REVIEW ARTICLE

Molecular Epidemiology of Breast Cancer: A Review

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ABSTRACT

The standard paradigm providing a general mechanistic explanation for the association of cumulative, excessive oestrogen exposure and breast cancer risk is that the proliferative stimulus provided by 17β-estradiol (E_2) leads to the appearance of spontaneous mutations. Thus, the key contribution of E_2 is the stimulation of breast epithelial cell proliferation. However, mounting evidence supports a complimentary pathway involving direct (oestrogen-quinone DNA adducts) and indirect (oxidative DNA damage via redox cycling) genotoxicity originating from oestrogen metabolites. While mutations in high penetrance genes such as BRCA1, BRCA2 and p53 confer a high risk for an individual, they represent a low overall attributable risk due to low allele frequencies in the population. On the other hand, mutations in phases I and II enzyme genes involved in xenobiotic and endobiotic metabolism, including genes encoding CYP1A1, N-acetyltransferase 2 and glutathione-S-transferase (GST) isoforms M1 (null), T1 (null), and P1 (low-activity allele), might confer a low relative cancer risk for an individual. However, because these mutations seem to be common among individuals, they represent a high attributable risk category of genes. The intent of this review is to examine current literature on the molecular epidemiology of breast cancer with emphasis on the role of polymorphisms in high and low penetrance genes on susceptibility to breast cancer. (*Afr J Reprod Health* 2003; 7[3]: 17–28)

RÉSUMÉ

Epidémiologie moléculaire du cancer du sein: un ré-examen. Le paradigme standard qui fournit une explication mécaniste générale pour l'association de l'exposition cumulative excessive de l'oestrogène et le risque du cancer du sein est que le stimulus prolifératif fourni par l'estradiol 17B (E_2) conduit à l'apparition des mutations simultanées. Ainsi, la contribution *clé de* E_2 *est* la stimulation de la prolifération de la cellule épithéliale du sein. Cependant, l'évidence s'accroît pour appuyer une voie complimentaire qui implique la génotoxicité directe (lésions d'AND oxydatif par voie de cycle redox) émanant des métabolités oestrogènes. Alors que les mutations dans les gènes à haute pénétrance telles BRCA1, BRCA2 et p53 confèrent un grand risque à un individu, elles représentent un faible risque attribuable occasionné par de faibles fréquences des gènes allélomorphes dans la population. Par contre, les mutations dans les phases 1 et 2 de gènes enzymatiques qui sont impliquées dans le métabolisme xénobiotique et endobiotique y compris les codages CYPIAI de gènes, N-acetyltransférase 2 et des isoformes M1 glutathione-S-transférase, T1(nul) et P1 (gens allémorphes et de faible activité) peuvent conférer un risque de cancer de faiblesse relative à un individu. Cependant, parce que ces mutations paraissent être communes chez les individus, elles représentent une catégorie de gens à un risque attribuable élévé. L'objectif de cet examen est d'étudier la littérature courante dans le domaine de l'épidémiologie moléculaire du cancer du sein en mettant l'accent sur le rôle des polymorphismes dans les gènes à haute et faible pénétrance sur la susceptibilité au cancer du sein. (*Rev Afr Santé Reprod* 2003; 7[3]: 17–28)

KEY WORDS: *Molecular epidemiology, breast cancer, genes*

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Introduction

Breast cancer is the most common cancer in Nigerian women and the incidence appears to be rising.[1] The actual incidence of the disease is unknown but in 1993, the estimated incidence of breast cancer in Nigeria was 33.6 per 100,000.[2] This is believed to be a gross underestimation of the true incidence of the disease. Late presentation is a marked feature of breast cancer in Nigeria, with about 70% of cases reporting to hospital with advanced disease.

The actual causes of most cases of breast cancer are unknown. Most studies on the aetiology of the disease have centred on the role of oestrogens. Oestrogen is a major female hormone influencing the development and maturation of the breast, and all available evidence implicates oestrogens as the final common pathway for the mediation of mammary carcinogenesis. Oestrogen and some of its metabolites induce mitogenesis in several tissues including the breast, and this has been shown to correlate with the chances of genetic mutations that can lead to the development of breast cancer.[1] Endogenous levels of oestrogens have been correlated with the risk of breast cancer, but the results of these studies have not been consistent.[2-5] One possible explanation for divergent result across populations may be differences in the prevalence of common inherited variations or polymorphisms in the genes that code for enzymes involved in steroid hormone production and metabolism. In this review, we highlight some recent advances in the molecular biology of the cancer cell that have enabled investigators to explore the role of high and low penetrance genes and polymorphisms in genes encoding oestrogen metabolizing enzymes in breast carcinogenesis.

