Denmark*
[g] *Cancer Genomics Lab, Fondazione Edo ed Elvo Tempia, Biella, Italy*
[h] *Dept. of Clinical Epidemiology, Viecuri Medical Centre, PO Box 1926, 5900 BX Venlo, The Netherlands*
[i] *Dept. of Clinical Psychology, Tilburg University, PO Box 90153, 5000 LB Tilburg, The Netherlands*
[j] *Dept. of Health Technology and Services Research, MIRA Institute of Biomedical Science and Technical Medicine, University of Twente, PO Box 217, 7500 AE Enschede, The Netherlands*

Received 8 December 2014; received in revised form 3 February 2015; accepted 3 February 2015
Available online 5 May 2015

KEYWORDS
Cancer registry
ERA-net
Programme owner
Linking databases

Abstract Population-based cancer registries (CRs) in Europe have played a supportive, sometimes guiding, role in describing geographic variation of cancer epidemics and comparisons of oncological practice and preventive interventions since the 1950s for all types of cancer, separate and simultaneously. This paper deals with historical and longitudinal developments of the roughly 160 CRs and their programme owners (POs) that emerged since

© **EUROCOURSE** was financed within the 7th framework of the European Union by the Directorate General (DG) Research and Innovation (EU grant agreement 219453): 'EUROpe against Cancer: Optimization of the Use of Registries for Scientific Excellence in research'.
* *Corresponding author at:* Dept. of Registration and Research, Netherlands Comprehensive Cancer Organization, PO Box 19079, 3501 DB Utrecht, The Netherlands.
[1] Executive Board of EUROCOURSE.
[2] Steering committee ENCR until November 2014.
[3] Since 2014 Netherlands Comprehensive Cancer Organization (IKNL).

http://dx.doi.org/10.1016/j.ejca.2015.02.018

Epidemiology
Biobank
Mass screening evaluation
Data protection
Quality of oncological care
Survivorship

1927 and accelerating since the late 70s especially in southern and continental Europe. About 40 million newly diagnosed patients were recorded since the 1950s out of a total of 100 million of whom almost 20 million are still alive and about 10% annually dying from cancer. The perception of unity in diversity and suboptimal comparability in performance and governance of CRs was confirmed in the EUROCOURSE (**EURO**pe against cancer: **O**ptimisation of the **U**se of **R**egistries for **S**cientific **E**xcellence in research) European Research Area (ERA)-net coordination FP7 project of the European Commission (EU) which explored best practices, bottlenecks and future challenges of CRs. Regional oncologic and public health changes but also academic embedding of CRs varied considerably, although Anno 2012 optimal cancer surveillance indeed demanded intensive collaboration with professional and institutional stakeholders in two major areas (public health and clinical research) and five minor overlapping cancer research domains: aetiologic research, mass screening evaluation, quality of care, translational prognostics and survivorship. Each of these domains address specific study questions, mixes of disciplines, methodologies, additional data-sources and funding mechanisms. POs tended to become more and more public health institutes, Health ministries, but also comprehensive cancer centres and cancer societies through more and more funding at project or programme basis. POs were not easy to pin down because of their multiple, sometimes competitive (funding) obligations and increasing complexity of cancer surveillance. But they also rather seemed to need guiding principles for Governance of 'their' CR(s) as well as to appreciate value of collaborative research in Europe and shield CRs against unreasonable data protection in case of linkages. Despite access to specialised care related shortcomings, especially of survival cohort studies, European databases for studies of incidence and survival (such as ACCIS and EUREG on the one hand and EUROCARE and RARECARE on the other hand) have proved to be powerful means for comparative national or regional cancer surveillance. Pooling of comparable data will exhibit much instructive variation in time and place. If POs of CRs would consider multinational European studies of risk and prognosis of cancer more to serve their own regional or national interest, then progress in this field will accelerate and lead to more consistent funding from the EU. The current 20 million cancer survivors and their care providers are likely to appreciate more feedback.

Conclusion: Most CRs remain uniquely able to report on progress against cancer by studies of variation in incidence (in time and place), detection and survival, referral and treatment patterns and their (side) effects in unselected patients, the latter especially in the (very) elderly. Programming and profiling its multiple and diverse clinical and prevention research is likely to promote involvement of public health and clinical stakeholders with a population-based research interest, increasingly patient groups and licensed 'buyers' of oncologic services.

1. Introduction

Population-based cancer registries (CRs) have been around in Europe for more than 70 years; their performance varies greatly despite uniform objectives and the methodology of acquiring standardised minimal data on all new cancer cases – altogether almost 3.5 million in Europe in 2012 [1]. About 55% of these cases were collected in one of the (currently 160) operational CRs serving between 250,000 (Iceland) and 56 million (England) people (median about 1.2 million) [2]. In the last 60 years data from almost 40 million newly diagnosed cancer patients may have been collected out of an estimated total of 100 million, and of whom 15–20 million are currently alive, about 10% with a second or third tumour, and of whom almost 2 million die each year from cancer (i.e. 1 in 10). The cancer burden can roughly be divided in as many epidemics as there are organ (sub)sites and subtypes, and caused by or related to a wide array of major exposures, e.g. to tobacco, alcohol, asbestos, UV, deficient diet and physical exercise, infections and less or late childbirths, etc. – often decades ago and changing by birth cohort. Emergence and declines of these cancer epidemics are simultaneously measured and comparatively described in population-based CRs to support optimal surveillance – i.e. anticipation and outcome. Surveillance is practiced for public health purposes (wider than just cancer) and for clinical stakeholders engaged in all sorts of improvement of cancer management, usually with long term effects only. Anno 2014, up to 50% of the patients with cancer ultimately died from a non-cancer death or another cancer.

Text Box 1 Major results from the EUROCOURSE project by work package (WP)

Major deliverables, products and recommendations to be found at: www.eurocourse.org

- WP 1.3 Survey on research and funding [2]
- WP 1.4 Best CR practices
- WP 1.5 In search of programme owners
- WP 1.6 Governance for programme owners
- WP 2.2 Confidentiality guidelines
- WP 3.3 Data quality control
- WP 4 Exploration of potential users by research domain
- WP 4.5 European Cancer Observatory
- WP 5 Guidelines for linkage of CRs to screening registries
- WP 6.3 State of the art of effective use of registry indicators in evaluating cancer care
- WP 6.5 Overview of clinical cancer registries in Europe
- WP 7 Guidelines on linkage between biobanks and CRs
- WP 8 International collaborative studies by research domain
- WP 9.2 Report of Cancer Registry Summit at ECCO Oncopolicy Meeting
- WP 9.3 Brochure on CRs in Europe and role of European Network of Cancer Registries [80]

Since 1988, two major overlapping European networks (Eurocare and ENCR) of an increasing number of CRs have been developed with modest support of Europe against Cancer (EaC). They were simultaneously coordinated by the epidemiological and biostatistical departments at the International Agency for Research on Cancer (IARC) in Lyon, showing a wide variety of incidence across the world and thus avoidability (also appearing from Cancer Incidence in 5 Continents (CI5)). The combined Istitutos Nazionale dei Tumori in Milan and Superiore di Sanità (ISS) in Rome mainly estimated survival rates in unfortunately heterogeneous cohorts of newly diagnosed cancer patients in as of 2007 almost 100 CRs. Despite great variation in governance and financing of CRs in the various member states (MSs) these CR networks have produced many eye catching studies on variation in time and place of incidence and survival across Europe. [1,3–5] Mortality data from traditional cause-of death statistics assembled by the WHO were often published by rivalling Milanese researchers [6]. The networks also developed quality standards for such population-based studies [7] and Eurochip developed a range of indicators for prevention, detection and oncological management financed by DG Sanco at the end of EAC and thereafter [8]. Since 2004 the European Commission (EC) through DG Research and Innovation financed coordination projects, the first on cancer prevention by scenario development, the Eurocadet project (www.eurocadet.org), still used for prevention of cancer in a few countries [9,10]. Since 2008, another coordination project by DG Research (EUROCOURSE) explored the strengths, weaknesses and perspective of the – European CR infrastructure for comparative and collaborative studies (including controversial legal aspects and costs), based on extensive participation of CRs, the various stakeholders, including professional care providers and patient groups and CR programme owners (POs) (Text Box 1). EUROCOURSE is the acronym for **EURO**pe against cancer: **O**ptimisation of the **U**se of **R**egistries for **S**cientific **E**xcellence in research.

Text Box 2 Cancer control versus cancer surveillance

The word 'registry' – disease and/or intervention related administrative activity – has become more popular throughout specialised medicine, aimed on improving its safety or its quality. It is often related to serving cancer control. Cancer surveillance is more dynamic, because it has elements of exploring, overseeing and looking ahead. It is about monitoring everything with effects on epidemiological and clinical indicators and relate them to technological innovation. Scenario development is an important element here because it advances anticipation, also of capacity, manpower and the research agenda. As long as oncology changes in terms of incidence, detection, staging and treatment, cancer registries are likely to be needed for research activities extending from early warning to quality of terminal care. But they are also needed to looking ahead and looking back, decades after extinction.

