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Research article

ORAL CONTRACEPTIVES AS A RISK FACTOR FOR DEVELOPING BREAST CANCER IN BREAST CANCER (BRCA) GENE CARRIER FEMALE IN- THE 30-60 YEARS AGE GROUP: A META ANALYSIS

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ABSTRACT

The literature linking breast cancer with oral contraceptives and BRCA mutation as possible risk factors is equivocal. Hence, to account for these conflicting results in the existing literature and to observe the net effect, this meta-analysis aims to investigate whether oral contraceptives are a risk factor for developing breast cancer in **br**east **ca**ncer (**BRCA**) gene carrier female in the 30-60 years age group. **Method:** Systematic review of the literature, both published and unpublished, and meta-analysis of relevant data. **Results:** Meta-analysis of data from five relevant studies, with a total of 6682 BRCA carriers (3,269 BRCA1 carriers and 791 BRCA2 carriers), revealed that use of oral contraceptives is associated with increased risk of breast cancer among BRCA mutation carriers (OR=2.267; 95 % CI= 1.311, 3.919). When the same risk was stratified by mutation type, both BRCA1 and BRCA2 were at increased risk. However, BRCA2 carriers (OR= 3.060; 95% CI=0.951, 9.848) were found to be at elevated risk compared to BRCA1 carriers (OR= 2.347; 95% CI=0.939, 5.865). **Conclusions**: This meta-analytical finding suggests that oral contraceptives are a risk factor for developing breast cancer in **br**east **ca**ncer (**BRCA**) gene carrier females.

Key words: Oral contraceptives, Breast cancer, BRCA gene, Familial breast cancer and hereditary breast cancer.

INTRODUCTION

Breast cancer is a major global public health issue and it is the most common cause of cancer death among females[1]. It is also the second most commonly diagnosed cancer in the world, after lung cancer, with 1.38 million cases[2]. Every woman is at the risk of breast cancer and every 13 minutes a woman dies of breast cancer in the world[3].

The literature concerned with the association between oral contraceptives and BRCA mutation as possible risk factors for breast cancer is equivocal; as numerous studies attempting to answer similar questions about the association exists but the individual studies show conflict in their estimation of net association. Some studies demonstrate no association between oral contraceptives use and development of breast cancer among women with a family history of breast cancer[4-7]. In contrast, others reported an increased risk[8-11]. Instead of imposing risk, there may be a protective effect of oral contraceptive use for BRCA1 mutation carriers and no effect for BRCA2 carriers[12]. A large retrospective, population based International BRCA1/2 Carrier Cohort Study (IBCCS) reported an elevated risk of breast cancer among mutation carrier females (both BRCA1 and BRCA2) who use oral contraceptives (RR=1.47 95% CI 1.16-1.87)[13]. A meta-analysis

found no evidence of a significant increased breast cancer risk in oral contraceptives users with germline mutation in BRCA1/2[14]. Hence, to account these conflicting results in the existing literature and to observe the net effect; this meta-analysis aims to investigate "breast cancer risk associated with oral contraceptive use in BRCA carrier women of age 30-60". Meta-analytical tool allows a more objective appraisal of the evidence than traditional narrative review, and hence contributes to resolve uncertainty when original research, reviews and editorials disagree[15]. Further this meta-analysis will also examine the quantitative significance of this association with respect to BRCA1 and BRCA2 individually.

MATERIALS AND METHODS

An intensive database search, updated to September 2011, was carried out in Science Direct, Pub Med and EBSCO Host. In EBSCO Host, only those databases relevant to nursing and medicine were included. These databases were AMED (The Allied and Complementary Medicine Database), British Nursing Index, and CINAHL Pus with full Text and MEDLINE with full text. To minimize the problem of publication bias or file drawer problem[16], an attempt was made to retrieve unpublished studies, dissertation reports, thesis and scientific paper presented in conferences. Search for such papers were carried out in CINHAL Plus and national research registers and Meta-register. Bibliographic search of abstracts presented at top scientific events in the field of breast cancer were also scrutinized. Further, dissertation abstracts international[17] was explored in order to retrieve any of the dissertations. An attempt was made to contact the leading researchers in the field via emails. For computerized search, a list of keywords based on Reed and Baxter[18] recommendation were developed. The following key words combination was used: Oral contraceptives, Breast cancer, BRCA gene/Breast cancer susceptible gene, Women/ females, Familial/ Hereditary breast cancer.

