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BREAST SURGERY

A single centre audit of genetic testing in early-onset breast cancer

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Background: This paper serves to audit the number of women who received genetic testing after diagnosis with breast cancer ≤ 35 years. Patients were diagnosed or sought treatment at the Breast Care Centre of Excellence (BCCE), a private accredited specialist breast unit in Johannesburg, South Africa. This study focuses specifically on genetic testing for pathogenic variants of the BRCA 1 and BRCA 2 genes.
Methods: Files of patients diagnosed ≤ 35 years were retrieved, and medical information was extracted. These patient files were then compared to records from the University of the Witwatersrand genetic service facility and the GC Network Pty (Ltd) genetic service facility, and genetic service data was recorded. All data was then compiled and analysed.
Results: Over 10 years, 196 patients were diagnosed with breast cancer ≤ 35 years, while only 5 received genetic testing.
Conclusion: In order to understand the relationship between BRCA1/2 genetic diagnosis and cancer diagnosis, greater emphasis must be placed on the availability of genetic services and testing. Ensuring that these services are available, accessible, and funded by either the State or medical insurance will greatly enhance the understanding between BRCA diagnosis, breast cancer diagnosis, risk reduction procedures, and quality of life in many young women.
Keywords: oncology, genetic testing, breast cancer, carcinoma

Introduction

Breast cancer is the foremost cancer diagnosis in South African women, accounting for 23% of all cancer diagnoses, according to the 2019 National Cancer Registry statistics.[1] Furthermore, the incidence rate for breast cancer in women under the age of 35 is reported at 18.5%.[1] A wide range of cancer treatment is available, which allows patients and physicians to select the most appropriate and beneficial treatment regime for each specific patient. A critical component of decision-making, and understanding who is at risk for new primaries, is fully understanding the patient's biological information. Genetic services, such as gene testing, can identify this crucial information.

Genetic testing is the process by which specific pathogenic gene variants can be identified within a patient's genome. In breast cancer patients genetic testing permits the identification of inherited pathogenic variants which may have an impact on local and systemic treatment. Statistically, hereditary breast cancer makes up between 5–10% of breast cancer diagnoses, with mutations in the high penetrance BRCA 1 and 2 gene accounting for 4.5% of hereditary breast cancer diagnoses.[2,3] Other, less penetrant mutations, include CHEK2 (breast and colorectal cancer), PALB2 (breast and pancreatic cancer), ATM, and BRIPI (ovarian cancer).

These inherited genetic variants are associated with an increased likelihood of developing cancer. However, not all variants increase cancer susceptibility.

Two factors influence cancer susceptibility – penetrance and expressivity. Penetrance describes the relationship between genotype and phenotype, specifically the statistical occurrence of a specific phenotype in a group with the same genotype. Penetrance can be either complete (100%) or incomplete (< 100%), while incomplete penetrance can be further categorised into low-, moderate-, or high-penetrance. Expressivity differs in that it describes the various degrees to which individuals with the same genotype express the specific phenotype.[4]

According to the South African Department of Health *Clinical Guidelines for Breast Cancer Control and Management*, women who meet the eligibility criteria must be referred to a genetic service provider for genetic testing and management. This criterion includes women with a personal breast or ovarian cancer diagnosis at age 40 or younger, as well as various other scenarios, such as the diagnosis of triple-negative breast cancer (Figure 1).[5]

All criteria outlined in the clinical guidelines indicate potentially inherited pathogenic cancer gene variants – i.e. mutations on the BRCA 1 and 2 genes. However, for this paper the criterion for audit of genetic testing was women diagnosed ≤ 35 in order to evaluate the uptake of genetic testing amongst women diagnosed at a very young age.

Genetic services, such as genetic testing and genetic counselling, are beneficial for individuals with a personal cancer diagnosis, as well as those with a family history of cancer, in that it informs medical treatment options,

Standard 1.5 – Referral to genetic services is offered to women whose family history meets the criteria for referral.

