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A Review of the Predictive Aspects of Breast Cancer among Women

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Abstract

Breast Cancer reports are on rise in human. In requirement human is discovering new methods, models and projects which are aimed at better diagnosis, prevention and to avoid it from recurrence. Till date numbers of technologies are available but early diagnosis of breast cancer still remain a big question. Number of present technologies, although indicating or predicting breast cancer in patients but the sensitivity and specificity still lacking among them. In this review, we reported number of factors which are responsible for getting breast cancer and on the other hand also mentioned the success of machines, drugs and computational biology which in together surely will contribute in to fight against breast cancer if investigated in together.

Keywords: Breast cancer, SNPs, Chemoprevention, Mammography, Bioinformatics, BRCA gene

Breast cancer is one of the major health problems. The reports of these cases are increasing in most countries and will be continue to rise in the next twenty years, despite of number of therapies and guidelines are available (Eccles SA *et al.* 2013; Arnold M *et al.* 1988; Rahib L *et al.* 2014; Colditz GA and Bohlke K, 2014). The incidences are on rise with number of reasons such as late age of first pregnancy, lower age of menarche, fewer pregnancies, late menopause and even low or no breast feeding. Not only that, several other reasons are also adding up the risk of breast cancer such as hormone therapy, alcohol consumption, obesity, slowness and other factors (Colditz GA and Bohlke K, 2014). The incidences of hereditary breast cancer also increased many folds with mutation in breast cancer 2 (BRCA2) gene increased fourfold in Iceland is one of the example. Not only that increased reports of breast cancer by the age 70 has been evidenced which was originally 2.5% and now it is reaching 11% of the total population, in a given time period (Tryggvadottir L *et al.* 2006). BRCA1 and BRCA2 also related with birth breast cancer incidences also (King MC and Motulsky AG, 2002; Evans DG *et al.* 2008). All these reports suggest that every individual may be male or female are at a risk of getting breast cancer.

It has been directed by group of researchers called as Collaborative Group on Hormonal Factors in Breast Cancer (2002) that overall incidence of breast cancer shall be reduced by half as estimated current 6.3 to 2.7 per 100 women by the age of 70, if women gave birth to more children and give them breast feeding for longer period as generally observed in developing countries (CGHFBC, 2002). Today's woman is becoming stronger, independent, economically strong and also she can control the pregnancies with number of aids. Still after pregnancies encouragement for breast feeding is the prime necessity in an order to prevent themselves from breast cancer (Cuzick J *et al.* 2013).

One success therapy as preventive measure (chemotherapy) is cardiovascular disease (CVD). The drugs capable of suppressing cholesterol synthesis, modifying platelet aggregation leads to steady drop in CVD incidences. Over past three decades, in the women ageing 85 years old (Jemal A *et al.* 2007). CVD death ratio reduced optimally by treatment, once it arises; the situation is applicable to breast cancer treatment also, in which by successful screening and proper treatment death rate has decreased by 33% in last twenty years. This brings about the success of advances in technology and treatment.

About 27% of population in UK reported positive for breast cancer are related with estimated lifestyle and environmental factors in 2010 (Parkin DM *et al.* 2011) and currently more than half of the breast cancer patient may be prevented if proper chemotherapy being given along with maintaining a good lifestyle such as maintaining proper body weight, exercise and minimum alcohol intake (Colditz GA and Bohlke K, 2014). By implementing these strategies incidences of breast cancer may come down in coming time. However, a major lack of knowledge prevails among woman about early treatment, diagnosis and guidance.

Models of risk evaluation

Numbers of Bioinformatics approaches have been developed to predict the probability of detecting cancer in patients. For example, possibility of mutation in BRCA1/2 genes, which is linked to small number of women patient with strong family history or to predict the chances of breast cancer over the period of time (Amir E *et al.* 2010; Meads C, 2012). Two computer models called as BRCAPRO (risk estimator for breast and ovarian cancer) and BOADICEA (the Breast and Ovarian analysis of Disease Incidence and Carrier Estimation Algorithm) have been introduced which scores and helps in predict, whether to perform genetic test or not (Evans DG *et al.* 2009; Kast K *et al.* 2014). Applicable to all women, number of models put forward to determine the risk of breast cancer over the period of time (for example, five years or lifetime). The model was put forward the risk prediction based on the number of risk factors woman is carrying (Parkin DM *et al.* 2011; Amir E *et al.* 2010; Meads C *et al.* 2012). These test are known as Cuzick (Tyrer J *et al.* 2004) and Gail (Gail MH *et al.* 1989) models, which consider both familial history risk factors and non family factors, BOADICEA (MacInnis RJ *et al.* 2013), a certain modified Claus model also include non familial risk factor (Evans DG *et al.* 2014) similar to Rosner-Colditz model (Rosner BA *et al.* 2013). Several other models are in process and require some validation and surely all of them may prove even more useful in Breast cancer testing (Meads C *et al.* 2012).