Studies that quantitatively estimate the association between oral contraceptives and breast cancer and providing sufficient statistical data to compute an estimated effect size of the correlation between oral contraceptive use and development of breast cancer were included in this meta-analysis. Studies conducted on breast cancer gene (BRCA) carrier female only and not on general female population were included. However, selection was not restrained by demographic or other sample characteristics (such as language, ethnicity etc.). Included studies should report risk of oral contraceptive use for breast cancer only and not on other types of cancer such as ovarian, cervical cancer etc. If the study reports risk of various types of cancer then the result of other types of cancer apart from breast cancer will be excludes in this meta-analysis. In this meta-analysis, studies will be included irrespective of their result in order to avoid inclusion criteria bias[19]. Similarly, studies with qualitative design, those carried out in subjects such as men, teenage female or women below 30 and above 60 years or other than human subjects and studies published in languages other than English were excluded during the selection process. This meta-analytical study was approved on 10th January 2011, by Centre for Health and Social care Improvement (CHSI) in the University of the Wolverhampton. The data was analysed by using software for Meta-analysis called 'Metanalysis'[20].

Table 1. Search process

Search process	Exclusion
1068 Studies Resulted (103 EBSCO Host + 238 Science Direct + 727 Pub Med)	433 excluded as the title and abstract analysis of these studies showed they were not relevant to aims and objectives of this meta analysis 427 paid and inaccessible articles
208 Further Screened	10 not reported in English 149 reviews and meta analysis 3 author's communications 2 study subjects were other than human
44 further screened to full text analysis	13 excluded as they did not consider oral contraceptive use 17 studies conducted on general females and not gene carriers
14 studies further screened	2 duplicates 7 studies had irrelevant data
5 studies included for the meta-analysis	

Table 2 List of included studies

Author	Narod *et al.* (2002)[5]	Gronwald *et al.* (2006)[21]	Haile *et al.* (2006)[7]	Brohet *et al.* (2007)[13]	Figueiredo *et al.* (2010)[22]
Title of study	Oral contraceptives and the risk of breast cancer in BRCA1 & BRCA2 mutation carriers	Phenocopies in breast cancer 1 (BRCA1) families: implications for genetic counselling	BRCA1 and BRCA2 mutation carriers, oral contraceptive use, and breast cancer before age 50	Oral contraceptives and breast cancer risk in the international BRCA1/2 carrier cohort study: a report from EMBRACE, GENEPSO, GEOHEBON, and the IBCCS Collaborating Group	Oral contraceptives and postmenopausal hormones and risk of contralateral breast cancer among BRCA1 and BRCA2 mutation carriers and non-carriers: the WECARE Study
Study design	Matched case control	Matched case control	Unmatched case control	retrospective cohort	Population based case control
Country	Multinational	Multinational	Multinational	Multinational	Multinational
Mutation status	BRCA1 & BRCA2	BRCA1	BRCA1 & BRCA2	BRCA1 & BRCA2	BRCA1 & BRCA2
No. of BRCA carriers	2622	1482	804	1593	181
No. Of BRCA carriers diagnosed with BC	1311	348	323	846	108
No .of BC diagnosed-BRCA carriers using OCs	914	56	255	607	91
No. of BRCA1/ BRCA2 carriers	-	-	497/307	1181/412	109/72
No. of BRCA1/ BRCA2 carriers diagnosed with BC	-	-	195/128	597/249	67/41
No. of BC diagnosed-BRCA1/ BRCA2 carriers using OCs	-	-	146/109	436/171	59/32

Summary of the search and search results: The search for relevant literature resulted in 1065 articles, which were subjected to screening of titles, keywords and abstracts. The inclusion, exclusion criteria were used as a guideline to exclude or include a study during the search process. The table 1 given below outlines the detail of search process. Hence, finally 5 studies met the inclusion criteria of this meta-analysis and were included for the process of data extraction. Duplications were avoided through a careful assessment of the abstract and full text of the two studies[20].