ELIGIBILITY CRITERIA FOR REFERRAL TO GENETIC SERVICES

Individuals who fulfil these criteria must be referred to Genetic Services for assessment and management:

- A person with ***breast/ovarian cancer*** who has any of the following:
  - Known mutation in a cancer predisposition gene (e.g. *BRCA1/2, p. 53*) in the family
  - Cancer diagnosed < 40 years for breast cancer and < 60 years old for ovarian cancer
  - Triple negative breast cancer < 60 years old
  - Two breast cancer primaries – ipsilateral or contralateral at any age
  - ≥ 1 close relatives with breast cancer < 50 years
  - ≥ 1 close relative with invasive ovarian cancer
  - ≥ 2 close relatives with breast or pancreatic cancer with at least one < 60 years old
  - ≥ 1 family member with male breast cancer
  - Any male with breast cancer
- A person with ***no personal history of cancer*** but with a ***close*** family history of any of the following:
  - Known mutation in a cancer predisposition gene (e.g. *BRCA1/2, p. 53*) in the family
  - Two breast cancer primaries (ipsilateral or contralateral) in a close relative at < 60 years
  - ≥ 3 individuals with breast cancer on same side of family with at least one ≤ 50 years old.
  - ≥ 1 individual with breast cancer ≤ 50 years old and ≥ 1 individual with ovarian cancer on the same side of the family
  - Other factors that you may take into consideration when occurring together with breast cancer – prostate cancer (aggressive type and onset < 60 years), male breast cancer, pancreatic cancer, Ashkenazi and Afrikaans ancestry, other syndrome-related cancers in family members on the same side of the family.

Figure 1: Eligibility criteria for referral to genetic services

including surgical options, and patient eligibility for clinical trials. Additionally, genetic information can impact a patient's family planning decisions, risk-reducing treatments and medical decisions of children and other family members.[6] Although there are many benefits to the use of genetic services, there is concern that this valuable service is not frequently utilised amongst patients of early onset breast cancer, likely due to the lack of availability of these services, psychological stressors or guilt around the diagnosis, and the unaffordability of these services, as some medical aids do not cover genetic testing, while others cover this service out of the patient's saving. Unfortunately, due to the costly nature of treatment, patients sometimes do not have available savings for this service, or do not prioritise genetic service.

The aim of the study was to conduct an audit of the number of women who received genetic testing after an early onset breast cancer diagnosis (≤ 35 years old).

Materials and method

This study included all women who received genetic testing, after referral, following an invasive breast cancer diagnosis ≤ 35 years of age at the Breast Care Centre of Excellence (BCCE) in Johannesburg, South Africa, and sought genetic services at either GC Network, a private genetic service facility, or the University of the Witwatersrand genetic service facility, which services both the private and public sector. Both genetic service facilities are located in Johannesburg, South Africa.

The procedure for patients diagnosed with early-onset breast cancer at the BCCE includes discussion of the treatment plan in the multidisciplinary meeting, and the need for a genetic consultation with a genetic specialist in the meeting. Patients receive contact details for various genetic specialists, as well as information relating to genetic services, as encouragement to undergo the necessary genetic tests.

