

## Non-genetic determinants of breast cancer risk in BRCA1/2 mutation carriers: A review of potential factors

KELSEY KLEIN



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*WRITER'S COMMENT: As genetic testing has become significantly less expensive and faster to complete, more and more people each year opt to learn what their own genes might tell them about their family history and personal health risks. One such person is Angelina Jolie, who announced in 2013 that she had tested positive for a mutation in a breast cancer gene known as "BRCA1." Because the mutation gave her an 87% chance of breast cancer and a 50% chance of ovarian cancer, she made the difficult decision to undergo a prophylactic double mastectomy. This was the first time many people learned about the BRCA mutation, but it is a topic I've been familiar with since I was young. After my aunt was diagnosed with advanced breast cancer in her early 30's, testing revealed a BRCA mutation that had made her susceptible to early-onset breast cancer. This led my father to get tested and discover that he was also BRCA-positive; he was later diagnosed with BRCA-related prostate cancer. Consequently, my younger brother and I both have a 50% chance of carrying the mutation as well. This made me especially interested in what daily lifestyle choices BRCA-positive women can make to lessen their risk of breast cancer, which is the question I explore in my literature review.*

*INSTRUCTOR'S COMMENT: Each year, hundreds of UC Davis students submit papers that they've written to the Prized Writing competition, hoping their essays will be among the twenty or so that are selected for publication. With such stiff competition, it is a mark of high achievement to have an essay accepted. Kelsey Klein doubled this achievement. Not one, but two of the papers that she wrote while she was a*

*student in my Writing in the Health Professions course (UWP 104F) were selected by the judging committee. When Kelsey was asked which of the two she'd like to have printed in the volume, she chose the literature review because, as she told me, the subject—BRCA 1 & 2 related breast cancer—was very important to her. Kelsey approached her work in the manner of a true researcher. The literature review was not simply a writing assignment; she genuinely wanted to discover the current state of knowledge on less invasive methods for decreasing breast cancer risk. The end result is a testament to the care and effort Kelsey put into this paper. This literature review gracefully synthesizes material from eighteen sources, tells a compelling research story, and leaves the reader with a sense of the knowledge gaps that future researchers need to fill in this crucial area of health science.*

*– Melissa Bender, University Writing Program*

## Abstract

Women who are carriers of a deleterious mutation in the BRCA1/2 tumor suppressor genes face up to an 800% increase in lifetime risk of breast cancer (B.C.) compared to the general population. While environmental risk factors for sporadic breast cancer in the general population are a popular area of current research, it is unclear how these factors modulate B.C. penetrance in the high-risk population of BRCA carriers. The purpose of this review was to identify which non-genetic factors, if any, have been found to significantly affect BRCA-related breast cancer risk. We limited the scope of our research to studies investigating one or more of the three most frequently-studied classes of proposed modifying factors: reproductive factors, physical activity, and diet/body weight. Biosis and PubMed databases were searched for peer-reviewed studies which included “BRCA” in the title and were published after 2002, with priority given to more recent date of publication. The only semi-consistent result we identified was that parity, and more specifically an increasing number of full-term pregnancies, appears to decrease breast cancer risk and delay cancer onset. Significant conclusions regarding the risk-modifying effects

of all other factors of interest were heterogeneous across studies and ultimately provided insufficient evidence for us to deduce the probable role of these factors in governing B.C. penetrance. These differences might be explained by various methodological limitations and highlight the need for future research that addresses the confounding factors proposed in this review.

## Introduction

Women in the United States have approximately a 12% lifetime risk of breast cancer (B.C.), and over 240,000 cases of invasive breast cancer were diagnosed in 2016 alone [1]. Women with a mutation in either the BRCA1 or BRCA2 tumor suppressor genes, however, are estimated to have anywhere between 37-90% lifetime risk, depending on the study and estimation method [2-8]. Individuals with such a mutation have only one functional copy of the BRCA gene, and thus are susceptible to genomic alteration and instability at a much higher rate [9]. With up to an 800% increase in breast cancer risk, the importance of preventative factors is indisputable. The large range of estimates for lifetime risk depend on the particular individual and predictive method, but indicate that non-genetic factors, such as lifestyle and environment, must play some role in the likelihood of B.C. penetrance [2,10]. Multitudinous studies have investigated the effects of such factors on breast cancer incidence in the general population, but the interaction of these factors with BRCA-related breast cancer remains largely equivocal [2-18]. Upon discovery of their genetic mutation, many BRCA1/2 carriers seek genetic counsel, where they are often advised to undergo prophylactic surgery or chemoprevention, both of which can cause significant physical and emotional harm [12,13]. There is limited public knowledge and education about less invasive preventative strategies for BRCA carriers.