Data analysis: By using 'metanalysis' programme, heterogeneity was explored statistically in terms of the I^2 statistic. As, this meta-analysis includes only five studies, use of Cochran's Q for assessing heterogeneity was limited because Q has low power when the number of studies is small.[23] Due to the presence of heterogeneity, the included studies were

assumed to have differences in study design, sampling, and characteristics of subjects; and thus were proceeded using a random effect model to calculate the odds ratio by Dersimonian-Laird method.[20] Sub group analysis, stratified for BRCA1 and BRCA2 carriers, was performed to estimate any difference in risk by type of mutation. Publication bias was expressed and interpreted, in terms of publication bias assessment (PBA), funnel plot and the test of funnel plot asymmetry. Publication bias assessment (PBA) is defined as a tool that helps to assess the number of unpublished studies (similar to those published and analysed) that are needed to make the results of the meta-analysis not statistically significant or meaningless.

RESULTS

The I^2 value for this meta-analysis was 97.2 % (95% CI = 99.4, 86.6), which suggest that maximum variation exists between the included studies. In this meta-analysis, oral contraceptive use was associated with breast cancer risk (OR=2.267; 95 % CI= 1.311, 3.919) among BRCA mutation carriers, under random effect model. Thus, a woman with BRCA mutation carrier is two times more likely to develop breast cancer, if she uses oral contraceptives; compared to those who does not use it.

AUTHOR	YEAR	Breast Cancer	Oral Contraceptive
Narod et al	2002	1311/2622	914/1311
Gronwald	2006	348/1482	56/348
Haile et al	2006	323/804	255/323
Brohet et al	2007	846/1593	607/846
Figueiredo et al	2010	108/181	91/108
Pooled (Random effect)		2936/6682	1923/2936 2.267(1.311/3.919)

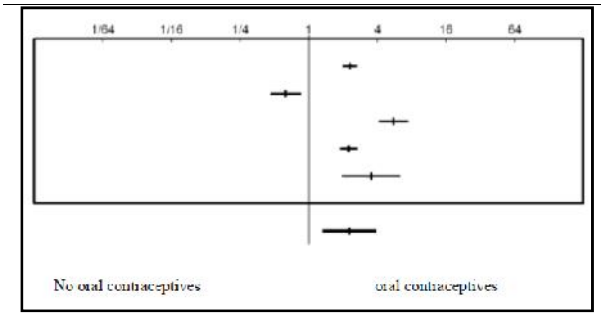

Fig 1: Forest plots for pooled odds ratio for BRCA

Subgroup analysis:

The I^2 value, for test of heterogeneity, for the meta-analysis of breast cancer risk associated with use of oral contraceptives among BRCA1 and BRCA2 carriers was highly significant (97.7%; 95% CI=99.7, 85.2 and 96.3%; 95% CI = 99.6, 64.2 respectively) and suggested the existence of heterogeneity between the studies. The pooled odds ratio for breast cancer risk associated with use of oral contraceptives among BRCA1 and BRCA2 carriers was 2.347 (95% CI=0.939, 5.865) and 3.060 (95% CI = 0.951, 9.848) respectively, under random effect model. Therefore, BRCA1 and BRCA2 carriers, who use oral contraceptives, are more likely to develop breast cancer than non carriers. Comparing the findings for BRCA1 and BRCA2 carriers, it can be interpreted that BRCA2 carriers are more likely to develop breast cancer than BRCA1 carriers if they use oral contraceptives.