In a comparative study, existing model showcase several advantages and linked disadvantages which have been tackled by new model algorithms. For example, Galli model describes risk factors:- age at menarche, age at first live birth, number of previous breast biopsies, benign disease and number of first degree relatives with breast cancer. Galli based studies are well investigated for regular check up in American women (Costantino JP *et al.* 1999) and also when using updated breast cancer incidence (Schonfeld SJ *et al.* 2010). However, in recent studies of the UK and US suggest that it may under predict the real risk compared to another Tyrer-Cuzick model (Amir E *et al.* 2003; Quante AS *et al.* 2012; Powell M *et al.* 2014), probablyjust because of limited family factor and by not considering the age of the onset of cancer.

All these models developed to predict the possibility of life time risk towards cancer. Still, these models will not be able to refer by confidence that you are the patient who will get breast cancer. So to fill this gap, number of molecular level techniques have been developed such as mammographic density (Huo CW *et al.* 2014; Cummings SR *et al.* 2009), single nucleotide polymorphisms (SNPs) (Michailidou K *et al.* 2013; Burton H *et al.* 2013), estimation of hormone level (Hormones E *et al.* 2011) and lifestyle factors that provides improved accuracy of risk prediction in female population.

Improved techniques for risk estimation

Mammographic Density

Use of mammographic density in the breast cancer has been reviewed in recent times (Huo CW *et al.* 2014; Cummings SR *et al.* 2009). As per Mammogram, dense tissue is always white, whereas fat tissue is radio-lucent and appears black. As per one research, relative risk of breast cancer for women with 70% or more density was 4.64 fold higher compared to women with less than 5% density (McCormack VA and dos Santos SI, 2006).

Many reports have already scored whether adding a measure of mammographic density improves risk estimation when compared to estimation using standard model alone. Where standard measure of improvement of risk assessment is called C-statistics. Here this study comes under receiver operative curve (AUC), which in turn is a reflection of the available sensitivity and obvious specificity of the model. As reported, high C-statistics (AUC), the greater is the accuracy of the model. So in scoring AUC with 0.5 identifies a model which detecting accuracy is not over scored than chance alone; score of AUC as 1.0 identifies a model with highest discrimination. In general, AUC of 0.7 or 0.8 are more consistent and recorded as good discriminatory accuracy (Amir E *et al.* 2010).

In two examples such as use of BI-RADS assessed density to the Gail model, C-statistics of Gail model is previously 0.67, but by adding density to Gail model it has increased to 0.68, even though the small rise in discriminatory accuracy but found to be significant (P<0.01). Barlow and colleagues also reported the increase of C-statistics which was 0.605 (95% Confidence Interval (CI) 0.60 to 0.61) to 0.62 (95% CI 0.62 to 0.63) by adding BI-RADS density to Gail method (Barlow WE *et al.* 2006).

Single Nucleotide Polymorphisms

Only small fraction of women found to be mutated for the high risk breast cancer gene BRCA1/2, whereas variation in other low impact, common susceptibly loci are responsible for major Breast Cancer situation (Pharoah PD *et al.* 2008). Mutation in DNA is recognized by SNPs also, which are alteration in DNA code that are mostly thought to be non functional genes. Hence relatively, SNPs are less harmful with maximum risk is about 1.43 fold and mostly have the effect of 1.1 fold. In a collaborative work, more than nine thousand breast cancer sequence reports were studied on large scale compared to control. Study on such a large scale is required to understand the effect of every SNPs with their associated risk factor. However, in combination of allele weighted by the comparative risk associated with every allele, combined SNPs may be related with substantial increases or decreases in risk factor. Till date, breast cancer marker SNPs are reported to be seventy, but it is considered that may be some hundreds of those must be present to bring about breast cancer (Michailidou K *et al.* 2013). Instead of using SNPs information alone, they have been added up with Gail model and results showcased interestingly high AUC score shift from 0.58 to 0.61 (P=0.001) (Mealiffe ME *et al.* 2010). As per Wacholder and colleagues (Wacholder S *et al.* 2010) by using 10 SNPs data increase in AUC from 0.58 to 0.62 was reported (Gail MH, 2009) and Gail *et al* predicted an increase in C-statistics from 0.61 to 0.63. In recent work Dite and workers (Dite GS *et al.* 2013) studied seven SNPs and recorded an increase in AUC from 0.58 to 0.61 (P<0.001).