An example: based on studies in the Netherlands and the NOCCA study in the Nordic countries, scrotal carcinoma may now have gone in extinction in Europe 240 years after its first notification by Sir Percival Potts. If one imagines that the modern smoking related lung cancer epidemics started at around 1925 still the end is not yet in sight for the next 50–100 years [24].

Preceding the Horizon 2020 research programme, DG Research also appeared interested in a co-funding role for POs of biomedical cancer research (including CR-based performance of pan-European studies). The potential for all sorts of data linkages of CRs with other clinical and public health research cohorts was likely to be essential, but thus far appeared rather dependent on national interpretation of the EU guideline on Data Protection of 1995, only gradually converging [11].

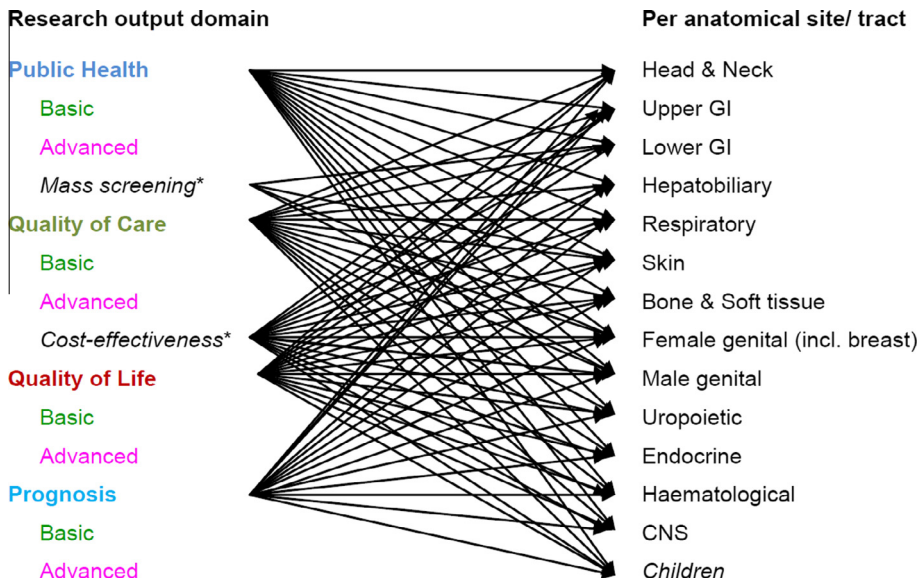

Fig. 1. Illustration of potential multitude of cancer research and/or service programme activities of population-based cancer registries (CRs): per anatomical site/tract. *_Mass screening:_ only colorectal, breast and cervix (Research ongoing of Prostate and Lung cancer and Melanoma). *_Cost-effectiveness:_ active input of CRs for such estimations from quality of care and quality of life domains.

As CRs are by definition recording the impact of geographic change in epidemiology, oncology and health policy, longitudinal developments within CRs at regional and national level affect the scope of its contribution to European studies as appears in the Annex Tables, listing the 160 General and specific CRs in Europe [2].

The 'lessons learned 'from and for' the format of this paper also illustrate that as an European Research Area (ERA-net project) EUROCOURSE did not only strive towards a big coordinative structure of epidemiologic/oncologic ('technocratic') datasets (as if it were a 'Big Cancer Data' project, it also led to soul-searching of identity and the clinical and public health environment. In most European countries 50–60% of all deaths at middle age (35–69 years) were due to cancer, making it the largest health burden, especially when death due to violence and vascular disease is relatively low, in peace and in non-smoking times. Although E-Health – of which CRs are gradually becoming a part – conveys rather short term realisable policies, often joined by Big Data and Big Pharma forces through our POs, traditional cancer prevention and cancer management in fact have very long time axes [12]. Taking into account that most cancers have a long history (of exposure and latency time) and an increasingly long duration, after (earlier) detection, and more effective therapeutic interventions, then it takes often more than five decades to emerge and to be counteracted effectively, often with long term side-effects, if not deranged by vested interests. Long-term survivors (the prevalence of cancer rose from 1% to 4% in the last 50 years and can be 20% over the age 70) [81] play a more predominant role in current cancer management and research, whether CR-based or not. Moreover, learning processes of clinical oncologic and supportive care are also spanning decades determined by investments in diagnostic and therapeutic infrastructure and sub-specialisation. Stimulated by increasing patient awareness the requirements for population-based data management have risen markedly as advocated by Donabedian already in the 1960s and likely more when there were population-based data available [13].

2. Registries and EUROCOURSE methods

The EUROCOURSE consortium consisted of 15 – mostly smaller – participating CRs, five POs (who delegated their Programme managers – (PMs)) and four stakeholder users in research institutes. The project, submitted during 2007, was finally coordinated by the Comprehensive Cancer Centre South (CCC/IKZ), one of the nine CCC's at the time in the Netherlands.[4] The project website www.eurocourse.org shows activities and deliverables per workpackage (WP) (see Text Box 1) also described in articles in this special issue. Exploration of strengths and bottlenecks in CR performance also included a search for the presumably heterogeneous group of scope-determining (POs), often facilitating funding rather than out of pocket.

[4] IKZ functioned as PO of the Eindhoven Cancer Registry, starting in 1955 and complete since 1970, part of the Netherlands Cancer Registry since 1989, and merged with the newly founded Comprehensive Cancer Centre the Netherlands (IKNL) in 2013 at request of its new Programme Owner, the Ministry of Health.

Technically, WP1 and WP3 of EUROCOURSE explored the various determinants of the history, governance, coverage, scope and timeliness of population-based CRs, also taking longitudinal regional and (inter)-national developments of European CRs into account, including epidemiological and oncological changes. Most CRs – logically more often responsible for good practices – sent senior researchers, often PMs, to meetings. POs mostly attended meetings of the Steering Board (WP10), the WP1 committee on Governance and the CR Eurosummit (WP9). Workshops and conferences were attended by about 250 experts, about 80 regularly, mostly epidemiological and clinical researchers, incidentally policy-makers and representatives of patient groups (like brain tumours, prostate cancer and leukaemia) (see the Appendix list). Most active CR-data users came from one of five distinct, but overlapping cancer research areas (Table 2), divided in *Public Health* (i.e. the research domains of Aetiology and Mass screening) and *Clinical* (research domains of Quality of care, survivorship and prognostics), each variably pertaining to a tumour or tract.

For the 2-day Summit in November 2011, in ECCO Oncopolicy format, invitations were addressed to about 150 broadly selected people, including Europarlementarians; one half of the 120 attendants had participated in the project and the rest represented European stakeholders of CRs or their POs (patient groups, professional oncologists (European CanCer Organization-ECCO, European Society of Surgical Oncology-ESSO, Academy of Cancer Scientists – at ECCO, International Society of Geriatric Oncology (SIOG) and Pediatric Oncology (SIOP), the European Partnership Against Cancer (EPAAC founded in 2010 through DG Sanco), numerous PMs of clinical CRs including EURECCA, mass screening evaluative experts from Italy, England and Finland and an EMA-expert. About 35 presentations dealt mostly with good CR-practices, bottlenecks, challenges ahead like the increasing need to estimate and evaluate the health impact of costly precision medicine as independently as possible, contributions to research on cancer management in the elderly and of survivorship. Numerous good practices of CR operations and methodological approaches, study designs and dissemination practices (increasingly web-based) were identified, usually from the more visible (i.e. regularly publishing) CRs and their context. In WP1 these publications have been summarised per WP for the aforementioned cancer research domains. Standards and Guidelines developed between 1992 and 2002 within the European Network of Cancer Registries (ENCR) [7] might also be considered as dissemination practices. Finally, there were mini-inventories on CR-practices in all WPs among the participants and about 350 oral presentations at the 30 WP-and 5 SB meetings. A WP8 meeting in Romania in 2011 was organised with the Romanian Ministry of Health and for CRs from the new MSs and other Balkan countries to explore the multitude of disruptive developments: medically, socially (effects of economic crisis [14]) but also from ill-conceived E-(public) Health and electronic patient record initiatives. The CR researchers from South-East Europe also devised a format for publishing trends in incidence and mortality of the most important cancers as a basis for more [15,17].

Synthesising the various WP end reports in 2013 and articles for this special issue in 2015, contributed to refining and broadening policy conclusions because of overlapping relevance and also affected by recent developments in operational and strategic conditions for European CRs (by WP):

- Worried excitement and confusion around privacy regulation in Europe (WP2), (since 2011)
- Increasing attention for conducting population-based clinical CR studies (WP6) of:
  - Medical and social aspects of survivorship,
  - Management of cancer in the (very) elderly,
  - Application and (side)effectiveness of high cost precision medicine,
  - Impact of regionalisation of highly complex oncologic and/or low volume treatments,
  - Proliferation of clinical cancer registries for quality assurance and awareness since 2006.
- Emergence of more interactive software for E-health with its broadening and disruptive features,
- Proposed migration by EC of the ENCR secretariat from IARC to JRC Ispra (2011-) (WP4,8),
- Frequent shifts in governing programme owners (POs) in the various MMs.