AUTHOR	YEAR	Breast Cancer	Oral Contraceptive
Gronwald	2006	348/1482	56/348
Haile et al	2006	195/497	146/195
Brohet et al	2007	597/1181	436/597
Figueiredo et al	2010	67/109	59/67
Pooled (Random effect)		1207/3269	697/1207 2.347(0.939/5.865)

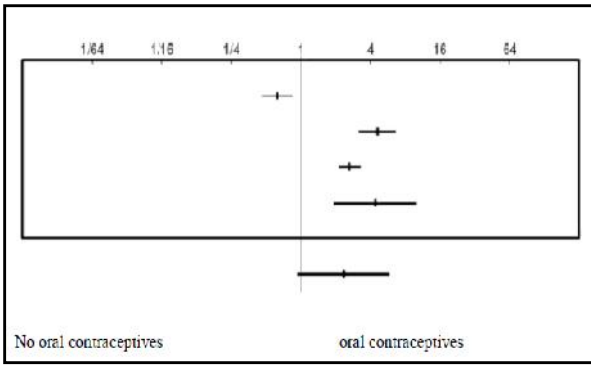

Fig 2: Forest plot for pooled odds ratio for BRCA1 carriers

Publication bias assessment: In this meta-analysis, publication bias assessment (PBA, table 3) is 335, which denotes that 335 studies with null or negative results are needed to make this meta-analytical result meaningless. The funnel plot (figure 4) and test for the symmetry of funnel plot (figure 5) does not appear to have any significant relevance to this meta-analysis because both the tests are significant only in those meta-analyses that includes a large number of

studies[20,24,25], whereas, this meta-analysis includes only five studies.

AUTHOR	YEAR	Breast Cancer	Oral Contraceptive
Haile et al	2006	128/307	109/128
Brohet et al	2007	249/412	171/249
Figueiredo et al	2010	41/72	32/41
Pooled (Random effect)		418//791	312/418
			3.060(0.951/9.848)

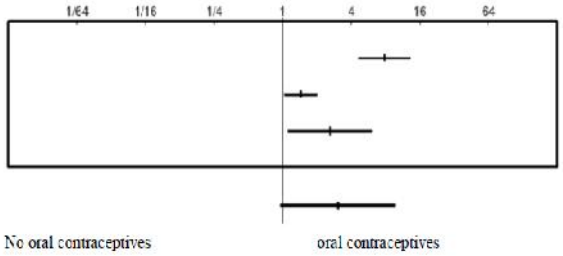

Fig 3 Forest plot for pooled odds ratio for BRCA2 carriers

Table 3: PBA, NNT and the test for asymmetry applied on the funnel plot.

PUBLICATION BIAS ASSESSMENT (number of void or trials necessary to render meaningless the meta analysis): 335
Number Needed to Treat (95% CI): 6 (5/7)
Number Needed to Treat (95% CI) (R.E.M.): 5 (3/21)
test of funnel plot asymmetry: α=-0.01 95% CI= -12.28/12.26 p(z)= 1.00

