

PhD Project Proposal

Funder details

Studentship funded by: ICR

Project details

Project title: Late-effects of hypofractionated radiotherapy for breast cancer

Supervisory team

Primary Supervisor: Amy Berrington

Associate Supervisor(s):

Secondary Supervisor: Montse Garcia-Closas

Divisional affiliation

Primary Division: Genetics and
Epidemiology

Primary Team: Clinical cancer
epidemiology

Site: Sutton

Project background

Radiotherapy is a crucial part of breast cancer treatment with more than 26,000 women treated annually in England. Whilst radiotherapy saves lives it also carries an emotional and physical toll, with both short and long-term side-effects. Short-term side-effects include breast hardening or shrinking, and the long-term effects include cardiovascular disease, subsequent malignancies and lung fibrosis. These toxicities have become increasingly important as more women survive breast cancer, which means the side-effects can pose more hazard than the risk of recurrence. ICR has spearheaded practice changing trials that have radically changed radiotherapy for breast cancer. Treatment that used to take 5 weeks was reduced to 3 weeks and can now be delivered in 1 week. Randomized trials showed that this shorter, hypofractionated, radiotherapy schedule did not compromise cancer control or safety. It also saved time for patients and clinicians and saved money for the NHS. The impact on long-term side-effects is not yet known but the national Radiotherapy Dataset (RTDS) was established in 2009 and provides a unique opportunity to study this question in the general population, and to evaluate the safety and efficacy in an unselected patient population (real world evidence). The UK Generations Breast Cancer Survivors Study has also been linked to the RTDS and can be used to investigate the additional role of lifestyle factors and genetic susceptibility. Causal inference methods including target trial emulation, propensity scores and quantitative bias assessment methods can be used to assess and control for biases in these observational studies.

Project aims

- Establish a real world dataset by developing a standardised method to utilize the national Radiotherapy Dataset and other national linkages to summarize breast cancer treatments and outcomes.
- Compare the risk of breast cancer mortality and recurrence from hypofractionated radiotherapy compared to standard fractionation in the general population of breast cancer patients in England using the RTDS and the Generations Study.
- Compare the risk of subsequent malignancies from hypofractionated radiotherapy compared to standard fractionation in the general population of breast cancer patients in England using the RTDS and the Generations Study.

Research proposal

The project will use state-of-the-art causal inference and quantitative bias assessment methodology and leverage two complementary cohorts developed from the national cancer treatment datasets and the UK Generation study. The PhD candidate will use advanced epidemiological methods and these rich resources to explore the long-term outcomes after hypofractionated radiotherapy for breast cancer to provide real world evidence on the risks and benefits in the general population.

Study Populations

The National Radiotherapy Dataset (RTDS) was established in England in 2009 to collect consistent and comparable data from all providers of NHS-funded radiotherapy (Sandhu et al., 2023). It contains clinical information on the primary disease being treated, modality and intent of treatment, dose and fractionation. This dataset will be linked to the Systemic Anticancer Dataset (SACT), the National Cancer Registration and Hospital Episode Statistics to provide comprehensive treatment and outcome information for all breast cancer patients in England. The ICR CTSU have developed an algorithm for identifying breast cancer recurrence using these national datasets and validated it using actively ascertained recurrence data from four randomized trials (Kilburn et al., 2017).

The Generations Study is a prospective cohort of 112,000 women in the UK designed originally to study the etiology of breast cancer (Swerdlow et al., 2011). Recruitment started in 2003 and to date 4,603 women have been diagnosed with breast cancer. The sub-study of these breast cancer survivors includes repeated questionnaires providing lifestyle data before and after diagnosis, treatment and outcome information from linkage to the national datasets described above and genotyping data. We previously described how to convert etiological studies to cancer survivorship studies and The Generations Study has many advantages for this purpose (Berrington de González and Morton, 2012).

The two datasets provide complementary resources for these study questions with the national data providing maximum sample size and complete data for the entire English population to minimize random error. Whilst the smaller Generations Study includes detailed lifestyle, genetic, socioeconomic and additional medical history data to evaluate systematic errors. We have previously shown how large-scale national datasets and specialist cohorts can be combined to leverage the strengths of each resource for cancer outcomes research (Veiga et al, 2022).

Literature references

- [1] Berrington de González, A. and Morton, L.M. (2012) 'Converting Epidemiologic Studies of Cancer Etiology to Survivorship Studies: Approaches and Challenges', *Cancer Epidemiology, Biomarkers & Prevention*, 21(6), pp. 875–880. Available at: <https://doi.org/10.1158/1055-9965.EPI-12-0131>.
- [2] Fine, J.P. and Gray, R.J. (1999) 'A Proportional Hazards Model for the Subdistribution of a Competing Risk', *Journal of the American Statistical Association*, 94(446), pp. 496–509. Available at: <https://doi.org/10.1080/01621459.1999.10474144>.
- [3] Lash, T.L., Fox, M.P. and Fink, A.K. (2009) *Applying Quantitative Bias Analysis to Epidemiologic Data*. New York, NY: Springer (Statistics for Biology and Health). Available at: <https://doi.org/10.1007/978-0-387-87959-8>.
- [4] Ramin, C. et al. (2023) 'Risk of second primary cancer among women in the Kaiser Permanente Breast Cancer Survivors Cohort', *Breast Cancer Research*, 25(1), p. 50. Available at: <https://doi.org/10.1186/s13058-023-01647-y>.
- [5] Rosenbaum, P.R. and Rubin, D.B. (1983) 'The Central Role of the Propensity Score in Observational Studies for Causal Effects', *Biometrika*, 70(1), pp. 41–55. Available at: <https://doi.org/10.2307/2335942>.

- [6] Sandhu, S. et al. (2023) 'Cohort profile: radiotherapy dataset (RTDS) in England', *BMJ Open*, 13(6), p. e070699. Available at: <https://doi.org/10.1136/bmjopen-2022-070699>.
- [7] Swerdlow, A.J. et al. (2011) 'The Breakthrough Generations Study: design of a long-term UK cohort study to investigate breast cancer aetiology', *British Journal of Cancer*, 105(7), pp. 911–917. Available at: <https://doi.org/10.1038/bjc.2011.337>.
- [8] Veiga, L.H.S. et al. (2022) 'Treatment-related thoracic soft tissue sarcomas in US breast cancer survivors: a retrospective cohort study', *The Lancet Oncology*, 23(11), pp. 1451–1464. Available at: [https://doi.org/10.1016/S1470-2045\(22\)00561-7](https://doi.org/10.1016/S1470-2045(22)00561-7).

Candidate profile

Note: the ICR's standard minimum entry requirement is a relevant undergraduate Honours degree (First or 2:1).

Pre-requisite qualifications of applicants: Master in Epidemiology, Public Health, Data Science or related field; or equivalent experience in these areas.

Intended learning outcomes:

- Develop expertise in real world evidence and causal inference methodology.
- Critically read and analyse scientific literature, fostering a deep understanding and the ability to integrate current research with historical perspectives.
- Develop hypotheses that build upon existing knowledge.
- Apply rigorous epidemiological methods for study design, data generation, analyses and interpretation, accounting for potential biases.
- Learn to work in a collaborative research environment, leveraging the support of internal teams and external collaborators to enhance research outcomes.
- Communicate research goals, methods, results and implications in both writing and orally.
- Understand and adhere to the ethical considerations and guidelines pivotal in research involving human samples and data.

Advertising details

Project suitable for a student with a background in:

- Biological Sciences
- Physics or Engineering
- Chemistry
- Maths, Statistics or Epidemiology
- Computer Science