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Clinical Validity and Utility of Epigenomic Profiling in Breast Cancer: Lessons for Population Screening and Policy

Nagawa Jackline Irene

Department of Clinical Medicine and Dentistry Kampala International University Uganda
Email: irene.nagawa@studwc.kiu.ac.ug

ABSTRACT

Breast cancer risk is shaped not only by inherited genetic variation but also by dynamic and potentially reversible epigenomic modifications that reflect environmental exposures, ageing, and life-course influences. Epigenomic profiling, particularly DNA methylation analysis, has emerged as a promising tool for breast cancer risk stratification, early detection, and personalized screening strategies. This review examines the clinical validity and clinical utility of epigenomic biomarkers in breast cancer and explores their implications for population screening and health policy. We discuss current epigenomic technologies, the biological basis of methylation-based risk prediction, and evidence supporting their capacity to identify individuals at elevated lifetime or early-onset breast cancer risk. The potential of epigenomic profiling to complement or transform mammography-based screening through personalized, risk-adapted pathways is critically assessed. Broader population-level considerations, including ethical, legal, economic, and health-system implementation challenges, are examined through lessons drawn from existing national screening programs. While epigenomic screening offers advantages in accessibility, acceptability, and predictive performance, significant barriers remain, including standardization, cost-effectiveness evaluation, regulatory oversight, and equitable access. Advancing epigenomic profiling from bench to population-level deployment will require robust longitudinal validation, multidisciplinary collaboration, and policy frameworks that balance innovation with public trust and health equity.

Keywords: Epigenomics, Breast Cancer Screening, DNA Methylation, Risk Stratification, and Health Policy.

INTRODUCTION

Genomes are stable; epigenomes are not. Risk of breast cancer, the leading cause of cancer among women worldwide, is not determined solely by inherited genetics; the acquired and potentially reversible layer of epigenetic regulation that modifies gene expression is, at least partly, non-heritable [2]. DNA methylation involves the addition of a methyl group (–CH3) to a cytosine when it is adjacent to a guanine (CpG), which generally, but not invariably, represses gene expression [1]. Cancerous cells tend to undergo global hypomethylation and locus-specific hypermethylation that affect genes involved in cell cycle control or apoptosis recovery, among others [2]. By analyzing a limited list of relevant genes to select the best methylation biomarker, it was possible to achieve a positive predictive value (PPV) of 75% (above recently established benchmarks) and a negative predictive value (NPV) of 98% on a cohort free of breast cancer events, even 20 years after analysis [3]. Appropriate utilization of epigenomic cancer risk profiling requires defining the market when it comes to screening. A first question relates to the target population: individuals with or without a family history of breast cancer; in particular, population screening might capture sporadic breast cancer vs. targeting a family history would favor familial breast cancer [1]. Other relevant questions are the ideal age of testing, whether breast cancer screening is performed within the same period, and, if population screening is pursued, whether the cohorts should be stratified [2].

Epigenomic Profiling in Breast Cancer: Concepts and Technologies

Epigenomic profiling is an emerging approach to the early detection and prognosis of breast cancer [1]. It encompasses the measurement of stable, quantitative changes in the epigenome of normal and cancerous cells, which arise from genetic and environmental influences during life. Critical epigenomic modifications include DNA methylation at cytosine residues in CpG dinucleotides, post-translational modifications of histone proteins, and the activity of non-coding regulatory RNA [5]. Epidemiological studies in breast cancer have identified numerous risk factors, both genetic and non-genetic; yet most of them have not been connected to the underlying biology, and even fewer have been translated into clinically useful epigenomic biomarkers [3]. Depending on biomarkers under consideration, epigenomic profiling based on non-invasively collected normal tissue may serve distinct purposes: early detection or stratification [6]. Early detection refers to the identification of individuals with cancer at a stage when removal of the tissue (e.g., via mastectomy, lumpectomy, or ductal excision) is expected to result in a good prognosis. Stratification, by contrast, indicates the detection of individuals at heightened risk of developing breast cancer over a specified time span. Under the regulation that restricts epigenomic analysis of tumours, profiling of pre-cancerous material constituting distinct and multiscale states between sampling and clinical manifestation assumes particular relevance [3]. Two pre-cancerous settings are candidates for further exploration: tissue adjacent to early-stage ductal carcinoma in situ (DCIS) and normal non-tumour tissue from breast cancer cases. Epigenomic profiling of women who had undergone the long-running UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), the largest ovarian cancer screening trial worldwide, illustrates the systematic study of risk factors far removed from cancer-induced changes [3]. Such a study generates unique insight into the validation of epigenomic biomarkers, including collection and long-term storage of samples, choice of analytical platforms, bioinformatics pipelines, population genomics, analytical models, experimental design, and platform compatibility [4].