Candidate Genes

The candidate genes involved in breast cancer susceptibility studied thus far can be divided into three main groups, namely, high penetrance genes such as TP53, BRCA2 and BRCA1; genes coding for proteins with roles in steroid hormone metabolism; and genes coding for carcinogen metabolizing enzymes.

Common Alleles of High Penetrance Genes

About 5–10% of cases of breast cancer are due to genetic susceptibility resulting from inheritance of BRCA1, BRCA2 and TP53 genes. Mutations in the BRCA1, BRCA2 and TP53 genes are associated with a high lifetime risk of breast and other cancers.[5-8] TP53 is a tumour suppressor gene whose protein product is produced in response to DNA damage through radiation or genotoxic agents, resulting in cell cycle arrest in GI and induction of pathways leading to DNA repair or apoptosis. Mutation in the TP53 gene results in decreased P53 activity, which may lead to failure of cells with DNA damage to arrest and thus continue to replicate with damaged DNA. In the case of BRCA1, the initial screening for germline mutations uncovered five sequence alterations in eight kindreds analysed.[9] Two were frameshift alterations, one was a nonsense mutation (Gln1313ter), and one was identified as a loss of mRNA from the linked allele. A fifth alteration was a missense mutation. Two misssense mutations have been identified in African-Americans, one (Cys64Gly) involves the final cysteine of the predicted C3HC zinc-binding RING finger located near the N terminus of the 1,863 amino acid protein[9] and the second is due to substitution of methionine by arginine (Met1775Arg).[10] In one study, two African-American kindreds were found to carry the second alteration, suggesting that this might be a common mutation in this population.[11] A single BRCA1 mutation, 185delAG, has been noted in approximately 20% of Ashkenazi Jewish women with early onset breast cancer and in 0.9% of the Ashkenazi population.[12,13] The majority of these mutations generate truncated proteins resulting in loss of function or reduced activity of the protein product.

In one report of BRCA2 mutations, eight of the alterations were small deletions with the exception of one nonsense mutation, and all were predicted to interrupt the BRCA2 coding sequence and to lead to a truncated protein product.[14] A recent study from Taiwan found three deletion mutations in the BRCA2 gene (2670delC, 3073delT, and 6696-7delTC).[15] All three mutations were predicted to result in frameshifts, leading to premature translational termination of the BRCA2 protein.

Four substitution mutations were also reported in that study. A particular deletion mutation, 617delT, has been reported in 8% of Ashkenazi Jewish women diagnosed with early onset breast cancer.[16] Although there is scanty data on the prevalence of mutations in these high penetrance genes in indigenous African populations, we speculate that genetic mutations similar to those in African-American women will exist in these populations since they share considerable genetic ancestry with African-Americans.

Steroid Hormone Metabolising Genes

Genes Involved in Oestrogen Biosynthesis

Genes involved in the metabolism of sex hormones are strong candidates for breast cancer susceptibility genes. Those in the sex hormone biosynthesis pathway may affect production of, and thus exposure to, the most active oestrogen, estradiol. The major genes in this pathway include the cytochrome P450 CYP19 (aromatase) gene and the cytochrome P450c17 (CYP17) gene.

CYP19 (Aromatase) Gene

The aromatase P450 (coded by the CYP19 gene) is responsible for the rate-limiting step in the metabolism of C19 steroids to oestrogens and is expressed in most breast carcinomas. Five different alleles containing 7, 8, 9, 11 and 12-TTTA-repeats have been described. A relatively rare allele (A1) containing the longest repeat (TTTA) was found significantly more frequently in breast cancer patients than in control individuals, indicating that individuals carrying the A1 allele of CYP19 may have an increased risk of developing breast cancer, OR 2.42 (95% confidence interval [CI] 1.03–5.80).[19]

CYP17 Gene

The CYP17 gene codes for the cytochrome P450C17-alpha enzyme, which mediates both 17-alpha hydroxylase and 17,20-Lyase activities and functions at key branch points in steroidogenesis.[20,21] Polymorphic alleles of CYP17 have been identified (A1 and A2), and the sequence present in the A2 allele create a new Sp1 promoter site (CCACC) that is hypothesised to enhance basal transcription of the gene.[22-24] Higher serum estradiol and progesterone levels have been observed among nulliparous pre-menopausal women carrying at least one A2 allele, compared to women homozygous for the A1 allele. Feigelson et al[20] found that among women of Asian, African-American and Latino descent, the presence of an A2 allele was significantly associated with the presence of advanced stage breast cancer but not in situ breast cancer. They also found that among controls, women with an A2 allele were more likely to experience menarche before 13 years than A1 homozygous (49% versus 39%). The protective association between later age at menarche and breast cancer was strong in women with the A1/A1 genotype than women with at least one A2 allele (OR 0.47 versus 0.48).