This review describes the current state of research on three classes of non-genetic variables that may play a role in modifying lifetime risk of BRCA1/2-related breast cancer: reproductive factors, physical activity, and diet/body weight. Each of these factors has been identified as a possible source of risk reduction for carriers. Understanding their specific influences would be a promising step in mitigating the lifelong impact of a deleterious mutation in BRCA1/2, but the effects remain largely contended and unresolved in the limited amount of related, and

predominantly retrospective, literature. Since significant questions have yet to be answered, it is critical that more comprehensive, prospective studies be carried out that specifically investigate the effects of lifestyle and environmental factors on BRCA-related B.C. penetrance.

## **Reproductive Factors**

A large portion of current research in the field focuses on the effects of reproductive factors on BRCA-related breast cancer, including (but not limited to) oral contraceptive use, parity, and breastfeeding. These determinants may be of particular interest because of their association with endogenous estrogen mechanisms, as several studies have implicated a protective effect from reducing internal synthesis of estrogen [3,7,9,11,13,14]. In this section, we will review the major positions of the most relevant literature on each of these three reproductive sub-factors.

The results of recent peer-reviewed literature on the risk-modifying effects of oral contraceptive use are extremely heterogeneous. In fact, significant ( $p < 0.05$ ) conclusions from these studies on the BRCA1/2 carrier population suggest that ever having used oral contraceptives had all of the following effects: no increase in risk for either BRCA1 or 2 [9]; significant increase in risk in only the BRCA1 (but not BRCA2) population [3]; earlier onset breast cancer in both BRCA1 and BRCA2 [2]; increased risk (as well as earlier onset of cancer) in both BRCA1 and BRCA2 [11]. These disparate findings clearly demonstrate a lack of consensus in the field. Each of their respective statistical significances also warrant general concern with the methodological comparability and integrity of the studies.

The unsettled research question of the effects of oral contraceptives is further complicated by the wide variety of oral contraceptives that women may use. The dose and type of both estrogen and progestin can vary across oral contraceptive and have substantially changed over time. Narod et al. acknowledge that oral contraceptives produced before 1975 typically contained higher doses of estrogen and stratified some analyses accordingly on the basis of first use before or after 1975 [3]. Subsequent studies used similar methodologies, but much like the previously discussed results of ever- versus never-use of oral contraceptives, the findings are relatively discordant. While Narod et al. found that significantly more BRCA1 case subjects first used oral contraceptives before 1975 ( $p < 0.001$ ), Brohet

et al. found that breast cancer risk did not change according to year at first use for either mutation type. Another study found “high-dose” oral contraceptive use (before 1975) was associated with increased B.C. risk [9], but this value was not statistically significant, and the last study did not stratify at all on the basis of pre- or post-1975 use [2]. It is important to note that even after controlling for period of first use (before or after 1975), these conclusions must be analyzed with caution. For example, although Narod et al. found with strong statistical confidence that using oral contraceptives prior to 1975 increased B.C. risk in the BRCA1 population, they also found that taking oral contraceptives for more than 5 years and prior to age 30 increased risk among these subjects, which could be confounding factors (that were not adjusted for) in reporting on pre-1975 use [3]. Further, if their results suggest that higher estrogen content increases B.C. risk, then it would be necessary to also control for differences in the estrogen dose of post-1975 oral contraceptives. It is clear that the effect of oral contraceptive use on BRCA-related breast cancer risk, even after controlling for year of first use, remains equivocal. While the contradictory results that we have reviewed in this section surely point to the need for prospective and longitudinal research studies that control for many of the proposed confounds, they also suggest that there must be methodological differences across the studies that warrant such conflicting results.