Clinical Validity of Epigenomic Markers in Breast Cancer

Approximately 95% of breast cancers are diagnosed at age ≥40 years, and screening mammography is typically recommended starting at this age [4]. Yet certain breast cancers arise before age 40 and advance more rapidly. Implementing a population-based epigenomic test to identify women at higher risk for early-onset disease may enable an earlier age of initiation for screening and improved access to supplemental screening modes such as magnetic resonance imaging (MRI) that are otherwise infrequently applied at younger ages[5]. Genetic susceptibility accounts for approximately 30% of early-onset breast cancer, and the remaining 70% of early-onset cases may reflect cumulative exposures and polygenic factors [6]. DNA methylation changes may also fulfill these requirements. The availability of 5mC and 5hmC methylation profiling technologies may enable the identification of methylation markers that capture risk exposures and polygenic susceptibility in population epidemiological data or other accessibility datasets [4]. Such markers may enhance risk stratification, expand access to earlier mammography screening, or target other screening opportunities that are infrequently offered to the general population [3]. Addressing risk aggregation through methylation, polygenic risk scores, or other approaches may also complement anticipation and prevention initiatives by directing younger cohorts to varying levels of strategies such as universal screening, accelerated screening, or enhanced awareness programs [5]. Methylation-based DNA, RNA, and protein age clocks and epigenetic elongation markers are broadly relevant because many exposures associated with breast cancer risk also influence biological age. Such clocks may capture organ-specific biological ages throughout the life course [3]. Consequently, screening may occur when an epigenome-wide-bidirectional-down-regulation age clock substantially exceeds the chronological age clock if age-excess measures are positively correlated with earlier-onset breast cancer. Enhancing the population screening pathway in these and related ways may amplify the early-onset breast cancer conversation and its intersection with other dimensions of systematic relevance [5].

Clinical Utility and Impact on Patient Outcomes

Breast cancer remains one of the most common cancers in women worldwide. Survival rates have increased due to early detection through breast imaging and increasingly effective treatments [5]. Women with mammographically detected lesions are 44% less likely to die from breast cancer than those without screening. In Canada, screening guidelines were developed in 2001 and are made available via the Canadian Task Force on Preventive Health Care [2]. Some women are at higher risk of developing breast cancer, necessitating earlier or more frequent screening. Several models now exist to assess an individual's breast cancer risk and eligibility for additional screening [6]. Epigenomics offers a promising avenue in breast cancer risk assessment. Unlike genomics, epigenomic modifications are dynamic and reversible and can be influenced by environmental exposure, thus facilitating risk assessment and risk-mitigation interventions [3]. Epigenomic profiling detects modifications on DNA methylation, histone proteins, and noncoding regulatory elements. Detection technologies include array-based and sequencing-based assays [4]. Features generated from these technologies can be assembled into epigenomic signatures, which are more efficient for clinical use than raw features, as they focus on the most relevant information. Profiled feature sets can be further converted into risk scores or epigenetic clocks. Like

chronological clocks, these help in estimating the future time of disease occurrence [2]. A striking and positive aspect of epigenomic screening is its wide applicability. The test can be performed on any accessible biofluid (saliva, plasma, urine, or fine needle aspirate) and at any age. Such screening is usually associated with better public and organizational acceptance [6]. The availability of self-sampling devices increases test accessibility and ease, furthering the likelihood of compliance and decreasing unexpected results. Currently, women at normal average risk of developing breast cancer, but at an age of 50 or more, and with a history of mammography screening, can be the target population for epigenomic profiling. An epigenomic risk stratification bench-to-population project is already underway [5].

