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Early breast cancer in England: Evidence into practice
What can national cancer registration and analysis service datasets tell us?

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ABSTRACT

The English National Cancer Registration and Analysis Service (NCRAS) holds several datasets which provide detailed information on the cancer patient pathway. Ascertainment, data quality and completeness issues persist. However, there are still critical research questions that can be addressed using these data, which will help improve outcomes for patients. Registry data will help us understand whether the outcomes seen in highly selected patients in randomised controlled trials are realised at a national scale. These data can also help us monitor adverse events and toxicity profiles of drugs, helping clinicians make better prescribing decisions, as well as provide long term follow up for patients beyond the timescales of a trial. In instances where there is strong evidence for the efficacy of a treatment, such as the use of hormonal therapy in oestrogen positive breast cancers, observational data can help monitor and support adherence to these therapies. Finally, the wide variation in care provided to patients, including evidence of inequalities linked to socio-economic status is a public health concern. This can be quantified through population level observational data to facilitate measures to improve care.

1. Introduction

In the past, cancer registries held population-level observational data on the main events occurring during the care and follow-up of patients with cancer. Information on whether a patient received surgery, chemotherapy or radiotherapy may have been available, but the specifics of what surgical procedure was performed on the patient, drug regimens and their timing, as well as the dose and fractionation of radiotherapy treatments was not routinely collected. There are now a number of rich data sources curated by the National Cancer Registration and Analysis Service (NCRAS) at Public Health England (PHE) which include these data. In addition to cancer registration, NCRAS routinely collates information on the patient pathway prior to, and following diagnosis. Since 2009, the National Radiotherapy Dataset (RTDS) has been collecting detailed information on radiotherapy targets, dose and fractionation. Similarly, since 2012 the Systemic Anti-Cancer Therapy [1] database has captured data on chemotherapy and other systemic therapies. Electronic case notes, results reporting and prescribing at hospital trust level have facilitated easier data capture and together, these databases now provide a detailed picture of patient demographics, imaging activity, cancer stage, pathology, treatment and outcomes for cancer patients in England. Table 1 provides an overview of the databases available through the Office for Data Release (ODR) at PHE.

Data completeness and quality have improved markedly in recent years, although in some circumstances these remain a challenge (see ODR website for links to information on quality and completeness for each of the databases [2]). Moreover, blood tests results and details of supportive medications such as analgesics and antibiotics are largely unavailable.

Despite these limitations, the datasets available through NCRAS provide opportunities to study serious treatment-related toxicity and mortality in routine clinical care. Critically, as a source of real-world data and continuous patient follow-up they can complement the evidence provided by randomised controlled trials (RCTs), support the translation of evidence into practice and by highlighting unwarranted treatment variation, help to ensure equitable access to optimal care. We discuss the opportunities provided by these datasets with a focus on the management of early breast cancer.

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Table 1
The following datasets can be made available through the Office for Data Release at Public Health England. Those denoted with an asterisk are collected and curated by NHS Digital, but can be linked to the other datasets via the patient's NHS number, and made available through ODR at PHE. Further details including data dictionaries and field definitions are available at https://www.gov.uk/government/publications/accessing-public-health-england-data/about-the-phe-odr-and-accessing-data.