3. Results and discussion: lessons learned from and for CRs

While eying at future challenges in oncology and epidemiology we considered that the rather homogeneous methodology lessons were largely learned from best and bad practices against background of differential longitudinal development of European CRs. CRs were so heterogeneous as of performance reflected by a diverse involvement of CRs in mass-screening evaluation, population-based clinical evaluation and the need for linking with emerging biobanks. Lessons were clearly learned by programming and profiling of cancer research within CRs by five major overlapping cancer research domains in clinical and public health research

and the evolution of European networks of EUROCARE and ENCR.

3.1. Longitudinal development of CRs: from professional database to horizontal information centre for cancer surveillance

CRs in Europe initially added to the already existing causes-of-death registries developed in the 19th century [18–20] that are still the source of regular 'quick and dirty' reports [6], incidentally also by Eurostat [21]. Most CRs exhibited gradual professional growth in production of incidence, since 15 years increasingly disseminated through websites, but with great diversity in research participation. They seem strongly attached to their original mission, often there before the arrival of electronic media: describing oncologic practices and/or serving public health. The latter objective logically prevailed with the apparent occurrence of the big cancer epidemics e.g. of lung, breast, prostate, skin and colorectal cancer, lymphomas and evaluation of organised mass screening projects. Screening often created their own tumour-specific CR whose function was sooner or later taken over by a general CR. Since the 70s and especially during the 80s worries about carcinogenic effects of atomic energy – nuclear testing (1961), Three Mile Island (1979), Chernobyl (1986) and leaking nuclear power plants in the UK (Sellafield, 1983), followed by such turmoil in France and Germany, provoked a multitude of CR-based analyses of clusters of especially leukaemia, lymphomas and also brain tumours in the young [22]. Worries lowered with plausibility of the frequently tested theory of popular mixing [23]. Surprisingly less attention went and still goes to the gradual disappearance of the epidemics of e.g. non-cardia stomach, scrotal [24], gallbladder [25], and even cervical (here and there) cancer, the latter partly by mass screening, partly a (behavioural) birth cohort effect. Some CRs also interacted with oncological care by developing scenario's (through trend analyses) for underpinning resource investments (e.g. for optimal delivery of radiotherapy), ever in need of adequate long-term planning everywhere due to preparation times of 10–20 years [26]. Such therapy scenarios might also be followed by a verifying CR research agenda of studies of adherence to care (lower in elderly patients?) and of effects of therapeutic interventions on survival and/or mortality [27]. It is now clear that this must be done in the broader context of Progress against Cancer [28]. Therapies might also improve and compete with the often dreamed effects of mass screening. Public health can be strengthened (from its eternal backward position in primary prevention) by scenario development of interventions, that may vary across Europe with levels of exposure, like tobacco, alcohol and physical exercise (www.eurocadet.org) [10].

CRs have often been started by medical pioneers from social medicine, pathology or radiotherapy, horizontal disciplines used to connect with most specialties, since 1927 (Hamburg) and 1943 (Denmark) and expanding in every decade since the 1950's [2]. The emergence of mostly regional (100) and national (20) general CRs within the EU area, including Switzerland and Norway, was for a long time largely in areas below 1 million (regional) or $\leqslant$8 million (nationally) inhabitants (Table 1). The bigger the country, the less strong a national initiative (still nowadays except in England). During the last decade Health authorities (POs or not) in most of the bigger MSs were increasingly trying to consolidate 'their' regional CRs into national network-organisations, sometimes overtaking loco-regional programme ownership albeit with invariably opaque funding arrangements. Childhood CRs have sometimes taken historical precedence based on their unique combination of rarity, specificity (embryonal tumours) and tailor-made complex and aggressive treatments. Children are a vulnerable group with great attention for clustering, emotional aspects and avoiding side-effects that have affected long term survivors more than expected in dedicated surveillance (idem for testicular cancer in young adults).

Although the CR oncological and public health movement was mostly (selectively?) regional and thus patchy, especially in bigger MSs, it showed multi-regional coalitions of 'willing' CRs to be very instrumental for later national efforts. The networks of regularly publishing regional CRs in Italy [29], Spain [30], France [31] and also Germany [32] illustrate this.

3.1.1. Conclusion

Historical development of CRs was and still is largely regionally heterogeneous, but with homogenous methodology: changes in often regional epidemiology and organisation of oncology, wealth and awareness of the public greatly affected the CR research agenda. Pioneering regional CRs in bigger countries seem pivotal for national developments by their intrinsic informational value and training researching experts.

3.2. Lessons learned from the search for our POs (WP1,4) (see Text Box 3)

Before Eurocourse POs had not been very prominent: every CR somehow has an authority (a sort of necessary evil) which supplies (some of) the funding and defines its scope (more or less) and cares (too much?) about privacy. But a PO can also – more or less suddenly – transfer its CR to another PO for financial and/or

Table 1
Overview of starting regional or national population-based cancer registries (CR) in Europe by decade of start (i.e. of publishing incidence data) and divided into small, intermediate and larger sized countries (derived from Siesling et al. [2]).

Starting period	<10 million (small)		10–19 million at the start (intermediate)		⩾20 million (big)	
	Regional*	National*	Regional	National	Regional	National
<1950		Denmark			Hamburg (Ge)	
1950–1959		Finland			East Anglia, Oxford, Northwest, West Midlands (Eng)	
	Iceland*	Norway			Scotland (UK)	
	6 regions (Swe)	Sweden				
		Croatia				
		Bulgaria	3 areas NL			
		Slovenia	Berlin, Thuringen Brandenburg,	Former East-		
1960–1969		Estonia	Saxen Frei + Anhalt	Germany (until	England (UK)	UK (CC)
			Meckelenburg	1990)	Northern Ireland (UK)	
		Slovakia				
1970–1979	Geneve, Neuchatel,	Austria	Eindhoven (NL)	Netherlands CL	Burgundy 3 for tracts, Bas Rhin, Calvados, Isere (Fr)	
	Vaud, Basel (Swi)				Saarland (Ge)	
		Czech Repu	South Portugal		Southwest, Trent, Yorkshire-Northeast (Eng), Wales (UK)	United Kingdom
		Lithuania			Varese, Parma (It)	
					Cracow (Pl)	
					Cluj (Romania)	
					Navarra (Sp)	
1980–1989	Zurich, SG-Appenzell		8 regional CRs of CCC's (NL)	Netherlands	Tuscany, Veneto, *Piedmonte (also CC)*, Ragusa, Romagna (It)	Germany (CC)
	Valais, Graubunden (Swi)				Kielce (Pl)	
	Tyrol (Aus)	Belarus CC	North Portugal		Basque Province, Granada, Tarragona, Mallorca, Asturia (Sp)	
					Hérault, Haut Rhin, Somme, Tarn (Fr)	
1990–1999	Malta*	Greece CL	Azores Portugal		Girona, Rioja, Cuenca, Canary, Albacete (Sp) + CC	
					Umbria, Alto Adige, Trento, Sassari, Salerno, Reggio Friuli, Ferrara, Latina, Napoli-Campania, Sondrio, Biella, Brescia (It)	
	Cyprus*	Ireland			Műnchen, Schleswig–Holstein, Westfalen (Ge)	
	Ticino (Swi)@	Latvia	Limburg Prov (Be)		Lower Silezia (Pl)	
2000–2009			Flanders (Be)		Loire, Gironde, Manche (Fr)	France (CS and CL) (only)
				Belgium	Bavaria, Niedersachsen, Nordrhein (Ge)	Spain (CC almost)
					Trapani, Milano, Mantova, Lecco, Como, Catanzaro, Catania-Syra (It)	
2010+		Switzerland		Netherlands (new)		England (UK) # (new)
2014	10 regional + 3 *national**	15 (+2 CC)	20	2 (+1 CL)	68 (+1 CC)	1 (+4 CC)

CC, childhood cancer; CL, childhood leukaemia; SCC, solid childhood cancer; CCC, Comprehensive Cancer Center.
NL, the Netherlands; Be, Belgium; Ge, Germany; Sp, Spain; Fr, France; It, Italy; Swi, Switzerland; Aus, Austria; Pl, Poland; Swe, Sweden; Eng, England; UK, United Kingdom.
@: after a plebiscite. **National CRs covering <CRs below 500,000 inhabitants classified as regional.*
#United Kingdom: virtual except for childhood cancer until devolution; English CRs merged into one database held by Public Health England as of 2014, including childhood cancer.
Lesson learnt: tendency to nationwide registry from the start in smaller countries and regional bottom-up approach in larger member states, including the UK (unless England, also with its sport teams, is (also) considered as a country).

strategic reasons: a power struggle. But the EC also wanted to bring POs in a co-funding role for research financing, while certainly with the financial crisis most of our POs wanted more funding from a.o. the EU, especially upon arrival of the new MSs [33]. The financial picture markedly varied for most of the 160 functioning CRs, that could be recognised as productive participants within the ENCR through their participation in international studies [2]. With some exceptions (Iceland, (northern) Ireland, Finland, England, France, the Netherlands and Belgium) a focused contact with POs as mentioned in Table 1 was not easy whether on content or finance.