Population Screening Implications: From Bench to Public Health

Breast cancer constitutes one of the leading causes of tumor-related mortality in women worldwide. The introduction of mammography screening programs has contributed to a downward trend in breast cancer death rates in several high-income countries [6]. Nevertheless, both the uptake of and continued participation in screening programs remain a challenge, with significant regional differences in access and equity due to socioeconomic status, cultural background, and health system factors[5]. An alternative or complementary approach addressing existing limitations of mammography-based screening is the implementation of population-based epigenomic profiling to stratify women by risk level across their lifetime and schedule personalized screening in accordance with population-wide risk thresholds [2]. Epigenetic alterations are present in the precursors of breast cancer and accumulate gradually during disease progression, making a woman's epigenetic profile a potential early indicator of her lifetime risk for the disease [5]. Several longitudinal cohorts are currently generating reference datasets on breast-tissue epigenomics from healthy women. Initial profiling on five of these cohorts has revealed robust-aged DNA methylation marks, all of which appear to be capable of stratifying women into low, intermediate, and high lifetime risk categories [3]. Extending epigenomic profiling to other neoplasms and longitudinal analysis over decades in cleared cohorts should facilitate an entire epigenomic profiling landscape that permits the construction of methylation clocks or (de)methylation-time maps informative of likely age at diagnosis and disease progression [3]. Genetic stratification of population screening on the basis of epigenomic profiling would offer distinct advantages relative to existing mammography-centric strategies: it would not only diminish the population screened within the normative ages of disease occurrence but would also introduce not screening at all as a legitimate option for a subpopulation at minimal risk, thereby decreasing the absolute number of false-positive tests and the consequent socioemotional detriment stemming from needless follow-up procedures[4].

Policy and Ethical Considerations in Epigenomic Screening

The population screening of multigene epigenomic biomarkers raises several policy and ethical considerations, given the personal nature of the data involved, the link to cancer risk, and the potential for broad societal implications [1]. Given the relatively early stage of biomarker development, many of these considerations are analogous to those associated with the introduction of genomic cancer risk prediction into screening [3]. From the technical perspective, the individual epigenome is more stable than the genome, but it does change in response to lifestyle and environmental factors. Nevertheless, periodic re-evaluation is still recommended, for example, every three to five years to take account of potentially important changes [2]. Consequently, patient counselling, informed consent, data management, and the handling of incidental findings remain pertinent issues. The risk estimates generated by epigenomic sequencing could, in principle, apply to cancers other than breast cancer, mandating effective communication to ensure appropriate follow-up and minimizing misunderstanding. Given that epigenomic data capture information about exposures to toxic metals, the prospect of retaining samples for future analysis must also be considered [5]. Population-wide screening raises additional questions, such as equitable access to tests and interventions, potential restrictions on availability to high-risk individuals, long-term storage of biological samples, and adequate provision for test capacity [3]. The move from laboratory research to clinical application and, ultimately, to population-wide deployment involves careful consideration of not only technical issues but also interconnected ethical, legal, and social questions. A similar situation pertains to the advent of precision screening for breast and prostate cancer, where the adoption of genomic data into risk stratification raises major technical, economic, and policy challenges [5].

Implementation Barriers and Facilitators in Health Systems

Breast cancer screening programs have shown significant success in early detection and mortality reduction, leading to interest in applying the same strategy to other health issues. Among the several markers studied, the epigenetic signature has been proposed as promising for breast cancer populations at lower risk than the median with an acceptable prediction level [2]. To assess its clinical utility, health professionals have been asked to implement such an epigenomic profiling test in the Spanish National Health System [4]. Barriers to the implementation were identified, with the need for well-structured and organized programs enabling decision-making, sampling, and results communication as main facilitators [3]. The action of professionals involved, such

as policy makers and health providers, and their opinion after the evaluation of risk-based screening through a six-month pilot study conducted in different regions of the country, was also taken into account [4].

Economic Evaluation and Resource Allocation

Economic evaluations are important in assessing the benefits, costs, and cost-effectiveness of new health technologies, including epigenomic breast cancer tests, which may be introduced into publicly funded healthcare systems with limited financial resources [3]. Key economic evaluation questions for epigenomic breast cancer tests include: how do the expected costs and cost-effectiveness of genomic tests compare to other health technologies with similar potential budget impacts and healthcare needs in the target population; would introducing an epigenomic breast cancer test trigger downstream healthcare budget impacts due to additional costs for complementary testing or treatment, and how does the likely health impact of the test inform the appropriate expected price from a value-based pricing perspective[5]. When considering early physical interventions, classic economic evaluation specifies the discount rate to be applied. However, risk projection and preventive interventions raise different issues [3]. Where interventions prevent later events, economic evaluations often present both the expected consequences of the prevention intervention and the linearised demand for the later events to determine the value of the present intervention. Early detection and the associated interventions present distinct additional complexities [2].