One potential explanation for the noted discrepancies is the different populations from which each study draws its sample. While one study limited residency to just Los Angeles County [9], another enrolled participants from throughout Austria [2], and two sampled from more than 11 countries around the world [3,11]. In the case of the most geographically small-scale studies especially, there is increased risk that the population might be selected for certain characteristics other than those of interest, thus that they may systematically differ from the general population of females with mutations in BRCA1 or BRCA2. Further, the methods and populations of comparison, which determine statistical analyses, vary substantially as a result of vastly different inclusion/exclusion criteria. One of the four studies includes only women previously diagnosed with breast cancer who are also carriers of a BRCA mutation [2], another includes all women who are carriers/non-carriers and B.C.-affected/non-B.C.-affected [9], and two include only BRCA carriers, both those affected and not affected by cancer [3,11].

A statistical analysis for difference among carriers who have developed breast cancer versus those who have not should naturally yield a different conclusion (or a different inference/significance of said conclusion) than an analysis of difference between carriers and the general population. The underlying reasons why each finding might differ on the basis of a given geographical region or comparison method is beyond the scope of this review, but ultimately indicates the need for more standardized methodologies and additional research.

Inference of breast cancer risk on the basis of parity yields more consistent findings. Many studies report that among carriers of BRCA1/2, there is an association between parity and decreased B.C. risk compared to nulliparous carriers [9,17]. Furthermore, there is substantial evidence to suggest that risk decreases nearly linearly with an increasing number of full-term pregnancies, although this value did not reach statistical significance in every study [9,17]. With four or more full-term births, Lee et al. reported a decrease in lifetime risk of almost 50%, although small sample size again limited the statistical power of their conclusion. Relatedly, in an analysis of breast cancer patients who were also carriers of either BRCA1/2 mutation, parous versus nulliparous women had significantly later onset breast cancer [2]. Additionally, more full-term pregnancies were correlated with a further delay in onset of B.C [2].

Breastfeeding, however, varies much like its oral contraception cofactor. It is well-established that breastfeeding aids in risk reduction of breast cancer for women in the general population [4,9,17]. In the most extensive study on breastfeeding and BRCA-related B.C. risk by 2004, Jernstrom et al. selected participants from an international cohort of women with BRCA1/2 mutations, using a randomized genetic database [4]. Each woman was matched in a case-control pair (one with breast cancer, one without) according to BRCA1/2 mutation, age, and country of origin. Using a retrospective questionnaire on pregnancies and breastfeeding practices, they found that BRCA1 mutation carriers affected by breast cancer breastfed for a significantly shorter period of time than their control-matched counterparts [4]. Additionally, breastfeeding for more than one year versus never breastfeeding effectively reduced risk of breast cancer by 45%. For BRCA2 carriers, conversely, duration of breastfeeding was not found to be significantly different between the case and control subjects, and was thus not seen to mitigate B.C. risk in any way [4]. Their conclusions suggest a mechanistic difference of

risk modification among BRCA1/2 carriers, further highlighting the importance of stratification of the two groups in all related studies for the purpose of generalizability and bias reduction.

The effects of breastfeeding were also investigated in two of the studies that we reviewed in our previous analysis of oral contraceptive use and parity [2,9]. Contrary to the relationship of their findings on oral contraceptives, the two studies accord with one another on the basis of breastfeeding. Both findings suggest that duration of breastfeeding does not modulate breast cancer risk or penetration in BRCA1/2 carriers, which contradicts the results obtained by Jernstrom et al. [2,9]. Such discrepancies again demonstrate a lack of congruity among major findings and confirm the critical need for future research.

## Physical Activity

While vigorous and frequent physical activity has been well-documented as a means of prevention for breast cancer in the general population [10], the extent of its role in risk mitigation, specifically for carriers of BRCA1/2, remains unclear. Nkondjock et al.'s 2006 study on diet and lifestyle in BRCA-related breast cancer risk was one of the first to explore the relationship between a carrier's specific exercise routine and her associated risk of breast cancer [5]. The researchers asked 89 B.C.-affected carriers and 48 non-affected carriers about their physical activity in the two years prior to B.C. diagnosis or the interview, respectively. They concluded that neither moderate, nor vigorous, physical activity differed significantly between the experimental (affected) and control (non-affected) groups [5].

Conversely, a 2009 study more narrowly focused on the effects of physical activity (excluding other lifestyle factors) found a significant reduction in risk associated with lifetime physical activity [10]. Women who reported a medium level of intensity and duration in sports participation had lower risk of breast cancer compared to women who reported a lifetime average of low-intensity/duration exercise, or no exercise at all. In this study, risk was calculated by comparing participants diagnosed with breast cancer in the 10-year period before the questionnaire to non-affected participants [10].