Text Box 3 In search of Programme Owners of population-based research oriented CRs in Europe

A programme owner (PO) is – according to DG Research and Innovation of the EU – responsible for the mission and funding of the programme of (biomedical) research activities and might thus invest with other POs in a common research programme carried out across the EU, e.g. in the Horizon 2020 programme. The more (proportional or in-kind) input from specific (the more the better) member states (MSs) the likelier or higher EU-contribution, provided relevant study questions are addressed. Although not fully aware, POs of research oriented CRs are thus also important in this respect, but until now being more interested in their national challenges. In the past POs of CRs were usually:

- Cancer Societies (charities), often in smaller populations in North-Western Europe
- Cancer Institutes (traditionally radiotherapy institutes), now also by other specialised oncological disciplines or evolving Comprehensive Cancer Centers (CCCs) oriented on coordination and integration, and/or driven by an academy, including epidemiological research in the various domains of prevention
- (more and more) Ministries of Health (national, provincial/state), often delegating PO-ship to:
- Public Health (traditional) or ICT focused (intelligence service/statistics) Institutes
- University departments (Biostatistics, Cancer Epidemiology, Medical Informatics, Pathology)
- Aforementioned (Comprehensive) Cancer Centers
- Quality of clinical care institutes (recent development)

A PO is finally responsible for funding certain programmes of activities also by enlisting a variety of stakeholders interested in its mission like Cancer Societies, Health Insurance Companies, Mass screening Organizers, patient groups and professional societies recommending spending on their lofty needs and responsibilities e.g. for prevention or quality assurance. However, the aim is to report on cancer surveillance comparably, timely and with scientific standards.

Historically, the modalities depend on the political climate: fear of cancer, need to improve cancer care, patient awareness, trust in science and care delivery. These are also elements of a national cancer plan in which the size of a country and its regionalisation play a role.

POs determine the mission and appoint programme managers (PM) to deliver information of a certain quality for stakeholders, increasingly also patient groups, based on a research programme with a profile. Logically POs would stimulate CRs in the process of writing all sorts of grants and build upon adequate software and research staff.

A geographic pattern of POs of CRs across the EU has emerged corresponding to the current variation in set-up and performance of CRs: the role of Cancer Societies –very strong originally especially in the Northwest- is shifting towards a funding role of projects whereas Ministries of Health and their Public Health and Quality Assurance Institutions are developing into POs. It results in mixed blessings of shifting political preferences, priority setting within prevention and management of – often multiple- chronic diseases and a great belief in modern ICT.*Source:* WP1.

Text Box 4 describes PO-ship, and its potential identity, being different for a cancer society or public health institute, a Ministry (of Health) or comprehensive cancer centre. The heterogeneity of CRs with respect to their research profile and visibility within the oncologic world and public health is therefore no surprise. This pertains especially to the widely varying attention to advanced cancer research with its own data, usually done with or affected by stake holding professionals, public health authorities and fund raising priorities. Most POs were not able to be very explicit on their guiding role, amidst all the challenges and good practices. Indeed, a potentially paralysing governance effect might also result from the combination of the homogeneous 'boring' quantitative CR methodology, constantly worried about completeness, with the dynamic research activities for changing cancer surveillance in the different

MSs. We can add to that the dynamic influences of regional developments in oncology, the wide differences within a country related to language and religion e.g. Switzerland, Belgium and former Czechoslovakia. The marked evolution of the various (sub)specialties also resulted differentially in more dedicated users of CRs while struggling for their share of the oncologic care pie and influencing POs as well. The Annex Table of all involved specialties in all phases of the disease provides a detailed overview of the very refined multi-specialty clinical network of a modern CR.

Text Box 4 Considerations for a unified population-based CR for all tumours versus specific tumour, tract, treatment or single research domain oriented CRs

- Up to 15% of newly diagnosed patients with cancer also get cancer in another organ or tract within 10 years: 3–5% synchronous (<6 months) and 10+% metachronous (>6 months)
  - Distinct from recurrences and/or metastasis
  - With either a similar or different aetiology and pathogenesis, e.g. as side-effect of treatment
  - Survival duration often shortened and cause of death (COD) often unclear
  - Occurring relatively more often in younger, absolutely in older patients
- Ability to recognise multiple cancer syndromes as potential epidemics
- Ability to classify and properly recognise (rare) tumour types, occurring in multiple organs, e.g. non-cutaneous melanoma, sarcoma, extranodal lymphoma, carcinoid and germ cell
- Need for adequate attribution of the 4–5% newly diagnosed cancers of unknown origin (CUO), often becoming clear later (6–24 months)
- Consistent involvement of horizontal diagnostic specialties like pathology, immunology, radiology, nuclear medicine and also radiotherapy or medical oncology (classification of long term side-effects, etc.)
- Methodological considerations and simplification:
  - Uniform ascertainment and determination of dates of diagnosis
  - Uniform classification and analysis of multiple primaries: both of risk and prognosis
  - One linkage only with other relevant data sources e.g. of vital status, COD, hospital discharge

Ideal situation: Because a general CR may take a long time to get started, with less flexibility, a tumour or tract specific registry can be a good (focussed) way to start on its own, i.e. function as a clinical registry, but sooner or later it preferably is included within the framework of a general CR because of the broader context. Beware of the validity, comparability and sustainability of (fragmentation-prone) clinical registries, it is better to include them as an enriched dataset within the clinical research domain of a general CR.

Since about 15 years ICT developments have facilitated the collection and storage of (more) clinical data, increasingly used for studies of quality of care which need another privacy regimen because of the identifiable data.

3.2.1. Conclusion

POs need a mission and rules of Governance to be shared with their stakeholders and CRs should adhere to a certain capacity to deliver information on cancer incidence, detection and survival for cancer surveillance, taking international standards into account and be comparable.

3.3. Lessons learned from role of CRs in support of specific evaluation and translational research activities

- 1. mass screening (WP5),
- 2. biobanking for aetiology and prognosis (WP7),
- 3. clinical oncology (symptomatic) (WP6),

3.3.1. Mass screening [34]

If mass screening for cervical, breast and colorectal cancer is indeed taking place everywhere in Europe, as recommended by the EC in 2003, then CRs for these tumours should function everywhere as well. The level of sophistication needed may be an indicator of oncologic and public health civilisation. CRs that played a proactive role in the (often already started or devised) evaluation of mass screening programmes -i.e. of process and long term outcome- clearly contributed more to the quality and speed of such screening activities. Especially when CRs are involved upfront, they largely avoiding problems with data protection (especially with respect to follow-up of screen-negatives). Moreover this helps to estimate – if only for logistical reasons – overdiagnosis and overtreatment and liaise better to attending pathologists and surgeons of breast, cervix or colorectal cancer. However, because screens are hardly represented as a – to be well informed – stakeholder in

the planning process, patient groups have difficulties in understanding the difference with screen detected cases. They however agree on expecting CRs to play an independent role, as recommended in the European guidelines [35]. Mass screening does not only open a new window on a cancer epidemic, it also provokes the presence of a common database for a variety of medical specialties, both collaborating and competing with their core skills for a never guaranteed (and well paid) stake in the process. This early CR involvement happened in places like Finland, Torino province, Firenze, Burgundy, parts of the UK and the Netherlands with already quite some oncologic awareness varying intensity. It lead to progress and informed debate, also involving CR researchers. The support of CRs across Europe for evaluation of effects of the experimental and incidental mass screening programmes of prostate (ERSCP) [36] and lung cancer [37], and melanoma [38,39] was indispensable. Five to ten years since the detection of (pre)malignant lesions CR involvement is essential for a more precise assessment of the synergistic *and* competing role of other mortality-affecting determinants, e.g. stage migration by refined diagnostics and potentially effective adjuvant *and* palliative treatments [40]. Changes in risk factor(s), favourable or not (often by birth cohort) may also affect the underlying frequency and severity of cancer, e.g. introduction of other HPV-types by global migration and other (and more) breast cancer by later arrival of children.

3.3.2. Linking to biobanks (WP7)

If one considers modern pathology laboratories also as biobanks (increasingly active in applying biomarkers) experience with linking may already exist, but is usually focused on validating old material to assess e.g. mitotic activity of a cancer as an indicator of aggressiveness [41]. A stronger and more interactive role is gradually being played by CRs that support population-based translational research of cancer aetiology and prognosis through linking its data (again) with those of biobanks and vice versa. Application of molecular diagnosis (WP6) as a basis for precision medicine is going to be a strong driver. Good examples can be found in the relatively often mono tumour clinical registries of France and Italy, in the Netherlands and Nordic countries [42]. There is also great potential for in-depth studies of causes and prognosis of rare cancers [43] that may also have the function of signalling the start or the end of a cancer epidemic.