Genes Involved in Oestrogen Metabolism

CYP1A1 Gene

Hydroxylation at the C-16 and C-2 positions is catalysed by the 16-alpha and 2-hydroxylases, and these enzymes are encoded for by the CYP1A1 gene. The CYP1A1 gene is a critical component of the inducible phase I cytochrome P450 supergene family and it is also responsible for the oxidative metabolism of 17-beta estradiol, and such toxicants as dioxin and benzo(a)pyrene. Over-expression of the enzymes in the C-16 pathway has been implicated in mammary carcinogenesis. Three polymorphisms in the CYP1A1 gene are known: an Msp I restriction fragment length polymorphism (RFLP) in the 3' non-coding region, a mutation in the exon 7, and a novel CYP1A1 polymorphism, which is exclusively present in African-Americans.[25] The frequency of each of these polymorphisms varies as a function of race.[26] The association of the Msp1 polymorphism with breast cancer was negative in Caucasian but highly significant in African-American women.[27] An increased frequency in post-menopausal breast cancer with the exon 7 polymorphism was recently demonstrated.[28]

CYP1B1 Gene

CYP 1B1 is expressed constitutively in the human mammary carcinoma MCF-7 cell line[29] and the enzyme product mediates the hydroxylation of 17

beta-estradiol to form 4-catecholestrogen, a compound with demonstrable carcinogenic activity in human mammary and uterine tissues.[30,31] Three polymorphisms have been described, a single base substitution resulting in amino acid substitution of Arg (CGG) by Gly (GGG) and Ala (GCC) by Ser (TCC) identified at codons 48 and 119 in exon 2 respectively, and a third single base substitution of thymine by cytosine in intron 1.[31] The frequency of the genotypes of Ala-Ser polymorphism in patients with breast cancer was found to be slightly but statistically significantly different from that in healthy control subjects.[31]

CYP2D6 (Debrisoquine Hydroxylase Gene)

The CYP2D6 gene is located on chromosome 22q and codes for debrisoquine hydroxylase,[32,33] which metabolises a variety of drugs and other xenobiotics. The CYP2D6 gene may activate procarcinogens or, conversely, detoxify carcinogens.[32] A number of alleles have been characterised at the CYP2D6 locus. The "poor metaboliser" phenotype (CYP2D6 mutant/mutant genotype), which is rare in Asians, occurs in about 5–10% of Caucasians and 2% of African-Americans.[33] Studies of the CYP2D6 genotype and the risk of breast cancer have yielded conflicting results. Ladero et al[34] found that Spanish women who were poor metabolisers had about a two-fold increased risk of breast cancer, and Pontin et al[35] provided some evidence of an association between the poor metaboliser phenotype and the risk of breast cancer. However, the studies of Smith et al[36] and Buchert et al[37] reported no increased risk of breast cancer among carriers of the various alleles of the CYP2D6 gene.

CYP3A4 Enzyme Activity

Several recent studies[38-40] have shown that CYP3A4 plays a major role in the 4- and 16-alpha hydroxylation of oestrogens, particularly oestrone, the predominant type of oestrogen in post-menopausal women.[41,42] CYP3A4 is also involved in the activation of many environmental carcinogens such as polycyclic hydrocarbons, heterocyclic amines, aflatoxin and nitrosamines.[43-48] Furthermore, CYP3A4 is present in human mammary epithelial cells,[48] suggesting that this enzyme may be involved in the in situ activation of mammary carcinogens in these target cells. A polymorphism in the 5'-flanking region (-290 A-G) of the CYP3A4 gene has recently been described and this polymorphism was shown to be related to the risk of prostate cancer[49,50] and treatment-related leukaemia.[51] Zheng et al[52] recently described two additional alleleic variants of the CYP3A4 gene. They also reported a positive association between urinary 6-beta-OH:cortisol ratio and breast cancer risk, and the association was stronger in post-menopausal women in whom oestrone is the major form of oestrogen.