Datasets made available through the Office for Data Release at Public Health England		
Dataset	Dates covered by data	Data available
Cancer Registry Data Patient, Tumour and Treatment Tables	Patients diagnosed 1 January 1985 - 31 December 2016	Contains patient, tumour, and treatment level information from the National Cancer Registry. The cancer registry provides information on patient demographics, tumour diagnosis, morphology, event dates, patient geography, treatment types and treatment providers.
Systemic Anti-Cancer Therapy Dataset	Patients diagnosed 1 April 2012 - 31 December 2016	Contains information on clinical management on patients receiving cancer systemic anti-cancer therapy (chemotherapy, immunotherapy, targeted treatments etc) in or funded by the NHS in England.
National Radiotherapy Database	Patients diagnosed 1 April 2009 - 31 March 2016	Contains treatment information on every NHS funded patient receiving Teletherapy, or Brachytherapy given using automated remote afterloading machines or any Brachytherapy given for treatment of malignant disease.
Cancer Patient Experience Survey	Wave 1: Patients discharged 01/01/2010 – 31/03/2010 Wave 2: Patients discharged 01/09/2011 – 30/11/2011 Wave 3: Patients discharged 01/09/2012 – 30/09/2012 Wave 4: Patients discharged 01/09/2013 – 30/11/2013 Wave 5: Patients discharged 01/04/2015 – 30/06/2015	The survey aims to collect information from patients about their cancer journey from their initial GP visit prior to diagnosis, through diagnosis and treatment and to the ongoing management of their cancer.
Hospital Episode Statistics* Admitted care, outpatient and A&E	Patients diagnosed from 1 January 1985 - 31 December 2016	Contains information on all hospital inpatient, outpatient, and hospital A&E admissions in NHS hospital in England. HES data will only be supplied as linked data to cancer registration data. HES contains details on patient demographics, admission and discharge date and times, inpatient episode duration, outpatient appointments, diagnosis, clinical coding, geography, treatment provider and GP practice.
Diagnostic Imaging Dataset*	Patients diagnosed from 1 April 2006 - 31 March 2013	Contains detailed information about diagnostic imaging tests carries out on NHS patients.
National Cancer Waiting times monitoring Dataset	Patients diagnosed from 1 January 2009 - 31 December 2014	Contains management and monitoring information of various defined cancer waiting times
Quality of life of Cancer survivors in England (breast, colorectal and prostate cancer and non-Hodgkin's lymphoma)	Questionnaire respondents in 2011 and sequentially sampled in 2012	The survey measured overall quality of life of representative samples of cancer survivors with four different tumour types (breast, colorectal and prostate cancer and non-Hodgkin's lymphoma (NHL)) and at four different time points after diagnosis (approximately one, two, three or five years).
Route to diagnosis	Patients diagnosed from 1 January 2006 - 31 December 2015	Cancer registration data are combined with Administrative Hospital Episode Statistics data, Cancer Waiting Times data and data from the cancer screening programmes. Using these datasets cancers registered in England diagnosed in 2006 to 2015 are categorised into one of eight Routes to Diagnosis.
The National Cancer Diagnosis Audit (NCDA)	Subset of patients diagnosed from 1 January 2014 - 31 January 2014	Contains primary care diagnostic pathway information from patients diagnosed with malignant cancer in 2014

2. Observational data as an external validation of RCTs

Robust clinical practice and decision making must be driven by the best evidence, and depending on the question being addressed, different research methodologies are used [3]. RCTs have often been described as the 'gold standard' in terms of comparative effectiveness research (CER). Randomisation and a well-designed and executed trial protocol can ensure high internal validity, and therefore a corresponding confidence of the causal impact (or lack thereof) of the intervention studied. Due to confounding factors, CER based on observational data is seldom robust [4]. However, this does not mean that observational data is redundant for the purposes of evidence based medicine. Observational data can have an important role in complementing the evidence generated by RCTs, and helping to address some of the significant limitations of RCTs.

Despite efforts to promote clinical trials, the numbers of patients treated in trials remain small at 5–10% of the total patient population [5]. Extrapolating the beneficial effect of evidence-based treatment from RCTs to the general population is compromised; trial patients are typically younger, of better performance status with fewer comorbitides requiring fewer concomitant medications [6,7].

Effect sizes reported in RCTs are also getting smaller [8,9]. As a consequence, RCTs have needed to become larger and correspondingly more costly. Nevertheless, small treatment effects determined by the accumulation of large-scale randomized evidence, collated in the main, by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), has shaped the management of early breast cancer.

Radiotherapy and SACT given in routine care may differ in many ways compared to that provided in RCTs [10–12]. SACT and RTDS databases are now better at recording patient-level treatment and, as the majority of NCRAS databases have population coverage, the risks of referral and selection biases are reduced. Scrutiny of these databases will be essential in ensuring that practice in routine care is comparable to that of RCTs, and that the corresponding benefits are being realised by patients. The possibility of using registries as an infrastructure to support cost-effective RCTs which have greater external validity has been highlighted as having the potential to generate better evidence more rapidly [13].

3. Monitoring adverse events

Patients participating in trials are more intensely monitored than those in routine care. As such, there is concern that the complications of treatments outside clinical trials are under-estimated [14,15].

Understanding the therapeutic index of chemotherapy is particularly critical, given the associated risks and toxicities of this treatment. Observational data is key for monitoring side-effect profiles of chemotherapy in the population.