3.3.3. CR role in population-based clinical evaluation (WP6)

An ENCR and EUROCARE combined initiative produced in 2003 a report [44] on the rapidly expanding field of population-based cancer care evaluation. This comprised a.o. special CR supported or even initiated studies on cancer in the elderly (uniquely represented in CRs with data on stage and primary treatment) and studies of survivorship issues in long-term survivors. The potential of European quality of care studies e.g. the EUROCARE 'high resolution' studies was also assessed in WP6.5 part 4. It advocates an adequate and simple approach despite rather selective participation of poorly performing regions (also without active POs of CRs). Secondly, quality of care studies need to be quicker. http://www.eurocourse.org/mm_files/do_944/D6%205def.pdf: A selection of recent contributions to clinical evaluation was added to this special issue: on relative survival methodology [45], an intriguing Danish/German cross-border comparison of management of colorectal cancer [46], an incomplete Belgian clinical registry on rectal cancer (also misleading Eurecca) but now embedded in the modernised Belgian CR [47], and an exemplary validation of the Swedish prostate CR [48]. Many patterns of stage and (primary) treatment studies often showed a substantial variation in time and place, often reflecting the clinical embedding and potential for feedback by the CR (an often implicit expectation from any PO). Recently promoted as a disruptive development for randomised controlled trials (RCTs) such patterns of care studies might also provoke conception and facilitate execution of RCTs with high recruitment rates because data collection was partly done. The physicians have become aware of uncertainty on optimal treatment of RCTs [49]. Routine recording of loco-regional recurrence after surgery seems only useful with a quality of care but also biological study question (deliverable 6.2) http://www.eurocourse.org/mm_files/do_944/D6.2.pdf. Few CRs have complete routine data on recurrence and progression of specific cancers. www.tumorregister-muenchen.de/.

Adding co-morbidity at diagnosis proved essential for studies of cancer management in the elderly either through linkages with other databases or recorded directly by the CR [50]; its prognostic value also illustrates a strong link with socio-economic status [51]. Albeit still with a few good examples, a prominent role is currently foreseen for population-based CRs to conduct or host (as sampling frame) phase 4-like studies of utilisation of 1st, 2nd, 3rd, etc. line costly systemic precision treatments, to be used for effectiveness modelling. One might consider this a combination of quality assurance with elements of prognostics and quality of life (QoL) assessment through translational research or postmarketing surveillance [52]. During the last 10 years CRs managed to organise or promote participation in survivorship studies, e.g. of long term side-effects of treatment [53]. These studies were increasingly carried out in or with the CRs of Saarland, Munich, Denmark, Eindhoven, Yorkshire and Burgundy. These also study presence of signs and symptoms, like

neuropathy or swelling, and include worries and social issues. Such patient oriented studies may also enlarge the interest of patients in population-based CRs and clinical research participation. Collaboration with the EORTC QoL group is already promoting common standards in use of QoL parameters in research of efficacy and effectiveness. Modern ICT can play a big role here, which does not necessarily derail in Big data graveyards. http://www.eurocourse.org/mm_files/do_944/D6_3.pdf.

3.4. Mono versus multiple cancer registries: 'either or' or 'either and' (Text Box 3)

Collecting (even) minimal data on all tumours requires a broader clinical network than on single tumours or in one tract like colorectal or gastrointestinal, leukaemia or haematopoietic cancers (see Annex Table and Table 4). There were about 20 such dedicated population-based CRs in Europe also recognised by CI5 [2], but many more as – also emerging – clinical registries [54]. A one tumour or tract registry was and is however easier to start (also with modern web based) software [55] (Text Box 4). However, clinical researchers (often PMs also playing PO) often tend to collect – unrestrained by data hunger and modern ICT – large amounts of data, forgetting the need for independence and verification of input and data protection. They risk 'their' datasets becoming less valid for the intended purpose of comparative quality assurance. Anatomically oriented disciplines like the various surgeries, gastroenterology and dermatology – are now regionalising driven by sub-specialisation and quality awareness, the latter also among patients and (politically) licensed 'buyers' of specialised care like health insurance companies and provinces. They instantly need tumour-specific databases that should be provided by CRs to avoid fragmentation of the CR landscape.

For childhood CRs the road maps are different because they, often managed by paediatric oncologists and biostatisticians, intend to collect data of all, mostly rare cancers occurring up to age 18–20. [5,55] Then inclusion of solid tumours requires the specific expertise of the various surgical specialties and radiotherapists, each with their own classifications and information needs in the domain of quality assurance. Longterm surveillance demands broadening into non-cancer fields, comparable to the fields of co-morbidity and survivorship. Since the 1960's there were also, depending on clinical oncological awareness, professional (network) organisations for often younger patients with rare tumours like sarcomas, bone, CNS and testicular cancers, leukaemia and lymphoma, choriocarcinoma and DES-victims. These organisations were often guided by specialised pathologists organising panels, flanked by dedicated surgical oncologists and radiotherapists. Such networking activities efforts were often supported by specific (more or less professional) databases of incident and prevalent patients, under permanent surveillance, sooner or later collaborating closer or even merging with general CRs.

To advance the knowledge on biology and treatments of such patients with these rare cancers [56] a large numbers of patients are needed, to be attained by pooling at (inter)national scale. It requirers the use of the same standards for classification and application in the multitude of disease states, into five to six phases in the cancer continuum: A. detection and diagnosis, B. classification and staging, C. therapeutics, D. surveillance – disease-free and/or E. advanced – and F. terminal palliative care) (Annex Table 1 for the varying disciplinary involvement in each of these phases).

There is another challenge for mono-tumour CRs. If up to 15% of all patients with a first cancer ultimately gets another one (including contralateral cancers of breast, lung, kidney, ovary and testis cancer and large surface area cancers in the lung, urothelium, colorectum and skin), links need to be made with many other CRs Also for the sake of comparability it requires clear algorithms for accurate estimations of risk, detection, prognosis and side-effects.

The Eurocourse paper on completeness and timeliness of CRs [57] showed the need for systematic and timely input checks, often in need of involvement of a diverse medical sources (Table 4). Based on a sample of 20 CRs, current expenses of registration in general CRs might seem rather modest [58] (ranging between €25 to €175 per newly diagnosed cancer patient), but also hard to attribute to the various payers, and omitting in-kind contributions by care providers or their institutions. It may come down to about €1.00 per inhabitant (varying with purchasing power and labour costs in a country) and <1% of total cancer care costs [59]. POs and PMs of mono-tumour CRs or clinical registries should not only avoid problems with validity and sustainability forthcoming from the do-it yourself formula, but seek synergy and coordination by general CRs covering the same patients and also using them as sampling frames for clinical data. The current variety in experiences in the Netherlands, Belgium, Denmark, France, Norway and Sweden could show the way forward. http://www.eurocourse.org/mm_files/do_944/D6%205def.pdf.

3.4.1. Conclusion

Close collaboration between general and mono-tumour CRs or clinical registries will avoid problems with recording adequate data on patients with cancers of unknown origin, multiple cancers and follow-up of vital status as well as public health research, especially in case of linking to other datasets. Any dedicated CR, whether regional or national, whether mono or multi-tumour oriented should continue to play their useful pioneering role in any consolidated (national) CR paradise.

3.5. Lessons learned from variable European arrangements for the regulation of data protection: the Nordic answer to long term side-effects of major dictatorial regimes

Old problems and new (for some, old for others) challenges were identified and solutions proposed [67] for data protection requirements to underpin an emerging new EU regulation. It would replace the rather variably implemented 1995 EU guideline on data protection [11]. The overriding collateral aim in 2007 was to elaborate a EUROCOURSE 'unisono' view on (European) health data protection [60]. During 2012, a staggering discussion has evolved on data protection between the major 3 EU-bodies affected by thousands of interest groups: the Commission, Parliament and Council of Ministers. They were after uniform regulation, an optimistic idea that ignores the heterogeneous nature of personal data, commercial and state forces and the lego-political cultures in the various MSs. But should the thorough and safe work by CRs of decades be brought on par with abuses by WIKI-leaks, intrusions by mobile phone hacking, Google mapping, secret services and Social Media absurdities, cloud computing, hacked or even sold Electronic patient records? And should it be bred as much by the war against terror as just fantasy E-Health? Added to that is the rather intrusive commercial venue of – largely unverified, and mostly clueless- Big Data, having arrived in genomics, molecular diagnostics, imaging, etc., without clinical relevance. Simple and medically bound CRs should remain 'hors concours', having preached and practiced more or less impeccable data protection during the last 60 years. They are aware that they worked with sensitive material, often highly self-regulatory. Modern ICT would undoubtedly advance step by step realisation of the modest aims of CRs to produce more timely (inter)national comparative information. Information on variation in cancer risk and prognosis, on the need for and effectiveness of cancer prevention, including of (ever imperfect) mass screening, and on the risks of over- and undertreatment, also beyond the detection and primary treatment phases. At the start of EUROCOURSE in 2009, the always implicit interests of cancer patients (and screenees) have been emphasised more clearly than before, along the perceived need of survivorship studies and to enlarge patient involvement with the decent work of CRs.