While both of the aforementioned studies investigated the preventative potential of physical exercise in the high-risk BRCA

population, they came to distinctly different conclusions. There are a number of factors and limitations that may aid in explaining the contradictory findings. Primarily, the first study only gathered information on physical activity in the two years prior to diagnosis or interview of 135 total subjects [5], whereas the other determined lifetime participation, as well as activity in more specific time periods (before and after age 30, for example) of 1,026 total subjects [10]. Secondly, the experimental and control groups as defined by Nkondjock et al. were not directly comparable, despite an attempt to match on the basis of age. Level of physical activity in the two years prior to diagnosis may systematically differ from semi-current level of physical activity (as measured for controls), meaning it is not an accurate predictor of the control's risk of breast cancer at the equivalent age of diagnosis [5]. Lastly, there are inherent limitations in both studies related to the use of self-reported data and simple correlations, which we cannot infer to predict causation. The disagreement and limitations in these studies brought about follow-up investigations, each more focused on the particular mechanistic effects of exercise on B.C.-related measures.

While the mechanism(s) of interaction and penetrance of breast cancer and the BRCA-mutated gene (1 or 2) are still equivocal, it has been shown that estrogen stimulates BRCA1 gene transcription, and that significantly reduced estrogen exposure may decrease breast cancer risk by as much as 70% in some cases (such as in the case of a prophylactic oophorectomy) [3,7,9,11,13,14]. Thus, when inquiring about the relationship between physical activity and BRCA-related breast cancer, the effect of exercise on estrogen levels becomes a vital question. In accordance with the 2010 finding that higher lifetime levels of physical activity significantly predicted breast cancer occurrence within a 10-year period [10], studies in 2011 and 2015 both recognized a significant decrease in follicular phase estrogen area under curve (AUC) in exercise groups compared to control groups of high-risk women [13,14]. The earlier study lacked the statistical power of the latter with a very small sample size of only 7 individuals versus 139, and had only one experimental exercise group mandating 300 minutes of aerobic exercise a week [14], while the other randomized participants into low-dose (150 minutes/week) and high-dose groups (300 minutes a week) [13]. Thus, it is likely the 2015 study by Schmitz et al. gives a closer approximation (for every 100 minutes of exercise, decrease in estrogen AUC of 3.6%) of



estrogen reduction than the more limited study in 2011 (18.9% exposure for 300 minutes of exercise) [13].

While the extent to which each found a decrease in total estrogen exposure was different, the consistent results point to a potential mechanism by which breast cancer risk might be reduced in women with a deleterious BRCA mutation. However, it is important to note that in both studies, the population of “high-risk” women included both confirmed carriers of the deleterious BRCA 1 or 2 mutations, as well as any women with a Claus risk model approximation of greater than 18% lifetime risk [13,14]. This, along with a lack of stratification for BRCA1 versus BRCA2 participants, restricts our ability to hypothesize a BRCA-specific mechanism relating exercise to decreased risk of breast cancer. Nonetheless, it remains a promising preliminary finding that warrants the need for a future prospective study limited to BRCA mutation carriers.

## **Diet and Body Weight**

Understanding the role of diet and body weight on BRCA-related breast cancer penetrance is especially crucial. There are fewer ethical and personal deterrents to making and implementing dietary lifestyle recommendations compared to advocating for changes in reproductive factors (i.e. oral contraceptive use or pregnancy) and physical activity [12,13]. However, analogous to our previous findings, there is a very limited amount of research available on the influence of these factors in populations of high-risk BRCA mutation carriers. Of the studies that have been completed, general methodological differences limit extensive comparability, but preliminary results suggest diet and body weight both may have significant effects that are modified according to menopausal status and/or BRCA mutation type.

Many studies on diet and breast cancer risk in the general population have focused on the intake of fruits and vegetables (both thought to modify risk for a number of other human diseases), and a majority have concluded that increased consumption of fruit and vegetables together, and in some cases, vegetables alone, reduces lifetime B.C. risk [18]. Conversely, two prominent studies published in 2006 and 2013, respectively, focused on BRCA carriers and found no significant associations between fruit/vegetable intake specifically and breast cancer risk [5,6,18]. The significant associations each did find, however, were predictably different. The first