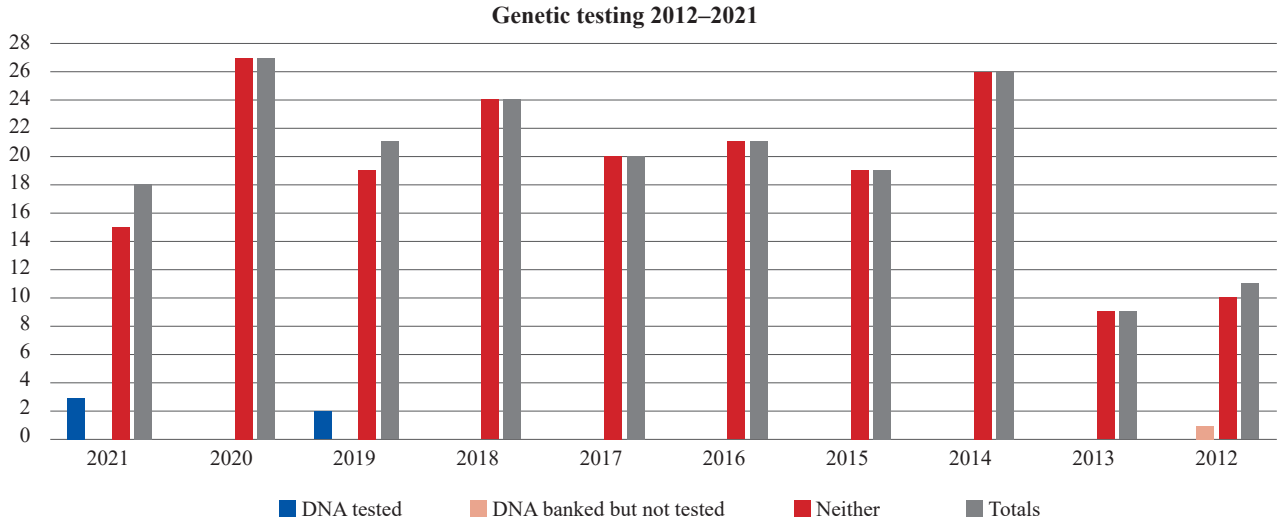

Figure 2: Graph showing the rates of genetic services employed between 2012–2021

Patient selection

Eligible patients were those diagnosed with invasive breast cancer ≤ 35 years of age between 2012 and 2021 and have sought treatment or consultation at the BCCE, a private medical facility in Johannesburg, South Africa. Patients excluded from this study were those who were diagnosed ≥ 36 years of age or who received a DCIS (ductal carcinoma in situ) diagnosis.

Data collection

The medical information of eligible patients was retrospectively retrieved from the patient files at the BCCE. This included the year in which the patient was diagnosed with invasive breast cancer.

Patient's genetic service history was collected from GC Network, a private genetic service facility, and the University of the Witwatersrand genetic service facility, which services both the private and public sector. This information included the year in which genetic services were received, the type of genetic services received, and the results of BRCA1/2 tests (if done).

The information received from the BCCE from both genetic testing facilities was then compiled to allow data analysis and descriptive statistical analysis. No other statistical analysis was used.

Results

Between 2012 to 2021, 196 women were diagnosed with early-onset invasive breast cancer (≤ 35 years) and sought treatment/consultation at the BCCE. In accordance with the National Cancer Association Guidelines, all patients were referred for genetic testing as these women were diagnosed under the age of 40 years. Of the 196 patients referred for genetic testing, seven sought genetic services, while only five patients received genetic testing over the 10 years. This comprised of two patients who received genetic testing in 2019, and three patients in 2021. However, no patients between 2012 to 2018, and in 2020, received any genetic testing.

Of the five patients who received genetic testing, one patient showed a positive test result for mutation on the BRCA 1 gene.

Although no patients received genetic testing in 2012 and 2013, it is noted that "Patient A" was diagnosed in 2012 with triple-negative invasive carcinoma and received genetic counselling in 2013. The patient had a blood sample drawn, and her DNA was banked in that same year, however, no gene tests were done. This could be due to cost or no follow-up appointment by the patient (Figure 2).

In 2013 "Patient B" was diagnosed with Luminal B invasive moderately differentiated carcinoma and received genetic counselling in 2015. However, she did not follow through with any sampling in order for her DNA to be banked or tested. Both "Patient A" and "Patient B" received this genetic counselling through the University of the Witwatersrand.

Discussion

The results showed that over the 10-year study period (2012–2021), five of the 196 women diagnosed with invasive breast cancer at the BCCE younger than 35 years of age received genetic testing. However, seven received genetic services through genetic counselling, with DNA samples being drawn, or testing for BRCA 1/ 2. This difference between the number of patients who sought genetic services and the number of patients who received testing is concerning as all women diagnosed within this age bracket are recommended to receive genetic testing – hence, it would be expected that all patients would have received testing. Patients may have sought an initial appointment with a genetic service provider, but due to high costs of genetic tests, opted not to proceed with further genetic services. Alternatively, patients may have sought genetic testing outside of the 10-year period assessed or sought genetic services at a facility other than the ones to which they were referred by the multi-disciplinary team.

There are a myriad reasons which impact a patient's decision to receive or not receive genetic services, including, but not limited to – costs, availability of services, understanding of what genetic testing is, medical decisions, family planning decisions, etc. We were unable to determine which of these factors applied to our patient cohort as the information was not available in the patient records.

A 2019 study by the American Society of Clinical Oncology (ASCO) highlighted factors which positively influenced a patient's decisions. These were concern about family member risk, results potentially affecting medical decisions, and concern about the risk of other cancers, at roughly 75%, 70%, and 68% respectively.[6]

These concerns are also evident in data from the GC Network genetic service facility between 2019 and 2021 which shows that 25% (4/16) of all patients who sought consultation at both BCCE and GC Network, regardless of their cancer status, had a personal diagnosis of early-onset breast cancer. The other 75% (12/16) of patients seen over this period received genetic counselling due to a family history of cancer.

