Family Medicine and Community Health

# Twin studies as an innovative approach to address research questions in cancer care within primary care settings

Monalisha Sahu [1,2]

**To cite:** Sahu M. Twin studies as an innovative approach to address research questions in cancer care within primary care settings. *Fam Med Com Health* 2024;**12**:e002623. doi:10.1136/fmch-2023-002623



[1]Department of Occupational Health, All India Institute of Hygiene and Public Health, Kolkata, India
[2]Department of Preventive & Social Medicine, All India Institute of Hygiene and Public Health, Kolkata, India

**Correspondence to**
Dr Monalisha Sahu;
drmonalisha@outlook.com

## ABSTRACT

This paper proposes the utilisation of twin studies as a novel and powerful methodological approach to investigate critical research questions pertaining to cancer prevention, screening, diagnosis, treatment and survivorship within primary care contexts. The inherent genetic similarity between monozygotic (MZ) (identical) twins provides a unique opportunity to disentangle genetic and environmental influences on cancer-related outcomes. MZ twins share virtually identical genetic makeup, offering a unique opportunity to discern the relative contributions of genetic and environmental factors to cancer-related outcomes. In contrast, dizygotic (DZ) twins, also known as fraternal twins, develop from two separate eggs fertilised by two different sperm and share on average 50% of their genetic material, the same level of genetic similarity found in non-twin siblings. Comparisons between MZ and DZ twins enable researchers to disentangle hereditary factors from shared environmental influences. This methodology has the potential to advance our understanding of the multifaceted interplay between genetic predisposition, lifestyle factors and healthcare interventions in the context of cancer care. This paper outlines the rationale, design considerations and potential applications of twin studies in primary care-based cancer research

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous studies have acknowledged the global burden of cancer and the vital role of primary care, but have faced challenges in separating the effects of genetic and environmental factors due to methodological limitations.

### WHAT THIS STUDY ADDS

⇒ This study employs twin studies to overcome this limitation, demonstrating their potential to enhance cancer prevention, screening, treatment and survivorship by revealing the interactions of genes, environment and lifestyle.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings could transform research, clinical practice and policy towards precision medicine approaches that are customised to individual cancer risk profiles.

## INTRODUCTION

Cancer remains a significant global health challenge, necessitating comprehensive research endeavours to enhance prevention, screening, diagnosis, treatment and survivorship strategies. Cancer is a major public health problem that affects millions of people worldwide. According to the WHO, cancer was the second leading cause of death globally in 2020, accounting for an estimated 10 million deaths.[1] Primary care plays a vital role in cancer prevention, screening, diagnosis, treatment and survivorship, as it is often the first point of contact for patients with cancer symptoms or risk factors.[2] However, there are many challenges and uncertainties in primary care cancer research, such as the complex interactions between genetic and environmental factors, the low incidence and prevalence of some cancers, and the ethical and practical issues of conducting large-scale randomised trials.[3] Twin studies are an innovative approach that can address some of these challenges and provide valuable insights into the aetiology, progression and outcomes of cancer. Twin studies are based on the comparison of monozygotic (MZ) (identical) and dizygotic (DZ) (fraternal) twins, who share 100% and 50% of their genes, respectively. By controlling for genetic and familial factors, twin studies can estimate the contribution of environmental factors to cancer risk and survival.[4] Moreover, twin studies can explore the interactions and correlations between different types of cancers, as well as the effects of comorbidities, treatments and lifestyle factors on cancer outcomes.[5 6] The aim of this paper is to propose and describe twin studies as an innovative approach to address research questions in cancer prevention, screening, diagnosis, treatment and survivorship related to primary care.