An NCRAS study has shown the potential for this type of analysis. Until recently, population level monitoring of deaths within a short period following treatment was not possible. The SACT database was used to study mortality within 30 days of SACT in patients with breast and lung cancer [16]. Reassuringly, early mortality for breast cancer patients treated with curative intent was 0.3%, and as such, similar to that reported in clinical trials. Importantly however, it was demonstrated that the risk of early mortality increased with age, which provides clinicians with additional information to consider [16]. This work has been followed up by making a 30 day mortality workbook available to trusts for 6 cancer sites, which allows trusts to investigate their outcomes further [1]. Trusts can also request the NHS number of affected patients treated at their trust via the SACT helpdesk. This information is designed to support mortality and morbidity meetings in oncology and provide an early indication of differential toxicity between RCTs and routine care.

Observational data has also been used to identify harms which occur several years following treatment [17,18]. Long term monitoring of patients and the detection of rare treatment-related adverse events, beyond trial completion, is generally beyond the scope of RCTs. Linkage to Hospital Episode Statistics (HES) can be used to monitor serious or infective adverse events requiring hospital treatment.

4. Treatment adherence

For oestrogen receptor positive (ER+) early breast cancer, RCTs have been used to demonstrate the substantial benefits of endocrine therapy [19]. A longer duration of treatment is beneficial in some populations, which underlines the likely importance of adherence [20]. Several observational studies have reported higher breast cancer mortality in non-adherent patients. However, for reasons including toxicity or cost, adhering to an endocrine therapy regimen is not straightforward for patients [21–24].

Routinely collected population-level data can be used to identify poor adherence and early discontinuation. The Primary Care Prescriptions Dataset has shown promise for studying patterns of endocrine therapy prescribing [25,26]. Linkage to wider PHE datasets could illuminate which patient and tumour characteristics are most predictive of non-adherence, and allow additional support to be made available to help these patients adhere to their prescribed treatment. Furthermore, the exploration of this effect may help to further predict and explain differences between RCTs and real world outcomes.

5. Treatment variation

National audits of the management of symptomatic and screen-detected early breast cancer or ductal carcinoma in situ (DCIS) have repeatedly revealed wide variations in systemic adjuvant therapy and radiotherapy that cannot simply be explained by case mix [27,28]. This variation persists despite, in many cases, robust evidence of treatment efficacy from RCTs.

NCRAS data has been used to provide information on patients' treatment (SACT, radiotherapy and surgery), split by cancer site, year, stage, age, sex, economic deprivation quintile, ethnicity and comorbidities. Wide variability in care has been identified, and reduced access to accepted treatments is linked to poorer outcomes [29]. Given the ease of availability of authoritative national and international treatment guidelines, such variability represents a public health concern and addressing this is a priority. Observational datasets can help to assess this variation, understand the contributory factors and the potential impact on outcomes. Routine data can be used to identify priority areas to focus efforts to drive practice change.

Many new therapies are also becoming available and treatment algorithms change quickly. Routine data can be used to study contemporary care and act as a stimulus to promote equitable access to optimal treatments following approval. A meta-analysis conducted by EBCTCG established that bisphosphonates in early breast cancer reduce the risk of bone metastases and breast cancer mortality by around 18%. It is now 3 years since this definitive publication and despite the availability of treatment guidelines to support the use of bisphosphonates in routine care, these simple and inexpensive drugs are still not routinely used in the UK [30]. RCTs are of no value if the evidence they generate is ignored.

In addition, Vas-Luis et al have shown that the transitions between the classes of chemotherapy treatment providing improvements in care in routine clinical use have lagged many years behind the availability of robust results from RCTs [31]. Many lives could have been saved if clinical implementation had occurred more quickly. Routine data could be used to monitor rates and completeness of implementation, and act as a catalyst for policy change that leads to equitable access.

6. Conclusions

The cancer datasets available through the ODR at PHE represent an inclusive, rich data source encompassing socio-demographics, comorbidities, diagnosis, staging, treatment and outcomes. There are multiple opportunities to use these data to improve care and outcomes for patients with breast cancer and also other malignancies. Data completeness and quality are steadily improving. Consideration should be given to how beneficial changes to practice can be effected when designing observational studies using these datasets, which can help address treatment variation, understand the rate of implementation of treatment advances and the translation of therapeutic indices from RCTs into routine care.

Conflicts of interest

None declared.

I confirm that none of the authors have any conflicts of interest in relation to this article.