What to learn from incidental existential threats to continuity of population-based CRs, i.e. in Hamburg (1982–1991), in former East Germany (1991), and more recently in Estonia, Slovakia and Bulgaria [61]? Germany and also France (still suffering from the late effects of policies by Hitler and Napoleon, respectively violating and overemphasising individual rights) still make life difficult for epidemiologic CRs, but also slow, frustrating and costly. By contrast, most if not all cancer patients implicitly expect to be offered adequate care and surveillance, also at long term, and expect its quality to be secured statistically (needed because of intriguing variation by differential schools of medical thought). Patients also expect their human tissue to be reused properly, i.e. for validation of new versus old biomarkers, and would generally not agree with hasty changes in their data management, even if long overdue for digitalisation of traditional procedures. In addition to the explanatory work of the principles of data protection in CRs by WP2 [62], WP1 developed a 'whistle blower' protocol for the Steering Committee of ENCR on how to support CRs threatened into discontinuity or even extinction by the toxic combination of an overload of data protection and E-Health. Both disrupt the continuity of routine data collection: cases have to be analysed upon trusted notification and mobilising its PO and stakeholders, including patient groups and members of the various (European or national) parliaments and saying loudly: that the Nordic model works well.

3.5.1. Conclusion

The political diversity of data protection practices of CRs across Europe has learned several things: practical solutions for e.g. an opt-out approach to consent or assent, in some places pseudonymisation, and in others specific supervisory authorities. Let CRs rather be exemplary than a suspect. Consider just to repair disutilities of the (by definition) imperfect 1995 European legal compromise for Health research, whereby the rights of patients on absolute data protection would be inversely related to the need for quality assurance.

3.6. Lessons learned from 'good basic CR practices' (all WPs)

An overview of good practices is shown by WP and research domain (http://www.eurocourse.org/mm_files/do_944/D1_4def.pdf), but the aforementioned IARC/ENCR report on standards and guidelines as well [7]. Given the main purposes of a population-based CR, attention for good practices prioritises removing obstacles for completeness, timeliness and validity, especially undue attention for privacy. It also promotes mistrust and lack of collaboration among institutions and professionals, because it ignores the idea of the medical commons where practice research is normal, often with notions of cost-effectiveness. A more specific Good Practice was the standard for coding and classification of multiple haematologic malignancies [63] following recommendations on coding of bladder cancer and basal cell carcinoma [7]. Attaining completeness of a CR may not sound exciting but is crucial for its added value to research with selected patients and its external validity. Examples are analyses of clustering, of time trends in

incidence, and for studies of process and outcome e.g. survival. This is especially important for the elderly and low SES patients, as they more often having a clinical diagnosis -only if recorded at all- because they may not reach the hospital, implying one of the major biases of survival studies that also may have incomplete follow-up in countries with strict privacy regulations [64,65]. Therefore it is good practice to rather study progress against cancer of which survival is only a part and be accompanied by trends in incidence, tumour size (indicator of detection) and mortality [66,27]. Dissemination practices have improved and quickened the pace of reporting (web-based). SEER (Surveillance Epidemiology End Results) efforts, based on more standardised data in about 15% of the USA (at much higher costs), a data file has been made available for external researchers [67]. An ongoing experiment with data sharing (2 years after data collection) in the Dutch CR-based Profiles study may be the way forward in Europe [68].

Very 'good practices' were also the widely used (often updated) software for relative survival analysis that was developed in and extensively tested by the staff of the Finnish CR during the last 30 years [69], building upon 20 years of work. This was enriched for period survival software (for survival analyses of recently diagnosed patients) since the 90s and often working with Saarland data [70]. This also allowed for a better estimation of conditional (upon being alive) survival of patients with ever cancer, with the Eindhoven Cancer Registry [71].

Provided there are verifiable data, CRs can generally fulfil the STROBE criteria for observational studies [72].

3.6.1. Conclusion

Completeness for observational CRs is so pivotal for comparability in time and place that any policies or rules that affect that negatively should be considered as bad practice unless they allow for exceptions.

3.7. Lessons learned from the evolution of CRs: profiling according to research involvement

EUROCOURSE reiterated earlier communications on the profile of CRs by Armstrong (then at IARC) in 1992 [73] and in 1998 [74], implying to become more patient-oriented and give patient groups more say in the research agenda with so many topics of interest for – longer living – patients. And that is what is happening now all over the world [52,53,68,82].

Despite similar overall purposes, methods of CRs for population-based coverage, and standards for minimal datasets, with a variable clinical emphasis and approaches to data collection, great variation existed in research participation or performance of the ±160 recognised population-based CRs in Europe [2]. The number of peer reviewed publications per CR (including co-authorship) varied from 1 to 150 in absolute terms and from 1 to 4 per 100,000 inhabitants per annum, regardless of age or starting period (Table 2). After attaining completeness, a period of about 15 years is generally needed for meaningful analyses of:

- Variation in incidence in time (trends) and place,
- 10-year survival, being a benchmark for cure,
- Impact of mass screening on incidence, tumour biology, overdiagnosis and mortality,
- Occurrence of metachronic multiple primaries.

A shorter period of time may be needed for studies of access to care (i.e. exploring age-specific trends in tumour size) and of processes and outcomes in the first months to year(s) after diagnosis. Other topic are studies of adherence to protocols for staging, referral patterns, use of adjuvant treatments and complications of (surgical) treatments, and presence of co-morbid conditions to explore complexities in management of cancer in the elderly. Go with the tide and develop risk communication when the CR-staff will be pulled in urgent (fear-mongering) studies of environmental causes of cancer, e.g. of clustering [22]. The list of topics for valuable, often 'negative' aetiologic studies is endless: from very modest long term cancer risks of exposure to nuclear energy or dioxin, to high risks by asbestos exposure since the mid-1970s. Intermittent UV exposures at young age started to pop up as a problem for those at middle age with a fair skin, since the mid-1970s in Australia and Norway, later fortified by imminent thinning of the ozone atmosphere layer, that could be corrected by worrying incidence scenarios. International orientation is of course crucial, for which our valuable IACR-meetings are not enough [74]. EUROCOURSE also established the need for foundation of a European Society of Cancer Prevention and Epidemiology (ESCAPE) for which statutes have been developed. Involvement in analyses of clinical or public health controversies such as concerning effectiveness of mass screening [75] is very useful, because it also provides the scope for a wider range of data collection in screen-positive patients.

Most long standing CRs indeed underwent gradual, sometimes abrupt processes of growth subsequent to specialisation of the research staff, mixing with relevant stakeholders as well. Attracting MSc, PhD or postdoctoral students from the whole range of health and medical sciences, including psychology, has often provided motivation for those in charge of data collection: 'their' data are used!

We discerned five major domains of cancer research in the field of both clinical and public health and policy research pertaining to each tumour or tract with the minimal datasets. More incidental and/or temporarily are study question related with enriched data at advanced level (Fig. 1, Table 3, Text Box 5).

Text Box 5 Potential course of a population-based cancer registry (CR): from scratch to catch or from roots to fruits (see Fig. 2a and b)

- Start of a CR by a pioneer from (horizontal) pathology, radiotherapy, social medicine:
  - Back office only, i.e. a secret operation due to the taboo nature of cancer and privacy

- After 5–15# years: first results -> research projects starting through stakeholders
  - Back office and epidemiologic/biostatistic researcher(s) -> increasing and specialisation -> research department at the CR or at institute selected by a Programme Owner
  - Peer-reviewed publishing – Co-responsible for (web-based) reporting
  - PhD students and post-docs; involved in writing grant proposals
  - Dialogue with patient groups, with outside world (journalists) on results and questions
  - Translating questions of stakeholders into feasible research questions -> studies and grants
  - Engagement in multiregional, (multi)national, mostly European studies, e.g. Rarecare

- After 10-25# years: specialising along with interested cancer research domains in:
  (Basic for all sites, advanced for special sites drawing more attention)

1 Public Health (population oriented)
- Aetiology: variation in time and place, clustering
- Linking to cohorts, recruitment to population-based case-control studies
- Mass screening: evaluation of mass screening and overdiagnosis (cervix, breast, colorectal)

2 Patient care oriented
- Quality of care: process and outcome
- Contribution to scenario development and cost-effectiveness
- Prognostics: long term (conditional) survival, second cancers, uncommon cancers
- Children, elderly, co-morbidity, translational studies of biomarkers
- Quality of Life: long term negative side-effects of treatments;
- Other aspects of survivorship;
- Baseline for interventions
- Negotiating, consulting and directing, piloting data collection (back office) as sampling frame
- Translating results of epidemiologic studies for patient groups and engage studies in 'their' problems

Other potential activities
- Active representation in European/International oncological and CR networks and collaborative studies
- Support scenario development either for prevention (impact assessment) or for treatment resources
- Involvement in graduate and postgraduate education, public education

#arbitrary time periods depending on mission and/or academic or cancer centre affiliations.