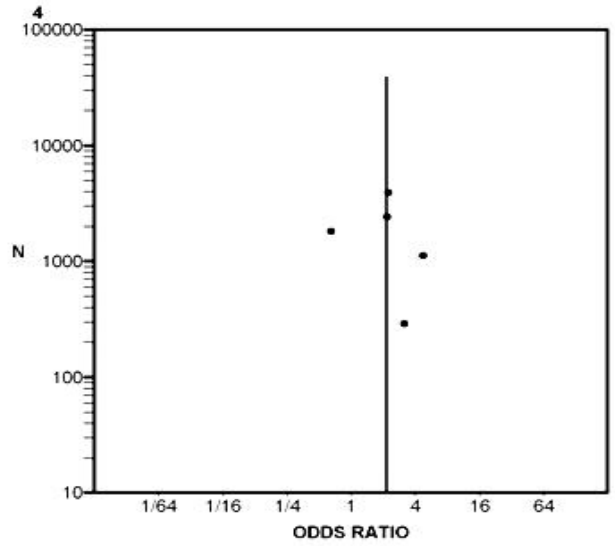

Fig. 4 Funnel plot

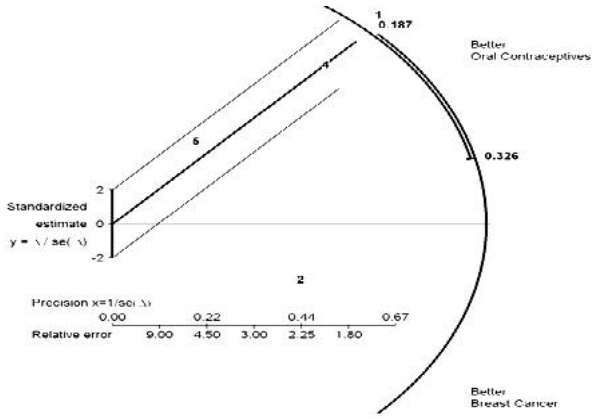

Fig 5: The test for funnel plot asymmetry

DISCUSSION

In this meta-analysis, oral contraceptive use, among BRCA mutation carriers, was associated with increased risk of breast cancer. (OR=2.267; 95 % CI= 1.311, 3.919). The findings of this meta-analysis are supported by many other evidences in the literature.[9,13] Oral contraceptive was classified as group 1 carcinogens by World Health Organization (WHO) in 2005. This means that oral contraceptives confer high risk for development of various types of cancers, including breast cancer. A woman's exposure to oral contraceptives contributes to the risk of breast cancer in general population.[26-28] Hence, it is more likely that the same effect will be observed among BRCA carrier females, who have already been identified as 'at risk population' for breast cancer due to their mutation status. In addition, several other histological, hormonal and genetic explanations also support the findings of this meta-analysis.

It has already been established that exposure to endogenous hormone (after Oophorectomy) confers a substantial risk of breast cancer among BRCA carriers.[29,30] Hence, it is probable that exposure to oral contraceptives (exogenous oestrogen and progesterone hormone) may induce similar risk. It is also believed that the faulty germline in BRCA may interact with oestrogen (a component of oral contraceptives) in breast carcinogenesis and participate in several cellular functions that are important in carcinogenesis, including DNA damage; repair and cycle checkpoint. [31]

The next evidence to support the findings of this study comes from the reports of in-vivo experiment conducted on some animals. The carcinogenic effect of hormones contained in oral contraceptives has been well established in animals like rodents, dogs,

and monkeys.[32,33] It would be unethical to experiment the same in human subjects. However, in vivo experiment conducted on these animals, closely related to human, suggests a possibility of similar risk in humans as well. Similarly, other experiments conducted in animals have shown that the risk of development of mammary glands (present in breast) into cancerous tumour is directly related to the proliferation rate of breast epithelial cells[34] and it is reported that the rate of breast epithelial proliferation is increased by oral contraceptives or oestrogen and progesterone.[35]

The increased susceptibility of BRCA1 and BRCA2 carriers to breast cancer is explained genetically on the basis of the functions of these genes. BRCA genes encode proteins that take part in the cellular response to DNA damage; hence, inactivating mutations in these genes enhance susceptibility to breast and ovarian cancers.[36] In the cells deficient in BRCA-1 and BRCA-2, double strand breaks are repaired in an error-prone fashion which leads to chromosomal rearrangements and instability, which is responsible for carcinogenesis[37]. When cells are exposed to radiation, BRCA-1 and BRCA-2 initiate homologous recombination and double strand breaks repairing. Hence, if a cell has mutated BRCA-1 and BRCA-2 it is hypersensitive to radiation and causes error prone repair of double strand breaks leading to faulty genes and carcinogenesis.[37] Hence, it is possible that BRCA1 and BRCA2 carriers develop breast cancer due to mutations in the gene, even if they are not exposed to oral contraceptives. Therefore, it can be said that if a woman carries a BRCA mutation or uses oral contraceptives, each of these factors (genetic and hormonal), individually impose risk of breast cancer to her. Hence, a simple logic says that this risk must be intensified among BRCA mutation carriers (who are already 'at risk population' for breast cancer) who use oral contraceptives.