Case Studies: Lessons from Current Screening Programs

Screening for breast cancer is part of preventive health programs in multiple countries. Articles detailing the status of screening in one or several countries offer transferable lessons for implementing epigenomic screening at the population level [2, 5, 1]. These lessons can guide policy analysis and consideration of broader implications for future cancer screening programs [2]. France has been successful in reducing breast cancer mortality via an organized screening program for women aged 50-74 years [5]. Attendance is around 50%, and the duration of the program and annual governmental appraisal reportedly facilitate transparency in evaluation and improvement. In the UK, geographical differences in screening access and uptake indicate the need for gradual implementation in Wales [4]. The screening program in Canada is limited by provincial rather than national decision-making [6]. A national screening program for Canada was recommended by the Task Force on Preventive Health Care, and an economic analysis indicated that screening women aged 50-69 years would be the most effective intervention to increase longevity across the population. Consideration of a fully decentralized system in England highlighted the regional variation issue, and recommendations for a national program were drawn up [5]. In the Netherlands, substantial investments to encourage attendance led to only modest increases in the already high participation rate. Consequently, the focus shifted towards secondary objectives such as improved communication and study of non-participants [5]. The role of genetics in breast and prostate cancer screening in the Netherlands has been analyzed, and the emergence of cancer predictive testing is seen as an opportunity to widen the debate about population screening and the involvement of asymptomatic individuals [4]. The intention to link epigenetic information to screening choices reinforces the relevance of earlier analyses [5].

Recommendations for Research, Regulation, and Practice

The translational pathway from epigenomic biomarker discovery to attendant population-level screening and policy decisions involves several key stages, spanning basic, preclinical, clinical, and population-oriented components [1]. At each stage, scientific and technical progress can indicate valid, i.e., compatible with generalizable analytical platforms, yet associated with clinically relevant endpoints, biomarkers, and associated platform-specific analytic practices [3]. Continuing momentum toward regulatory approval or guideline endorsement can then signal preparedness for wider uptake [6-10]. Ongoing clinical activity remains necessary for epigenomic profiling and acquisition of policy-relevant epidemiological or economic insights [5]. Improved assay, analytic, and validation standards are also required to support further evaluations of epigenomic markers across different cancers, populations, and health statuses. Conversely, the extensive adoption of breast cancer genomics—a pathway similar to that of epigenomics offers a rich corpus of experience relevant to other key translational dimensions and to shaping the future research agenda [4].

CONCLUSION

Epigenomic profiling represents a significant advance in the understanding and assessment of breast cancer risk, offering insights beyond those provided by inherited genetic variation alone. By capturing the cumulative biological effects of ageing, environmental exposures, and lifestyle factors, epigenomic markers, particularly DNA methylation signatures, hold considerable promise for refining early detection strategies and enabling personalized screening pathways. Evidence to date supports the clinical validity of selected epigenomic biomarkers in stratifying breast cancer risk across the life course, including the identification of women at increased risk of early-onset disease. From a clinical utility perspective, epigenomic profiling has the potential to complement existing mammography-based screening programs by guiding decisions on the age of screening initiation, screening frequency, and the use of supplemental imaging modalities. Its non-invasive nature, compatibility with self-sampling, and applicability across age groups enhance feasibility and public acceptability, positioning epigenomic

screening as a viable population-level intervention. Importantly, risk-adapted screening informed by epigenomic data could reduce overdiagnosis and false positives while improving early detection among high-risk subgroups. However, the transition from research innovation to population-wide implementation raises complex ethical, legal, economic, and health-system challenges. Issues of data governance, informed consent, equity of access, cost-effectiveness, and long-term infrastructure capacity must be addressed alongside scientific validation. Lessons from established breast cancer screening programs underscore the importance of organized systems, transparent evaluation, and sustained public engagement. In conclusion, epigenomic profiling offers a compelling opportunity to reshape breast cancer screening and prevention strategies. Realizing this potential will depend on continued longitudinal research, rigorous standardization of assays and analytic methods, and the development of policy frameworks that integrate scientific innovation with ethical responsibility and public health priorities.

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