Data collection and coding activity of the CR are, for reasons of uniformity and complexity, done largely by registration clerks (connecting with the many specialties in the Annex Table) and low profile data analysts. Researchers discuss and devise study questions and study designs, analyse the data with or requested by the various stakeholders, put them into context and gradually develop an academic profile through their publishing and speaking – and probably also teaching – record. The CR research department may thus follow clinical but also public health sub-specialisation (e.g. mass screening evaluation and/or aetiologic research) by tract (e.g. haemopoietic, female genital, skin) and/or research domain. They are framing study questions and adopt classifications through knowledge of the literature. The data collectors are currently continuously adapting to hospital-specific applications of Electronic Patient Records (EPR).

A potentially exponential growth in research projects may happen in a multi-tumour CR with some oncologic regional embedding (Fig. 1). Sooner or later, a more explicit arrangement develops of research activities and matching expertise, or profiling with the CR-staff (linked to the data collection 'machinery') and one or more multi-CR networks within a country or Europe (Text Box 5). During the last 20 years this development has more or less explicitly taken place in more and more CRs, especially those that interact with major cancer and academic oncology departments that provide MSc and PhD students for research trainee and fellowships. The PM of the CR (in fact its patient data) can thus

Table 2
Informational needs of the various stakeholders of population-based cancer registries translated in disease parameters and ordered by research domain.

Type of user/stakeholder	Question: progress against cancer? Targets, goals/objectives	Disease and QoL and Care parameters Indicator, Study design and type	Involved research domain
A. General	*Basic questions*		
All	Prevention needed? General or High risk only? For whom is mass screening safe and effective? Are new treatments effective? Burden of cancer	Epidemiologic surveillance. (Tumour-specific) trends of incidence, especially at young and middle age. Prevalence, survival, stage and mortality	Burden/Aetiology (PH)/ Mass screening (PH) Prognosis
All	Variation (or inequality) in risk and outcome? Adherence to guidelines/ textbooks? Long term side-effects? Insight in future demand for specialised care through input in scenarios for required/desirable services, care and education/ training facilities	Age-specific variation in time and place of: access, variation in processes ? Outcome, follow-up care, cured proportion Also by SES (postal code/ education); (Relative) conditional survival, prevalence Also geographic comparisons	Quality of care Aetiology (PH)
All	Burden of cancer: combination of risk and Quality of Life, aspects of survivorship, long term side-effects related to therapies, aggressiveness of cancer?	Patient Reported Outcome Measures (PROM); Age-specific studies of children/adolescents/ middle age/elderly	Quality of Life (PL) Prognosis (PL)
B. Specific	*Aspects of Surveillance*	*Methods Study type*	
Ministry of Health/Hospital board (provider)/ Health insurance companies (buyer)	Economic implications Resources allocation Cost-effectiveness	Scenario development Health services utilisation Studies of safety: recurrence rates Complication rates, side-effects	Quality of Care (PL)
Ministry of Health/Politicians	Quality of care as determinant of prognosis. Equity? Access to specialised care/regionalisation? Infrastructure adequate for changes in demand?	Incidence, staging, mortality, co-morbidity, (societal) interventions, bio-banks, social class differences	Burden (PH) Prognosis
Specialised care givers (incl. General Practitioner)	Assessments of variation of old and new treatments, effects of therapy. Anticipation on elderly, rare cancers, expensive/orphan drugs, complex procedures	Cohort studies of recurrence/ progression, linkage to bio-banks for genomic analyses, side-effects. Incidence, treatment choice and outcome, co-morbidity	Prognosis (PL) Quality of Care (PL) Quality of Life (PL)
Home care organisation/General Practitioner	Estimation of number of cancer patients for palliative (and end-of-life) care, mortality	Duration of metastatic/terminal phase, Mortality	Prognosis (PL)/ Quality of Care (PL)
Health authorities/Parents/ School/Community/Press	Panic control, clustering explained, early warning Ingredients for risk communication Vaccinations warranted/needed?	Incidence and (proportional) mortality, time trends, (conditional) survival	Aetiology (PH) Prognosis (PL)
Public Mass Screening Authority	Effectiveness of screening programme, interval rate, overdiagnosis and overtreatment	Cohort studies of effects, trends of in-situ cancers; patterns of care	Mass screening (PL) Quality of Care (PL)
On behalf of Patients (Patient groups)	Prognosis at diagnosis, after treatment and after several years; long term treatment side-effects, influence of BMI/smoking/UV on QL and prognosis	Estimate conditional survival, PROMS# Complication rates; influence of comorbidity	Prognosis (PL) Quality of Life (PL) Quality of care (PL)

NB: Table summarises contents of seminal books and articles on cancer registration [2–6] and based on best practices and an Eurocourse WP4 inventory. PL = patient level comprising quality of care, prognosis and quality of life. Population level = Public Health (PH).
Lesson learned: CRs serve and interact with many different stakeholders with specific but also overlapping demands which need ordering.

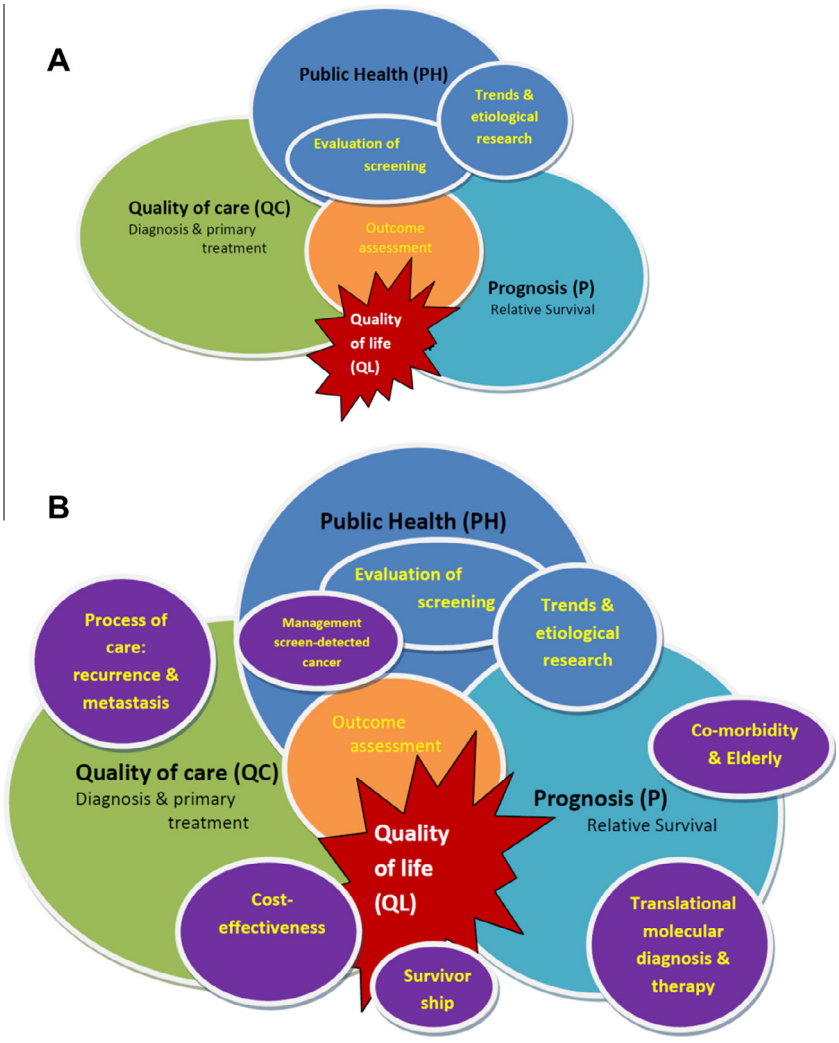

Fig. 2. Research domain description of the basic type (A) and advanced population-based CR (B). (A) Basic (minimal datasets only). (B) Research domains being served by advanced, in-depth[#], diversified CRs.
[#]Advanced application, always based on study questions, enriched data (either recorded by CR as sampling frame or through linkages), by definition temporary and for (changing) specific tumour sites or tracts (preferably to be considered as a clinical registry within CR).

attract 'cheap' energy and offer talented students a career in cancer epidemiology.[5] Although one might expect that funding opportunities for CRs are driven by the combination of good data, infrastructure and talent, the financial meltdown of 2008 has affected this negatively in recent years. [14].