In the sub group analysis, the increased in breast cancer risk associated with use of oral contraceptives among BRCA1 and BRCA2 carriers is explained by molecular signature and functions of BRCA1 and BRCA2. BRCA1 is responsive to oestrogen levels and the oestrogen-dependent and oestrogen-independent transactivational activity of oestrogen receptor (ER) is repressed by BRCA1.[38] Mutation in BRCA1 may inhibit this regression process and increase the epithelial proliferation of breast tissue thus leading to breast cancer. Similarly the function of BRCA2 is influenced by the presence of oestrogen and leads to increased DNA repair responses in ER positive breast cancer cells.[39] These theories explains the increased risk of breast cancer associated with oestrogen exposure among BRCA1 and BRCA2 and as oral contraceptives is a synthetic form of oestrogen, the same explanation justifies the increased risk found in this meta-analysis.

In this meta-analysis, it was observed that the risk of breast cancer is higher among BRCA2 carriers who use oral contraceptives, compared to BRCA1 carriers. A distinct hormone receptor levels and a distinct hormone receptor profile is observed between the tumor by BRCA1 gene and tumour by BRCA2 gene.[40] Similarly, BRCA1 and BRCA2 gene acts by different pathways.[41] BRCA1 associated breast cancer are generally oestrogen-receptor/progesterone-receptor negative. While BRCA2 associated breast cancer are progesterone-receptor positive.[42] Hence difference in breast cancer risk associated with use of oral contraceptives among BRCA1 and BRCA2 may be due to these differences in the hormone receptor profile.

The heterogeneity or the variability between studies may have occurred due to a number of characteristic variations among the studies such as variation in definition of breast cancer and definition of ever use of oral contraceptives among the studies, different level/duration of use of oral contraceptives, variation in matching and adjustment factors as well as study design and method of data collection. Similarly, age, race, culture, ethnicity and geographical boundaries of the subjects, age of female at diagnosis of breast cancer, the woman's age at the start and cessation of use, type of breast cancer diagnosed and genetic testing technique used for mutation detection varied among all of the five included studies.

In this study, bias might have been introduced by the biased studies or during the conduct of this meta-analysis. This meta-analysis may be prone to various biases as it includes observational studies and most of the observational studies are biased in themselves and provide a challenge to investigators and readers to scrabble out and judge about the result.[43] As the sample studies included in this Meta-analysis are only the one published, so there might be sampling bias and publication bias. The publication bias in this study may be due to the fact that statistically

significant positive results are more likely to be published. It is reported that 95% of the studies with non significant results are found in the file drawers at the laboratory and the studies published in the journal include the remaining 5% of the studies with significant results.[44] Most of the studies presented at scientific meetings, conferences and academic dissertation are not always published in journals or included in the reference list of database.[20] It is assumed that 16% of the total studies conducted are not traced while doing a meta-analysis because either the studies are not published for commercial publishing interest or they are under review for publication.[20] As this meta-analysis is exclusively based on English language reports it is subjected to language bias[45] because there are many investigators, who work in non-English speaking countries and publish their work in local journals in local language.

The next limitation of this meta-analysis is unable to incorporate relevant data from two of the relevant studies[5,28] because both the studies reported data indirectly in the form of hazard ratio[28] and odds ratio[5] with 95% confidence interval and a p value, which was beyond the scope of the software used in this meta-analysis. Another limitation of this meta-analysis is the use of crude odds ratios (ORs) instead of adjusted ORs. Due to the lack of relevant data on adjusted ORs, this meta-analysis has failed to adjust for many potential confounders.

CONCLUSION

The finding of this meta-analysis is clinically relevant as the understanding of the association between oral contraceptives use and breast cancer risk among BRCA carriers will guide future recommendations in contraceptive health. To date very few published studies have tried to intervene this association and even the existing literature seems to be inconclusive in estimating the net association. This clearly demands the need of more studies and research in this field.

CONFLICT OF INTEREST: None declared.

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