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References

[1] SACT, SACT Homepage, Retrieved from (2019) http://www.chemodataset.nhs.uk/home.
[2] ODR, Office for Data Release, Retrieved from (2019) https://www.gov.uk/government/publications/accessing-public-health-england-data/about-the-phe-odr-and-accessing-data.
[3] T.R. Frieden, Evidence for health decision making - beyond randomized, controlled trials, N. Engl. J. Med. 377 (5) (2017) 465–475, https://doi.org/10.1056/NEJMra1614394.
[4] N. Freemantle, L. Marston, K. Walters, J. Wood, M.R. Reynolds, I. Petersen, Making inferences on treatment effects from real world data: propensity scores, confounding by indication, and other perils for the unwary in observational research, Bmj 347 (2013) f6409, https://doi.org/10.1136/bmj.f6409.
[5] C.M. Booth, I.F. Tannock, Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence, Br. J. Cancer 110 (3) (2014) 551–555, https://doi.org/10.1038/bjc.2013.725.
[6] L.F. Hutchins, J.M. Unger, J.J. Crowley, C.A. Coltman Jr., K.S. Albain, Underrepresentation of patients 65 years of age or older in cancer-treatment trials, N. Engl. J. Med. 341 (27) (1999) 2061–2067, https://doi.org/10.1056/nejm199912303412706.
[7] J.H. Lewis, M.L. Kilgore, D.P. Goldman, E.L. Trimble, R. Kaplan, M.J. Montello, et al., Participation of patients 65 years of age or older in cancer clinical trials, J. Clin. Oncol. 21 (7) (2003) 1383–1389, https://doi.org/10.1200/jco.2003.08.010.
[8] C.M. Booth, D.W. Cescon, L. Wang, I.F. Tannock, M.K. Krzyzanowska, Evolution of the randomized controlled trial in oncology over three decades, J. Clin. Oncol. 26 (33) (2008) 5458–5464, https://doi.org/10.1200/jco.2008.16.5456.

[9] B. Seruga, P.C. Hertz, L. Wang, C.M. Booth, D.W. Cescon, M. Krzyzanowska, I.F. Tannock, Absolute benefits of medical therapies in phase III clinical trials for breast and colorectal cancer, Ann. Oncol. 21 (7) (2010) 1411–1418, https://doi.org/10.1093/annonc/mdp552.

[10] B.S. Bloom, N. de Pouvourville, S. Chhatre, R. Jayadevappa, D. Weinberg, Breast cancer treatment in clinical practice compared to best evidence and practice guidelines, Br. J. Cancer 90 (1) (2004) 26–30, https://doi.org/10.1038/sj.bjc.6601439.

[11] D.A. Lazovich, E. White, D.B. Thomas, R.E. Moe, Underutilization of breast-conserving surgery and radiation therapy among women with stage I or II breast cancer, Jama 266 (24) (1991) 3433–3438.

[12] A. Taghian, R. Jagsi, A. Makris, S. Goldberg, E. Ceilley, L. Grignon, S. Powell, Results of a survey regarding irradiation of internal mammary chain in patients with breast cancer: practice is culture driven rather than evidence based, Int. J. Radiat. Oncol. Biol. Phys. 60 (3) (2004) 706–714, https://doi.org/10.1016/j.ijrobp.2004.04.027.

[13] M.S. Lauer, R.B. D'Agostino Sr., The randomized registry trial–the next disruptive technology in clinical research? N. Engl. J. Med. 369 (17) (2013) 1579–1581, https://doi.org/10.1056/NEJMp1310102.

[14] S. Niraula, B. Seruga, A. Ocana, T. Shao, R. Goldstein, I.F. Tannock, E. Amir, The price we pay for progress: a meta-analysis of harms of newly approved anticancer drugs, J. Clin. Oncol. 30 (24) (2012) 3012–3019, https://doi.org/10.1200/jco.2011.40.3824.

[15] B. Seruga, L. Sterling, L. Wang, I.F. Tannock, Reporting of serious adverse drug reactions of targeted anticancer agents in pivotal phase III clinical trials, J. Clin. Oncol. 29 (2) (2011) 174–185, https://doi.org/10.1200/jco.2010.31.9624.

[16] M. Wallington, E.B. Saxon, M. Bomb, R. Smittenaar, M. Wickenden, S. McPhail, et al., 30-day mortality after systemic anticancer treatment for breast and lung cancer in England: a population-based, observational study, Lancet Oncol. 17 (9) (2016) 1203–1216, https://doi.org/10.1016/s1470-2045(16)30383-7.

[17] S.C. Darby, M. Ewertz, P. McGale, A.M. Bennet, U. Blom-Goldman, D. Bronnum, et al., Risk of ischemic heart disease in women after radiotherapy for breast cancer, N. Engl. J. Med. 368 (11) (2013) 987–998, https://doi.org/10.1056/NEJMoa1209825.