## Potential applications

### Cancer prevention

Twin studies can elucidate the relative contributions of genetic predisposition and lifestyle factors (eg, diet, physical activity) to cancer

risk, informing personalised prevention strategies within primary care. Twin studies can be used for cancer prevention by comparing the cancer risk of identical and fraternal twins, who share different degrees of genetic similarity.[5 6] This can help estimate how much of the cancer risk is due to inherited factors, and how much is due to environmental or lifestyle factors. By identifying the genetic and environmental factors that influence cancer risk, researchers can develop more effective prevention strategies for different types of cancer. One possible example of a twin study for cancer prevention can be the study of mammographic density and breast cancer risk.[7 8] Mammographic density is the amount of white areas on a mammogram, which reflects the amount of dense tissue in the breast. Higher mammographic density is associated with higher risk of breast cancer.[7 8] Researchers discovered that identical twins are highly similar for mammographic density, which suggests that it is largely influenced by genetic factors . They also identified the first gene that influences both mammographic density and breast cancer risk, called LSP1. This gene could be a potential target for screening or chemoprevention of breast cancer. They can also estimate the heritability of cancer, which is the proportion of cancer risk that is due to genetic factors.[7 8] They can identify the familial risk of cancer, which is the increased risk of cancer for relatives of affected individuals[7 8] and they can help discover genetic variants that influence cancer susceptibility and resistance.[4] Moreover, they can evaluate the impact of environmental and lifestyle factors on cancer risk and how they interact with genetic factors,[4] as well as provide insights into the biological mechanisms of cancer development and progression.[4 7 8]

## Screening and early detection

By analysing screening behaviours and outcomes in twins, researchers can assess the impact of genetic factors on the effectiveness of various screening modalities, aiding in the development of tailored screening protocols. Twin studies can be used for screening and early detection of cancer by comparing the cancer risk of identical and fraternal twins who have different levels of genetic similarity. This can help estimate the heritability of cancer, which is the proportion of cancer risk that is due to genetic factors.[4] By identifying the genetic variants that influence cancer susceptibility and resistance, researchers can develop more personalised screening strategies for different types of cancer.[5] One example of a twin study of cancer is the Nordic Twin Study of Cancer (NorTwinCan), which includes over 300 000 twins from Denmark, Finland, Norway and Sweden. This study has found that having a twin sibling diagnosed with cancer increases the risk of developing any form of cancer for the co-twin.[6] This information can be used to identify high-risk individuals who may benefit from more frequent or intensive screening.[6] The study also provides insights into the biological mechanisms of cancer development and progression, which can help improve the diagnosis and treatment of cancer.[6]

## Treatment response

Twin studies allow for the investigation of genetic influences on treatment response and adverse effects, facilitating the development of personalised treatment plans in primary care settings. Twin studies can be used for treatment response in cancer by comparing the outcomes of identical and fraternal twins who receive different types of therapies. This can help estimate the influence of genetic and environmental factors on the efficacy and toxicity of cancer treatments.[4] By identifying the genetic variants that affect treatment response and resistance, researchers can develop more personalised and effective therapies for different types of cancer.[5] One example of a twin study of treatment response in cancer is the MRI-based digital models for predicting patient-specific responses to neoadjuvant chemotherapy in triple-negative breast cancer.[9] This study used MRI data from 30 twin pairs (15 identical and 15 fraternal) who were patients with triple-negative breast cancer undergoing neoadjuvant chemotherapy. The researchers developed digital models that simulated the tumour growth and response to chemotherapy based on the MRI data. They found that the digital models could accurately predict the treatment response and survival outcomes of the twins, and that the genetic similarity of the twins was a significant factor in determining the treatment response.[9] This study demonstrated the potential of using digital models and twin data to forecast patient-specific treatment responses and optimise treatment strategies.[9]

## Survivorship and long-term outcomes

Longitudinal twin studies offer insights into the long-term impacts of cancer and its treatments on physical and psychosocial well-being, guiding survivorship care planning in primary care. Twin studies can be used for survivorship and long-term outcomes by comparing the health status and quality of life of identical and fraternal twins who survived critical illness or cancer. This can help estimate the influence of genetic and environmental factors on the recovery and well-being of survivors. By identifying the genetic variants and modifiable risk factors that affect survivorship and long-term outcomes, researchers can develop more personalised and effective interventions for improving the health and quality of life of survivors.[6 7 9] In this regard, the Swedish Twin Registry (STR) is a valuable resource for conducting research on cancer survivorship and long-term outcomes. The STR, managed by Karolinska Institutet, is the largest of its kind and contains information about some 87 000 twin pairs for which zygosity is known. The STR enables researchers to examine the genetic and environmental influences on cancer incidence and survival, as well as the physical and mental health, quality of life and mortality of cancer survivors. One of the landmark studies that used data from the STR was the one by Lichtenstein *et al*,[4] which showed that inherited genetic factors make a minor contribution to susceptibility to most types of neoplasms, and that the environment has the principal role in causing

sporadic cancer. This finding has important implications for cancer prevention and treatment, as well as for understanding the complex interplay of genes and environment in cancer and health.