Genes for Phase II Enzymes

The phase II enzymes consist of different classes of enzymes that are involved in the conjugation and inactivation of oestrogen metabolites and various carcinogens.

Catechol-O-Methyltransferase Gene

The catechol oestrogens (2-hydroxylated estrogens) are the major metabolites of estrogens in humans and animals. The 2-catechol oestrogens have been reported to demonstrate both cancer-promoting and cancer-inhibiting activities through interaction with macromolecules (cellular proteins) and DNA. The catechol-O-methyltransferases are involved in the conjugation and inactivation of the catechol oestrogens. An amino acid change (valine to methionine) at position 158/108 in the membrane-bound/cytosol form of the protein has been linked to decreased methylation activity of the enzymes.[53] This amino acid change is believed to be closely associated with the observed trimodal distribution of COMT enzyme activity in the population associated with high COMT (Val/Val), intermediate COMT (Val/Met) and low COMT (Met/Met) activity.[54] Thompson et al[55] showed that genetic polymorphism in COMT is associated with enzyme activity and was differentially associated with breast cancer risk among pre-menopausal and post-menopausal women.

Glutathione-S-Transferase Genes

The GST family are phase II enzymes that detoxify carcinogens and their reactive intermediates such as

those produced by CYPIAI, by facilitating their conjugation to glutathione and subsequent excretion. To date, four polymorphic families of cytosolic soluble GSTs (α, μ, φ and θ) have been identified in humans. For both GSTMI and GSTTI, a high percentage of the Caucasian populations are homozygous for null alleles (up to 60 and 20% respectively) and have no detoxifying GST activity.[56] About 22–35% of African-Americans are also homozygous for the null GSTMI and GSTTI alleles.[32] Levels of DNA adducts, sister-chromatid exchange and somatic genetic mutations may be increased in carriers of GSTMI and GSTTI null genotypes, and these individuals may have a higher risk of cancer of the breast and other sites because of their impaired ability to metabolise and eliminate carcinogens.[56]

The GSTMI genotype has been related to the individual breast cancer risk in several recent studies,[57] some of which suggested an association between GSTMI null genotype and breast cancer risk in post-menopausal women,[58,59] whereas others found no association.[60,61]

GSTP1 Gene

For GSTP1 gene, two variant alleles, GSTP1*B and GSTP1*C, have been detected in addition to the wild type allele GSTP1*A.[62] In both variants, a point mutation at nucleotide 313 results in a single amino acid change from isoleucine (Ile) to valine (Val) at codon 105. This residue lies in close proximity to the hydrophobic binding site for electrophilic substrates,[63] and the Val variant allele has been demonstrated to exhibit altered specific activity and affinity for electrophilic substrates.[64] In contrast to GSTMI, there is little data on the potential role of GSTP1 and GSTT1 genotypes in breast cancer risk. Two recent studies[65,66] revealed no significant association between the GSTP1 genotypes and breast cancer proneness, although one study[59] suggested a trend for increasing risk with higher numbers of GSTP1 Val alleles.

Uridine Diphospho-Glucuronosyltransferase 1A1 Gene

UGTs catalyse the glucuronidation reaction, which represents a major route for the detoxification of a diverse range of molecules including carcinogens and biologically active endogenous compounds such as steroid hormones. An additional role of UTG enzymes is to maintain intracellular steady-state levels of steroids including estrogens in target tissues.[67] Various polymorphisms in the UTG1A1 gene have been described. Lower expression of UTG1A1 might lead to an increase in the level of estradiol and expose cells to a higher local concentration of active hormone and, therefore, have considerable impact on tumour initiation and growth. The low activity UTG1A1 alleles have been observed to be positively associated with invasive breast cancer in women of African ancestry.[68] This association was negative for Caucasian women.

N-Acetyltransferases

The N-acetyltransferases, NAT1 and NAT2, are also phase II enzymes and they participate in the detoxification of the arylamines, some of the main carcinogenic components of tobacco smoke and the amines produced during cooking of meat.

However, the action of NATs on these carcinogens can produce electrophilic ions that may induce point mutations in DNA.[69] Polymorphisms in both genes result in two phenotypes: slow acetylators who are homozygous for low activity alleles and fast acetylators who carry one or more high activity alleles.[70]

N-Acetyltrasnferase 1 Gene

The association between NAT1 phenotypes and the risk of breast cancer has been investigated in various studies with some demonstrating a relationship between these genotypes and breast cancer risk. Zheng et al[71] found that the NAT*11 allele was associated with a four-fold increased risk of breast cancer. The risk was particularly increased among women who smoked cigarettes, consumed high level of red meat, or had a preference for consistently well-done meat. The NAT1*10 allele was related to a slightly elevated risk of breast cancer, and this association was primarily confined to former or light smokers.