In many works value added features of SNPs to risk model has been assessed the changes in risk group stratification as before and after addition of SNPs. For example, reclassifying the women truly at high or low risk would be clinically important. All the studies referred above showcase that changes in risk classification at higher and lower part resulting in a 'widening' of the risk distribution curves as suggested by researchers. For example, Comen and colleagues (Comen E *et al.* 2011), with the combination of 10 risk SNPs and the Gail model, 20% of women being reclassified into lower and similarly, 20% into a high risk group as proposed by quintiles. In recent work, Brentnall and colleagues (Brentnall AR *et al.* 2014) and Evans and colleagues (Evans DG *et al.* 2012) understood the effect of risk of combining 18 or 67

SNPs with Tyrer-Cuzick model. They found that adding more SNPs changes the risk distribution in the manner so that they were in high and low risk groups respectively.

All above studies depicted that potential of SNPs for improved risk prediction in high risk clinics and in general use is showcasing their potent features. Hence, better detection rate could be possible by involving SNPs and it can even detect breast cancer subtypes, such as ER^+ (Stacey SN *et al.* 2008), ER^- (Garcia-Closas M *et al.* 2013), grade III (Purrington KS *et al.* 2014) and triple negative (Purrington KS *et al.* 2014) tumors and probably be useful in preventive approaches (Garcia-Closas M *et al.* 2014).

Hormonal changes

Hormone based analysis with long term follow up showcase that hormones and growth factors are responsible for increasing risk of breast cancer. The most important question arises whether they could be incorporated into model of breast cancer risk prediction. Many groups reported that risk of breast cancer was associated with the hormonal steroid namely testesterone, estradiol and sex hormones-binding globulin in pre- and post- menopause women and related that these are important hormone for further investigation (Key TJ *et al.* 2003; Hormones E *et al.* 2013; James RE *et al.* 2011; Kaaks R *et al.* 2014). Very interesting finding is that, the relation of Body Mass Index (BMI) with risk is reduced by adjusting for estrogen, but the relation of estrogen with risk is not controlled by BMI. Thus estrogen may put forward the increased risk of breast cancer in obese post-menopausal women, although number of other hormones and cytokines also affect the process (Key TJ *et al.* 2003; Ritte R *et al.* 2012).

Use of hormone measurement in breast cancer could be a better attraction. However, its measurement probably in post-menopausal women is not feasible for many instance, as it show assay variation based on low level of hormone over time (Jones ME *et al.* 2014). Interestingly, Jones and colleagues related change in estradiol and testesterone must be a good biomarker for the promising weight loss and it supported by recent data of many research (Jones ME *et al.* 2013; Tworoger SS *et al.* 2014). Additionally, insulin like growth factor-1 (IGF-1) is also associated with cancer risk, particularly post-menopausal women and may possibly be utilized in model study (EHBCCG, 2010; Tworoger SS *et al.* 2013; Tikk K *et al.* 2014; Kaaks R *et al.* 2014).

Detection of Risk by Recent methods

As every day new protein is getting discovered, chances of them to be a biomarker in risk evaluation is promising but, it is always a long and tedious process which involves validation to make any protein a marker. At present, number of new techniques are coming and for sure few of them will become the part of standard model. For example, gene expression in peripheral blood white cells (Sharma P *et al.* 2005), blood epigenetic markers (Almouzni G *et al.* 2014), functional proteomics (Anderson KS *et al.* 2011), and epithelial antigen (Macdonald IK *et al.* 2012). All these methods proving their potential and surely in coming time may be the part of standard model.

How to prevent Breast Cancer

How women can prevent to be get affected by Breast Cancer ? Many reviews were highlighting prevention aspects including SERMs and AIs for the chemoprevention of ER^+ cancers (Advani P and Moreno-Aspitia A, 2014; Chlebowski RT, 2014), chemoprevention for ER^- cancers (den Hollander P *et al.* 2012; Steward WP and Brown K, 2013) and changes in the lifestyle (Colditz GA and Bohlke K, 2014; Colditz GA *et al.* 2014; Harvie M and Howell A, 2012). All these reviews pointing number of potentially useful areas and further investigation is required.

Chemoprevention- A battle

As per number of clinical trials and use by the breast cancer positive patients, drug tamoxifen 20mg/day reducing about 38% of cancer ($P<0.0001$) (Cuzick J *et al.* 2013) with an estimated 10 years of reduction cumulative incidence. Tamoxifen was significantly superior to Raloxifene in long term use for preventing

invasive breast cancer. Never the less, raloxifene also produce fewer side effects than tamoxifen, particularly in uterus and may be preferable in post-menopausal women.

In comparison, AIs are generally proved superior for treatment when especially given after surgery to prevent relapse of breast cancer. One worker reported AI exemestane when tested, a reduction in breast cancer risk of 65% for 5 years of treatment has been evidenced (Goss PE *et al.* 2011).