[18] K.E. Henson, P. McGale, C. Taylor, S.C. Darby, Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer, Br. J. Cancer 108 (1) (2013) 179–182, https://doi.org/10.1038/bjc.2012.575.

[19] EBCTCG, Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials, Lancet 365 (9472) (2005) 1687–1717, https://doi.org/10.1016/s0140-6736(05)66544-0.

[20] H.J. Burstein, S. Temin, H. Anderson, T.A. Buchholz, N.E. Davidson, K.E. Gelmon, et al., Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: american society of clinical oncology clinical practice guideline focused update, J. Clin. Oncol. 32 (21) (2014) 2255–2269, https://doi.org/10.1200/jco.2013.54.2258.

[21] J.H. Chirgwin, A. Giobbie-Hurder, A.S. Coates, K.N. Price, B. Ejlertsen, M. Debled, et al., Treatment Adherence and Its Impact on Disease-Free Survival in the Breast International Group 1-98 Trial of Tamoxifen and Letrozole, Alone and in Sequence, J. Clin. Oncol. 34 (21) (2016) 2452–2459, https://doi.org/10.1200/jco.2015.63.8619.

[22] B. Ejlertsen, M.B. Jensen, H.T. Mouridsen, Excess mortality in postmenopausal high-risk women who only receive adjuvant endocrine therapy for estrogen receptor positive breast cancer, Acta Oncol. 53 (2) (2014) 174–185, https://doi.org/10.3109/0284186x.2013.850738.

[23] D.L. Hershman, T. Shao, L.H. Kushi, D. Buono, W.Y. Tsai, L. Fehrenbacher, et al., Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer, Breast Cancer Res. Treat. 126 (2) (2011) 529–537, https://doi.org/10.1007/s10549-010-1132-4.

[24] B. Makubate, P.T. Donnan, J.A. Dewar, A.M. Thompson, C. McCowan, Cohort study of adherence to adjuvant endocrine therapy, breast cancer recurrence and mortality, Br. J. Cancer 108 (7) (2013) 1515–1524, https://doi.org/10.1038/bjc.2013.116.

[25] G. Emanuel, K.E. Henson, S. Darby, K. Horgan, D. Dodwell, The prescribing of endocrine therapy in primary care for women with breast cancer: a proof of concept study using the primary care prescription database, Paper Presented at the Cancer Services, Data and Outcomes Conference (2018).

[26] K.E. Henson, R. Brock, B. Shand, V.H. Coupland, L. Elliss-Brookes, G. Lyratzopoulos, et al., Cohort profile: prescriptions dispensed in the community linked to the national cancer registry in England, BMJ Open 8 (7) (2018) e020980, , https://doi.org/10.1136/bmjopen-2017-020980.

[27] D. Dodwell, K. Clements, G. Lawrence, O. Kearins, C.S. Thomson, J. Dewar, H. Bishop, Radiotherapy following breast-conserving surgery for screen-detected ductal carcinoma in situ: indications and utilisation in the UK. Interim findings from the Sloane Project, Br. J. Cancer 97 (6) (2007) 725–729, https://doi.org/10.1038/sj.bjc.6603945.

[28] S. Nicholson, A. Hanby, K. Clements, O. Kearins, G. Lawrence, D. Dodwell, et al., Variations in the management of the axilla in screen-detected ductal carcinoma in situ: evidence from the UK NHS breast screening programme audit of screen detected DCIS, Eur. J. Surg. Oncol. 41 (1) (2015) 86–93, https://doi.org/10.1016/j.ejso.2014.09.003.

[29] H. Moller, V.H. Coupland, D. Tataru, M.D. Peake, A. Mellemgaard, T. Round, et al., Geographical variations in the use of cancer treatments are associated with survival of lung cancer patients, Thorax 73 (6) (2018) 530–537, https://doi.org/10.1136/thoraxjnl-2017-210710.

[30] BCN, 27,000 Women Being Denied 43p Osteoporosis Drug That Can Prevent Breast Cancer Spread, Retrieved from (2016) https://breastcancernow.org/news-and-blogs/news/27000-women-being-denied-43p-osteoporosis-drug-that-can-prevent-breast-cancer-spread?deep_link=bisphosphonate.

[31] I. Vaz-Luis, M.E. Hughes, A.M. Cronin, H.S. Rugo, S.B. Edge, B. Moy, et al., Variation in type of adjuvant chemotherapy received among patients with stage I breast cancer: a multi-institutional study, Cancer 121 (12) (2015) 1937–1948, https://doi.org/10.1002/cncr.29310.