N-Acetyltransferase 2 Gene

Studies on the relationship of breast cancer risk to interactions between NAT2 genetic polymorphisms

and tobacco smoking are inconsistent. Ambrosone et al[72] showed an increased risk of breast cancer from smoking in slow acetylators, while Millikan et al[73] and Hunter et al[74] showed some limited smoking effects among fast acetylators but no dose response relationships. Delfino et al[75] found no associations between NAT2 genotypes and breast cancer risk in both passive and active smokers.

Other Genes

Oestrogen Receptor (ER) Polymorphisms

Mutations in the coding region of the oestrogen receptor gene have been described in only a small percentage of breast cancer patients. More common are genetic polymorphisms of the ER gene that do not alter the encoded amino acid. Andersen et al[76] reported that the allele frequency with the XbaI restriction site (in exon 2 or flanking introns of the ER gene) was 1.4 times as great among breast cancer patients as in controls (95%CI, 1.0–1.9). Among breast cancer patients, there was a borderline association between the XbaI restriction site and older age at onset. Several neutral polymorphisms in codons 10, 87, 243, 325 and 594 have been described in both ER positive and ER negative tumours. However, a statistically significant association was found between the polymorphism in codon 325 and a reported family history of breast cancer (OR, 4.3; 95% CI, 1.8–10.1).[77]

XRCC1 Gene

One of the DNA repair genes exhibiting polymorphic variation is XRCC1, which is located on chromosome 19q13.2 and encodes a M70,000 protein. XRCC1 has no known catalytic activity but appears to play a pivotal role in BER by bringing together DNA polymerase beta, DNA ligase III and PARP at the site of DNA damage.[78] BER targets endogenous DNA damage induced through hydrolysis, oxidative stress and alkylation as well as adducts and fragmented bases caused by exogenous agents such as ionizing radiation and alkylating or oxidative agents. Thus, XRCC1 may participate in the removal of "non-bulky" DNA adducts, the repair of oxidative DNA damage, and the repair of DNA damage attributable to ionizing radiation. While some studies have demonstrated some association between polymorphisms in this gene and breast cancer risk, others have reported contrary findings.[79,80]

Manganese Superoxide Dismutase (MnSOD) Gene

Oxidative stress, resulting from the imbalance between pro-oxidant and anti-oxidant states damages DNA, proteins, cell membranes and mitochondria, and seems to play a role in human breast carcinogenesis.[81] Dietary sources of anti-oxidants (chemical) and endogenous anti-oxidants (enzymatic), including the polymorphic manganese superoxide dismutase (MnSOD), can act to reduce the load of oxidative stress. Ambrosone et al[81] found a positive association between MnSOD genetic polymorphism and breast cancer risk.

Promoter Hypermethylation of DNA Repair Genes

Methylation is the main epigenetic modification in mammals and abnormal methylation of the CpG islands located in the promoter region of the genes leads to transcriptional silencing. Examples include the p16, p15, p14, Von Hippel-Lindau (VHL), the oestrogen and progesterone receptors, E-cadherin, death-associated protein (DAP) kinase and the first tumour suppressor gene described, retinoblastoma (Rb) gene.[82] Recent investigations[83] of promoter hypermethylation of DNA repair genes have shown that loss of BRCA1 mRNA and protein does occur in sporadic breast and ovarian cancer. Studies[82] have demonstrated that BRCA1 hypermethylation leading to loss of BRCA1 function is present in breast and ovarian primary tumour cell lines. Bi-alleleic inactivation of BRCA1 is achieved in many cases by retention of one allele silenced by methylation in association with loss of other allele by genomic deletion in this region.

Conclusion

The search for the aetiological factors for breast and other cancers has intensified in the past decade due to advances in molecular biology and ongoing efforts to map the more than 80,000 genes in man. There is no doubt that carcinogenic metabolites of oestrogen and other carcinogens play a central role in complex

cellular mechanisms resulting in carcinogenesis. Polymorphisms in genes encoding the various enzyme systems involved in metabolism of various carcinogens considerably influence racial and inter-individual variations in cancer susceptibility. It is obvious that interactions between genes and environmental factors such as diet, cigarette smoking and heterocyclic and aromatic amines contribute to breast cancer susceptibility, but the nature of these interactions are complex and not completely understood. These gene-environmental interactions may help to explain the differences in breast cancer risk between women of different racial/ethnic backgrounds. In particular, it may account for differences in breast cancer risk between African-American women and West African women since both populations share considerable genetic ancestry.