Living Pattern

It has been reported that 40% menopausal breast cancer cases could be prevented by reduction in alcohol intake, excess body weight and increasing inactivity (WCRFI http://www.wcrf.org/). Along with, these many reports mentioned earlier (Colditz GA and Bohlke K, 2014; Parkin DM *et al.* 2011) always indicated the importance of lifestyle that human is living and needs to change as per health requirement for better lifespan.

Food and weight control

Number of reports highlighted that weight gain in the pre-menopausal period and to put weight after menopause always increases chances of cancer incidents (Colditz GA and Bohlke K, 2014; Renehan AG *et al.* 2008). Worker estimated that for human 5 kg/m^2 increase in BMI increases the risk of breast cancer to about 12%. It is also been evidenced that pre- and post-menopausal weight loss minimizes the incidences of post-menopausal breast cancer. In Iowa, with the weight reduction of 5% of body weight has been related to reduce the cancer risk by 25% to 40% compared to woman keep on gaining body weight (Harvie M *et al.* 2005). In another study, post-menopausal women when did not take HRT and also maintain a body weight, by reducing 10 kg or more do have 50% reduction in the risk of breast cancer (Eliassen AH *et al.* 2006). It is also suggested that weight reduction after the age of 36 is also preferential to avoid breast cancer (Cecchini RS *et al.* 2012).

Food and Cancer Prevention

Food with important content such as protein, carbohydrates, lipids and nucleic acids are always an important factor to be considered for better health. According to, WHI reduction in fat in diet also reduces the chances of risk of breast cancer but showed non-significant relation statistically (Prentice RL *et al.* 2006). Patients with breast cancer surgery advised to take low fat diet which reduces 23% of risk of recurrence (Chlebowski RT *et al.* 2006). No significant reduction in risk of breast cancer was recorded even if vegetable and fruit intake has increased in an adjuvant trial (Pierce JP *et al.* 2007). Increased carotenoid improves the health and reduces the chances of ER$^-$ but not with the risk of ER$^+$ disease, but still need investigation (Jung S *et al.* 2013; Eliassen AH *et al.* 2012). Increase intake of vegetables was associated with a 15% reduction in breast cancer risk (85% of CI 0.76 to 0.95). In one report consumption of fruits, vegetables, fish and soy are associated with a decreased risk of breast cancer (Albuquerque RC *et al.* 2014; Ferrari P *et al.* 2013).

Exercise and Physical work

Many countries like US have published a report that their >50% population do not meet the recommendation of PA guidelines. In addition, countries like England reported that 40% of adult women (minimum 19 years) do not perform physical activity for necessary 150 minutes-75 minutes per week and increasing their chances of breast cancer (HSCIC http://www.hscic.gov.uk/catalogue/PUB13218; Hastert TA *et al.* 2013). It has been reported that moderate to rigorous PA decreases breast cancer risk by 25% in both pre- and post-menopausal women compared with inactive women (Lynch BM *et al.* 2011).

Beverages with Alcohol

As it is clearly known that intake of alcohol in a high concentration/amount always leads to ill effect in human. Here leads to ill effect in human. Here the chances of getting breast cancer increases by 7% to 10% with every one unit consumption of alcohol per

day. In one study, woman consuming 4 to 9 units per week also have about 15% of increased chances to develop breast cancer compared to non-drinkers (Chen WY *et al.* 2011). Whereas, woman with heavy alcohol intake (27 units per week) were at the risk of 51% for breast cancer compared to non-drinkers. Overall, it has been suggested that woman should not prefer to take more than one unit per day and in a week at least two days should remain devoid of alcohol intake to be get avoided by the risk of breast cancer (Zhang SM *et al.* 2005). To live better life, moderate alcohol intake compared to none is preferable (Ferrari P *et al.* 2014). As per research, women with alcoholic influence have more chances of getting carcinogenesis in the period of menarche and first pregnancy (Pike MC *et al.* 1983; Colditz GA and Frazier AL, 1995).

CONCLUSION

Review of literature published till date explored us the Breast Cancer is preventable by bringing the changes in human activity such as exercise, breast feeding, proper life style which is prerequisite. Once affected proper chemotherapy at early stage surely can minimize the chances of death and afterwards proper food and lifestyle is prerequisite to avoid any recurrence. In second point number of technologies have developed and many more are coming which will surely benefit to check the probability and prevention of cancer in women. Women needs to be educated and informed by number of resources to check back the early detection of Breast Cancer and even more important what could be done to avoid getting Breast Cancer. It always remains a thrust area of research which could be fasten up by Bioinformatics research giving the complete gene expression, mutation and proteome information at a very fast speed which was not feasible a decade ago.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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