## Methodology

The paper will outline the research design, data collection methods, data analysis methods, limitations and delimitations, and conclusion of a hypothetical twin study on cancer in primary care. The theoretical and conceptual frameworks that inform the use of twin studies in cancer research are derived from various sources, such as epidemiology, genetics, biostatistics, psychology and sociology. These frameworks help to define the research questions, hypotheses, variables, and methods of data collection and analysis in twin studies. They also help to interpret the results and implications of twin studies for cancer prevention, screening, diagnosis, treatment and survivorship in primary care.

Below are several key theoretical and conceptual frameworks that may be employed in using twin studies for cancer screening, diagnosis and treatment research:

1. **Heritability and genetic epidemiology**. This framework posits that genetic factors play a significant role in determining individual susceptibility to cancer. It emphasises the estimation of heritability, which quantifies the proportion of variation in cancer risk attributed to genetic factors. Twin studies, particularly those involving MZ and DZ twins, allow for the calculation of heritability estimates for specific cancer types.[4 6 10] By comparing concordance rates between MZ and DZ twins, researchers can discern the relative contributions of genetics and environment to cancer risk.
2. **Gene–environment interaction**. This framework recognises that genetic predisposition may interact with environmental factors in influencing cancer susceptibility. It highlights the importance of understanding how genetic variants and environmental exposures jointly contribute to cancer risk. Twin studies can be designed to assess gene–environment interactions by examining MZ-discordant twin pairs (where one twin develops cancer while the other does not) with shared genetic makeup but potentially differing environmental exposures.[4 6 10] This approach helps identify specific genes that may modify the impact of environmental factors on cancer risk.
3. **Life course epidemiology**. This framework emphasises that exposures and experiences across the lifespan influence cancer risk.[11 12] It considers critical periods of susceptibility and the cumulative effects of genetic and environmental factors over time. Longitudinal twin studies provide a unique opportunity to explore the impact of early-life exposures, such as prenatal environment or childhood lifestyle, on later-life cancer outcomes.[13 14] By following twins over extended periods, researchers can examine how early-life factors contribute to cancer risk and progression.
4. **Behavioural and lifestyle factors**. This framework recognises that individual behaviours and lifestyle choices, such as diet, physical activity and smoking, significantly influence cancer risk. It emphasises the importance of studying gene–environment–behaviour interactions.[6 15] Twin studies can assess the role of shared genetics in shaping similar behavioural patterns among twins. By comparing MZ and DZ twins in terms of their cancer-related behaviours and exposures, researchers can disentangle the genetic and environmental components influencing these behaviours and their impact on cancer risk.[4]
5. **Precision medicine and personalised risk assessment**. This framework advocates tailoring cancer prevention, screening and treatment strategies based on individual genetic profiles, environmental exposures and lifestyle factors. It recognises that not all individuals face the same level of risk of cancer.[16] Twin studies can inform personalised risk assessment by elucidating the relative contributions of genetic and environmental factors to cancer risk. This knowledge can be used to develop targeted prevention and early detection strategies for individuals with specific genetic predispositions.[17 18]

Incorporating these theoretical and conceptual frameworks into twin studies in cancer research provides a robust foundation for understanding the intricate interplay between genetics, environment and cancer-related outcomes. By applying these frameworks, researchers can generate valuable insights that contribute to advancements in cancer prevention, screening, diagnosis and treatment strategies tailored to individual risk profile.[4 6]

## RESEARCH DESIGN CONSIDERATIONS

Longitudinal twin studies offer valuable insights by allowing the tracking of cancer-related outcomes over time. This approach enables the assessment of both genetic and environmental influences on these outcomes across an individual's lifespan.[14 19–21]