Future research efforts should focus on improving on research designs to overcome some of the biases of current molecular epidemiologic studies It should be recognised that breast cancer is a heterogeneous disease with differences in relevant risk factors depending on tumour sub-type. Pooling of data from large cohorts is necessary to enhance sub-group analysis. In addition, efforts should be directed at continued identification of functionally significant candidate genes and the incorporation of platforms to rapidly interrogate the associations between allele variability, exposure and risk. The introduction of high throughput, DNA-based methodologies such as DNA micro-arrays and multiplex analysis on fluorescent microspheres, which provide simultaneous assessment of tens to hundreds of alleleic variants in large numbers of samples, promises rapid, accurate and cost-effective iterative hypothesis testing for gene-based complex diseases.

Molecular epidemiology has tremendous role to play in the ongoing efforts to unravel ethnic/racial differences in breast cancer susceptibility as well as fine-tuning strategies for breast cancer prevention. Present risk assessment tools for breast cancer such as the Gail Model[84] and the Newman-Gail Model[85] are based on established risk factors for breast cancer such as age at menarche, parity, family history and biopsy history. Although these tools have been shown to significantly predict a woman's risk of breast cancer, there are some drawbacks in the use of the current models in different population groups. For example, the Gail model was developed from largely white populations and has been found to significantly underestimate breast cancer risk in blacks. Recently, working with Gail, Newman and colleagues[85] evaluated and revised the Gail Model's risk factor and baseline risk/population attributable risk (PAR) components in a mixed ethnicity data set. The revised model (Gail-Newman) uses the same risk factors (age at menarche, parity, family history and biopsy history) and relative risks as those in the current standard model. However, the updated calculations of population attributable risk fractions for these risk factors has resulted in markedly different estimates for the ethnicity and age-stratified baseline risks that are entered into the prediction model. Specifically, use of the revised PARs yields higher baseline risk estimates for African-American women. The Gail-Newman model was retrospectively validated on evaluations of a multicentre case-control population of 3,283 African-American women and 5,974 white American women. The risk identification rate for African-American women in the Gail Model is 5.6% while the Gail-Newman model identifies 19%.[85] This is equivalent to the risk identification rate in white women evaluated by the Gail model. Molecular epidemiological research has the potential of improving current risk assessment tools by identifying susceptibility genes for breast cancer in different sub-groups of women in different population groups. Such women with high susceptibility for breast cancer will benefit from current prevention strategies such as tamoxifen chemoprevention.

There are currently no reports in literature on use of risk assessment tools for breast cancer susceptibility in women in sub-Saharan Africa. While earlier reports indicated that breast cancer is a rare disease in women in the region, recent observations seem to suggest otherwise. For populations in sub-Saharan Africa to benefit from these recent advances in breast cancer risk assessment and prevention efforts, we recommend the following strategies: First, there is urgent need to ascertain the true incidence of breast cancer in the region through the establishment and adequate funding of population-

based cancer registries in various countries in sub-Saharan Africa. Secondly, there is need to establish broad-based breast cancer screening programmes. Mammographic screening in the developed countries of Europe and North America has demonstrated a 44% reduction in breast cancer mortality in women aged 40–69 years.[55] The screening programmes should be integrated into the current health care delivery systems existing in these countries. As a matter of urgency, public health practitioners and other health care providers should embark on intensive culturally sensitive health education programmes to create awareness of the disease in the population. Nurses working at the primary health care centres should be trained to conduct periodic breast examination in addition to teaching women within their locality the techniques for breast self-examination (BSE). Individuals at risk should be referred to local hospitals and tertiary institutions for screening mammography. These screening programmes should be funded by appropriate agencies such as the health insurance schemes.

Developing countries of sub-Saharan Africa are currently not investing adequately in the area of molecular and genetic epidemiologic studies. Unfortunately, the burden of breast and other cancers are increasing and are likely to become major public health problems in this region in this millennium. Efforts should be made to encourage both basic scientists and clinicians working in these regions to engage in collaborative research with investigators in the developed countries. In addition, more funding and better focused health policies will enhance capacity for the evolution of molecular and genetic epidemiologic research in these regions.

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