This is corroborated by the ASCO study which showed that roughly 65% of participants regarded family history as a positive factor for genetic testing, especially in a first-degree relative. Only around 58% regarded a personal diagnosis as a contributing factor towards being tested.[6]

Additionally, the most notable factors against genetic testing, as listed by the aforementioned American study, were concerns about cost of testing (13%), and insurance not covering test costs (15%).[6] Genetic testing services are expensive, while full gene sequencing is even more costly. However, should genetic testing be done at a state-owned facility, this would be at no cost to patients who would otherwise be unable to afford this service.

Furthermore, according to Discovery's Screening and Prevention benefit, certain breast cancer treatments will be covered either under the member's allocated fund or under day-to-day benefits (if applicable). These treatments include a once-off BRCA gene test for high-risk members.[7]

Current costing (2023) information received from the GC Network showed that certain genetic tests can be paid from the patient's pathology benefits. These tests include Familial Gene Mutation test (R2200.00); Common Founder Mutation tests (R3500.00); Full Gene Screening for BRCA 1 and 2, with hereditary cancer panel included, (R7000.00); and BRCA 1, BRCA 2, and TP53 tests (R8000.00–R12000.00, at private laboratories). Additionally, in cases where a patient is diagnosed with breast cancer, the facility may motivate for tests to be paid from the patient's oncology fund.

Although many medical aid schemes fund testing, and cost-free testing is available to patients aware of the service, many additional factors may influence a patient's decision to refuse testing. There are other indirect costs for low-income, or no-income patients, who qualify for free testing. The facilities are often located in major cities which can be quite distant for individuals in remote or rural areas and thus become too expensive or difficult to access. Additionally, these patients would likely be unable to afford a medical aid scheme which covers testing costs at other recognised facilities, thus leaving genetic services inaccessible and unavailable to these patients.

In the case of patients who would typically be able to afford medical aid and/or the cost of testing, the patient may avoid BRCA testing to conserve funds for other treatments. The accumulating costs of chemotherapy, radiation, surgery, and genetic testing soon becomes too expensive for many people, thus leaving the patient to decide to remove certain aspects of their treatment plan. These cost factors are thus a major determining factor for all patients.

Further research into costs and other factors affecting a patient's decisions regarding genetic testing in South Africa will allow physicians and other healthcare providers to better understand how to serve and benefit their patients. This research could also allow for great improvement in this sector and medical care.

Limitations

Although analysis of this data is possible, various factors limit the scope of this paper and thus allow for improvement and deeper research into this field of study. The limiting factors pertaining to this paper include:

1. This data subset is limited as the sample between 2012 and 2021, which only yielded 196 eligible women.
2. Dataset is limited as only patients of one private facility were considered.
3. The genetic testing statistics do not account for patients who may have received genetic services at a facility not recommended by the BCCE.
4. The genetic testing statistics also do not account for patients receiving testing outside the selected 10-year period.
5. The research scope does not include any type of survey or feedback on the reasons and factors influencing these specific patients' decision for or against receiving genetic testing.
6. Data is also limited because some genetic services may not have been available to patients during 2020 due to the COVID-19 pandemic.
7. Being a retrospective study, certain data is limited as it was not consistently included in patients' files, or where information was included, the patient fell outside the edibility criteria. As a result, data such as molecular subtype, and exact age of patients could not be reported on as it was not available for all patients selected for this study.

Expanding the research scope to include any/all of the above will allow for more extensive and exhaustive results to be produced in the future.

Conclusion

Our study showed that there is a very low prevalence of genetic testing amongst women diagnosed with early-onset invasive breast cancer. Greater emphasis must be placed on the importance and relevance of genetic services and further research into the factors limiting the uptake of these services is required. Making genetic services more widely accessible and available will significantly improve treatment options and the quality of life of women with breast cancer in South Africa.

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Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

Ethical approval was obtained from the Ethics Committee of Pharma-Ethics, through the Breast Care Centre of Excellence. To ensure confidentiality, patient's data was de-identified, by excluding significant identifying information such as patient name, and identification number. Ethics approval was obtained from Pharma-Ethics (Ref: 170416525).

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