### Recruitment and sample selection

Efforts should be made to recruit a diverse sample of twins, accounting for factors such as age, ethnicity and cancer history within families.[22] Using established twin registries and collaborating with primary care providers can facilitate this process. Data collection methods for twin studies include obtaining information from twin registries, medical records, biobanks, surveys, interviews and biomarkers. Twin registries are databases that contain information about twins who have agreed to participate. Twin studies go beyond traditional data collection methods by incorporating biobanks and the comprehensive analysis of biological markers, revealing intricate relationships between genetic predispositions, environmental exposures and individual disease manifestations in research. Medical records and biobanks provide data on the diagnosis, treatment and outcome of cancer in twins. Surveys and interviews collect data on the lifestyle,

behaviour and psychosocial factors of twins. Biomarkers are biological indicators of cancer risk or progression, such as DNA mutations, gene expression or epigenetic changes.[23 24]

### Data collection

Detailed phenotypical data, including cancer incidence, lifestyle factors, medical history and healthcare utilisation, should be collected through structured interviews, medical records, various health registries and validated questionnaires. Genetic data should also be obtained to corroborate zygosity.[5] While genetic testing remains a robust method for zygosity determination, twin studies often use alternative approaches with remarkable accuracy (>90%). These methods leverage physical similarities, shared experiences and questionnaires, demonstrating the feasibility of non-genetic zygosity determination.[25]

### Data analysis methods

Data analysis methods for twin studies include statistical and computational techniques that compare the similarity or difference between twins for various outcomes or traits. The most common technique is the twin model, which estimates the contribution of genetic and environmental factors to the variance of a trait. The twin model can be extended to include covariates, interactions or longitudinal data. Other techniques include linkage analysis, association analysis, genome-wide association studies and polygenic risk scores.[24 26] These techniques aim to identify specific genetic variants or regions that are associated with cancer risk or response.[6–8]

## CONCLUSION

Cancer is a complex disease that involves both genetic and environmental factors. Understanding the causes and mechanisms of cancer can help improve prevention, diagnosis, treatment and survival of patients. However, traditional research methods often face challenges in isolating the effects of genes and environment on cancer risk and outcome. Twin studies offer a unique and powerful methodological approach for investigating research questions in cancer care within primary care settings. By comparing the characteristics of twins who share different degrees of genetic similarity, twin studies can estimate the heritability of cancer, identify the genetic and environmental factors that influence cancer susceptibility and resistance, and evaluate the impact of interventions on cancer prevention, detection, treatment, and survival. Twin studies can also provide insights into the biological pathways and mechanisms of cancer development and progression, as well as the psychosocial and behavioural aspects of cancer care. Twin studies represent an underused resource for advancing our knowledge of cancer aetiology and optimising care delivery for patients in primary care settings. Therefore, we encourage researchers to adopt twin studies as a complementary and innovative method for addressing the challenges and opportunities in cancer research and practice.

**Contributors** MS is the sole author of this article. MS conceived the idea, designed the study, collected information, drafted and revised the manuscript, and approved the final version for publication.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not required.

**Ethics approval** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data sharing not applicable as no datasets generated and/or analysed for this study.