Each of the research domains primarily hosts the basic CR functions (minimal data sets, etc.). However, for some tumours an advanced research opportunity might appear with extra data, collected or acquired through linkage, depending on the research focus e.g. mass screening evaluation or other whatever changes in epidemiology or oncology are occurring. These changes are therefore not necessarily the same within each CR (Fig. 2a and b). Regular interaction with the back office, will lead to more feedback to common practise and opportunities for awareness (Tables 3 and 4).

The more CR staff becomes involved in anticipatory, strategic activities e.g. scenario development for planning, investment or testing a mass screening programme, the more opportunities also arise for subsequent evaluative activities together with experts. CRs then attain centre stage which has happened several times in quite a few MSs after future explorations.

At the EUROCOURSE CR summit conference for stakeholders, most CRs appeared active at basic level in the research domains of prevention and quality of care for most cancers. A growing minority (<20%) was active in 3–4 domains and a tiny minority of CRs within all

[5] Eurocourse WP8 also identified great needs for certification of adequate training and a policy forum on European policy issues among cancer epidemiologists, being a partner in so many policy processes and research collaborations, including science policy at the EU, professional bodies and the like. for which statutes were developed for European Society of Cancer Epidemiology and Prevention (ESCEP).

Table 3
Nature of research activities in population-based cancer registries (CRs) in Europe by research domain

	Relevant results at				
	Population level (public health research domain)		Patient level (clinical research domain)		
	Burden, aetiology (primary prevention)	Early diagnosis and mass screening (secondary prevention)	Quality of care	Prognosis	Quality of life
Epidemiologic surveillance					
Exploring Environmental threats (real or perceived)	++				+
Monitoring time trends (in incidence) (by age and gender)	++	+			
Monitoring social class differences and Migration	+	+	+		+
Monitoring prevalence (care, all)	++	+	++	+	++
Hypothesis generating and testing					
CRs as follow-up source for epidemiologic cohort studies	++	+	+		+
CRs as source of cases for population-based case-control studies	++	++	+		+
Cross-sectional studies of variation in occurrence (incl. clusters)	++	+	+		+
Evaluation of impact of preventive interventions on populations (scenario development and research)					
Primary: e.g. smoking cessation (lower rates of lung cancer?)	++		+		+
Secondary: (side)effects of mass or targeted screening	+	++	+		
Anticipating and monitoring changes by new diagnostics	+	+	++	++	++
Evaluation of cancer care (progress?)					
Studies of trends in survival and mortality	++	++	++	++	+
Changing burden of cancer on health services	+	++	++	+	++
Definition of targets and outcomes for new cancer centres			++	+	++
Monitoring of process indicators and quality of information		+	++	+	+
Translational research of prognostic biomarkers			+	++	+
Host determinants like co-morbidity			++	++	++
Economic evaluation and planning of cancer care policies					
Scenario planning and resource allocation for specialised care/centres		+	++	+	+
Contribution to cost-effectiveness analyses (or doing them)		++	++	+	+
Registry methodology					
Completeness/Accuracy of population-based registration and statistics	+	+	++	++	+
Survival analysis (relative survival, cured fractions, conditional, etc.)	+	+	+	++	+
Validating classifications (ICD-O)	+	+	+	++	+

SCORE: +, relevant; ++, pivotal.
Lesson learned: with a common dataset for all 5 research domains specific datasets available within or to be generated soon need to be enriched.

possible five cancer research domains. They relate with regional or national tumour study groups that may also be research consortia, depending on the size of a country. Observational studies by CRs of enormous variation in (thus under- or over)treatments may then provoke performance of randomised trials with high recruitment [49].

Table 4
Medical, administrative and statistical sources of patient data for population-based cancer registries that affect internal validity (accuracy) and external validity of data (representativeness/completeness) [7].

Sources and linkages	Relevance for validity		
	Internal	Stage	External
Notification			
Cause of death statistics	x		xx
Hospital discharge diagnosis	x		xx
Hospital billing code		x	x
Laboratory			
Pathology	xxx	xxx	
Cytology	xx		
Haematology	xxx	@	xxx
Immunology	xx	@	x
Clinical chemistry	xx		xxx
Imaging/Radiology			
Thorax/mediastinoscopy	xx	xx	x
Neuro CT	xx	xx	xx
Gastro-Intestinal/ERSCP	xx	x	xx
Echography	xx	x	xx
Mammography	x		x
MRI	x	xx	xx
PET-scanning		xx	
Elderly			
General Practitioner			x
Nursing Home			x
Extra regional diagnosis/treatment	xx	xx	xx

Other aspects of interest:
Verification (distinction between pre- and malignant).
- Endoscopy, biopsy, imaging and pathology, immunology and haematology.

Surveillance (registry often used as sampling frame and with verification of diagnosis/death).
- Toxicity/late side-effects.
- Recurrence/metastasis.

Contribution to validity: x = partial/modest: replaceable by another source; xx = substantial; xxx = pivotal; @ = in case data on stage or tumour mass need to be collected.

3.7.1. Conclusion

Population-based CRs need at least a decade for organic growth in information generating activities, which can be accelerated by adding research staff early in the process, preferably interacting with stakeholders and then followed by specialisation and a visible research profile based on expertise. This may also result in more focused multi-regional or national European research and in a process of consolidation in larger MSs, also facilitating for better trend analyses [83].

3.8. Lessons learned from evolution of the European Network of Cancer Registries (ENCR) (WP4)

Since 1989 the ENCR has informally developed as an initiative of the cancer expert committee of the EU, consisting of Calum Muir, Ole Möller-Jensen, Jacques Estève and Michel Coleman as first secretary at the Cancer Information section of IARC. The networks of the Association of Nordic Cancer Registries (ANCR), the Latin Language Registry Group (GRELL) and the International Association of Cancer Registries (IACR) were also a part [76]. Many initiatives for pan-European comparative population-based studies on incidence and survival have been realised (i.e. EUROCARE, 5th edition) in parallel with regularly repeated extensive studies of cancer incidence and mortality [1]. Mortality studies occur rather quickly with the WHO-database but hamper by rather variable quality in the different MSs related to widely varying quality of care and coding practices [6]. Unfortunately, most of the multinational studies of variation in time and place of cancer incidence and survival, and even more the current high resolution studies of quality of oncologic care, (deliverable 6.5) were 'slow' research, based on patients diagnosed 7–15 years earlier. But POs in most MSs might not have pushed enough for something which was or should have been important to them if they would have reflected more on its potential impact. The impact is comparable CR-based information on cancer risk, detection and prognosis that would offer a realistic perspective of their own cancer picture to their stakeholders, but also needs to be done promptly to improve prevention or cancer management or just the quality of the data. This – often extra for the CR – European work unfortunately slowed down further in many CRs when European funds dried up, and the ENCR and EUROCARE study groups were struggling badly to advance their work, collaborating and competing. But developments in oncology cried for extra efforts and progress, especially when in 2004 ten new, less wealthy MSs entered the EU, mostly with 'bad' survival rates and minimally functioning CRs [33], that were not helped by shallow E-Health plans and a stricter focus on informed consent.

WP4 redeveloped the common epidemiologic database as part of the emerging European Cancer Observatory (ECO) at IARC [77]. ECO combines cancer incidence and WHO-mortality data for its cinquennial CI5 publications. Two major trend analyses of incidence of tobacco-related and of obesity-related cancers show the way [78,79]. With modest efforts from participating CRs (having to submit their data anyhow to IARC for CI5) this database is to become the cornerstone of multi-MSs (possibly encompassing all Europeans) timely cancer surveillance in Europe at low cost. It remains to be seen whether collaboration between IARC and JRC is good enough to result in European studies of cancer risk and prognosis. The best way to let this succeed is to develop an alternative in a multi-institutional (cancer centres), multi-registry approach and considering optimal results per research

domain. When no clear perspective might be visible at the end of 2015, then the PMs and POs of the CRs, should be able to find other solutions advised by the European Academy of Cancer Scientists where all the major stakeholders are represented.

3.8.1. Conclusion

Adequate and timely input and quality control of cancer incidence and survival data of CRs in partnerships with IARC, EUROCARE and JRC Ispra should serve the interests of their POs in any European country so much that their data becoming comparable and they should be supplied as in-kind contribution. Then European CRs truly qualify for added value acquired through an EU scheme of data analysis and interpretation. It should be carried out by a pool of CR researchers and led by study questions together with experts from major cancer research domains: aetiology, mass screening, quality of care, quality of life and prognostics.

Conflict of interest statement

None declared.

Acknowledgements

EUROCOURSE was devised by the Steering Committee of the European Network of Cancer Registries (ENCR) within the 7th Framework Program of the European Union. We acknowledge the contributions of the EUROCOURSE Steering Board, comprising the workpackage leaders and ENCR Steering Committee and all EUROCOURSE participants (see Appendix) and those who attended the 30 or so meetings and workshops actively during 2009–2012. ECCO's Oncopolicy staff were of great help in the organisation of the ONCOPOLICY–Cancer Registry summit conference in Brussels in November 2011.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2015.02.018.

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