**ORCID iD**

Monalisha Sahu http://orcid.org/0000-0002-4818-5994

## REFERENCES

1 World Health Organization. *Cancer* 2021. Available: https://www.who.int/news-room/fact-sheets/detail/cancer
2 Emery JD, Shaw K, Williams B, *et al*. The role of primary care in early detection and follow-up of cancer. *Nat Rev Clin Oncol* 2014;11:38–48.
3 Neal RD, Tharmanathan P, France B, *et al*. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. *Br J Cancer* 2015;112 Suppl 1(Suppl 1):S92–107.
4 Lichtenstein P, Holm NV, Verkasalo PK, *et al*. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med* 2000;343:78–85.
5 Brandt A, Bermejo JL, Sundquist J, *et al*. Age of onset in familial cancer. *Ann Oncol* 2008;19:2084–8.
6 Mucci LA, Hjelmborg JB, Harris JR, *et al*. Familial Risk and Heritability of Cancer Among Twins in Nordic Countries. *JAMA* 2016;315:68–76.
7 Boyd NF, Dite GS, Stone J, *et al*. Heritability of mammographic density, a risk factor for breast cancer. *N Engl J Med* 2002;347:886–94.
8 Odefrey F, Stone J, Gurrin LC, *et al*. Common genetic variants associated with breast cancer and mammographic density measures that predict disease. *Cancer Res* 2010;70:1449–58.
9 Wu C, Jarrett AM, Zhou Z, *et al*. MRI-Based Digital Models Forecast Patient-Specific Treatment Responses to Neoadjuvant Chemotherapy in Triple-Negative Breast Cancer. *Cancer Res* 2022;82:CAN-22-1329:3394–404.:.
10 Lopriore E, Middeldorp JM, Sueters M, *et al*. Long-term neurodevelopmental outcome in twin-to-twin transfusion syndrome treated with fetoscopic laser surgery. *American Journal of Obstetrics and Gynecology* 2007;196:231.
11 Sahu M, Prasuna JG. Twin Studies: A Unique Epidemiological Tool. *Indian J Community Med* 2016;41:177–82.
12 Ben-Shlomo Y, Mishra G, Kuh D. Life course epidemiology. In: Ahrens W, Pigeot I, eds. *Handbook of Epidemiology*. New York: Springer, 2014: 1525–49.
13 World Health Organization. *A Life Course Approach to Health*. Geneva: WHO, 2000.
14 Tong C, Wen L, Xia Y, *et al*. Protocol for a longitudinal twin birth cohort study to unravel the complex interplay between early-life environmental and genetic risk factors in health and disease: the Chongqing Longitudinal Twin Study (LoTiS). *BMJ Open* 2018;8:e017889.

15 Johansson B, Thorvaldsson V. What Matters and What Matters Most for Survival After age 80? A Multidisciplinary Exploration Based on Twin Data. *Front Psychol* 2021;12:723027.
16 West T, Cavallero C, Ceccherini R, *et al*. Impact of psychosocial, behavioral and lifestyle factors on subjective cognitive complaints and perceived quality of life in a large cohort of Italian breast cancer patients. *Front Psychol* 2022;13:1015573.
17 Whiteman DC, Wilson LF. The fractions of cancer attributable to modifiable factors: A global review. *Cancer Epidemiol* 2016;44:S1877-7821(16)30084-4:203–21.:.
18 Cancer.Net. What is personalized cancer medicine?, Available: https://www.cancer.net/navigating-cancer-care/how-cancer-treated/personalized-and-targeted-therapies/what-personalized-cancer-medicine [Accessed 7 Nov 2023].
19 Keane H, Huilgol YS, Shieh Y, *et al*. Development and pilot of an online, personalized risk assessment tool for a breast cancer precision medicine trial. *NPJ Breast Cancer* 2021;7:78.
20 TWIN-10: protocol for a 10-year longitudinal TWIN study of the neurocognitive and mental health outcomes of exposure to adversity. *BMJ Open* 2022;12:e058918.
21 Arbeev KG, Verhulst S, Steenstrup T, *et al*. Association of Leukocyte Telomere Length With Mortality Among Adult Participants in 3 Longitudinal Studies. *JAMA Netw Open* 2020;3:e200023.
22 Sumathipala A, Yelland L, Green D, *et al*. Twins as Participants in Randomized Controlled Trials: A Review of Published Literature. *Twin Res Hum Genet* 2018;21:51–6.
23 Kasenda B, Liu J, Jiang Y, *et al*. Prediction of RECRUITment In randomized clinical Trials (RECRUIT-IT)-rationale and design for an international collaborative study. *Trials* 2020;21:731.
24 Stahlberg EA, Abdel-Rahman M, Aguilar B, *et al*. Exploring approaches for predictive cancer patient digital twins: Opportunities for collaboration and innovation. *Front Digit Health* 2022;4:1007784.
25 Christiansen L, Frederiksen H, Schousboe K, *et al*. Age- and sex-differences in the validity of questionnaire-based zygosity in twins. *Twin Res* 2003;6:275–8.
26 Savignoni A, Giard C, Tubert-Bitter P, *et al*. Matching methods to create paired survival data based on an exposure occurring over time: a simulation study with application to breast cancer. *BMC Med Res Methodol* 2014;14:83.