study (published in two different forms in 2006) concluded that total caloric intake increased B.C. risk in BRCA carriers, and further, caloric restriction of less than 1724 kcal/day, significantly reduced risk compared to daily consumption of more than 2339 kcal/day [5,6]. In addition to caloric intake, diet quality also had a general modifying effect. Women who earned a high score on the Canadian Healthy Eating Index (CHEI), which suggests they maintained a high-quality diet, had a reduced lifetime risk of up to 82% [6]. In fact, the correlation between scores on this index and breast cancer risk was so strong that the CHEI score could predict, with relatively high accuracy, whether a given participant had breast cancer or was a control. Importantly, no individual food group or component was found to significantly modify risk [5,6]. However, the results of the 2013 Ko et al. study indicate that increased soy intake alone significantly lowered risk in the BRCA population [18]. Furthermore, one method of analysis found that the highest quartile of meat intake predicted higher risk, but this effect was more prominent for carriers of BRCA2 than BRCA1 [18]. These differences warrant further analysis of methodological differences and yet again necessitate more standardized approaches to future research.

As we have previously seen, geographical isolation may play a role in the disagreement among findings. Both studies compared participants to family members with BRCA mutations, but Ko et al. used families from Korea and enrolled a total of 2271 subjects [18], whereas Nkondjock et al. limited subjects to members of French-Canadian families and enrolled a total of only 137 subjects [5,6]. The considerable difference in sample size (and thus statistical power) may explain only one of the two studies having found significant modifying effects for individual food groups. Further, the 2006 study by Nkondjock et al. did not stratify conclusions on the basis of BRCA mutation type, which might be a critical confound, given the results of the other study [5,6]. The more recent findings are also subject to methodological limitations; the methods do not specify that comparison between family members took age into account or controlled for differences in age, which necessarily mediates breast cancer risk. Additionally, dietary consumption was only recorded for the year prior to the study, which the researchers note could be biased by post-diagnosis dietary changes [18].

Correlations between caloric intake, diet quality, and body weight are well established in the general population, such that higher

caloric intake and generally “lower” diet quality (definition depends on particular index used) predicts increased body weight/obesity [7]. It follows that one might hypothesize if increased caloric intake increases BRCA-related B.C. risk, then body weight and/or obesity would have the same effect. This effect, however, is further modulated by age and menopausal status at breast cancer diagnosis and varies depending on the study [5,7,8]. For example, a 2010 study on body weight in BRCA carriers found that current body weight, BMI, and changes in weight did not significantly alter premenopausal breast cancer risk, but current body weight of greater than 72 kg significantly increased postmenopausal risk [8]. Interestingly, BMI and adult weight gain predicted a 50-60% increase in risk of postmenopausal cancer, but this association was not statistically significant [8]. One critical limitation of this study is that only 43% of participants had natural menopause. 57% had surgically-induced menopause, with a higher proportion in B.C.-unaffected subjects. Preventative surgeries (i.e. surgically-induced menopause) are thus a confounding factor in the study, as they have previously been shown to significantly reduce lifetime BRCA-related breast cancer risk [2,3,11].

Another study found that losing 10 pounds between the ages of 18 and 30 significantly reduced the risk of breast cancer incidence between the ages of 30 and 40, but no association was found for risk of breast cancer after 40 years old [7]. While the researchers chose to analyze on the basis of age, rather than menopausal status, median age of menopause in BRCA carriers is later than 40 years old (approximately 50, depending on source), so breast cancer between the ages of 30 and 40 is assumed here to be equivalent to premenopausal B.C. [15]. Therefore, the results of the two studies are directly at odds with one another. One study found that current body weight significantly increased risk of only postmenopausal B.C. [8], while the other found no impact at all [7]. Instead, the second study concluded that weight change significantly modified only premenopausal breast cancer risk [7], while the first study found no significant associations with weight change in either the pre- or post-menopausal group [8]. Nkondjock et al.’s 2006 findings accord with the second study: weight gain at both younger (18+) and older (30+) ages significantly correlated with breast cancer risk, but menopausal status upon diagnosis was not specified [5].

In accordance with the available literature on other non-genetic

factors as previously discussed, highly inconsistent results suggests the immediate need for future comprehensive research studies that stratify on the basis of age, BRCA mutation type, and menopausal status—all of which have been shown to modify the significance of the effects of diet and body weight in different ways. It is important to note that one such randomized controlled trial on diet and physical activity has been officially proposed, but has yet to be carried out or published [17].

## Conclusion

In this review, we identified and analyzed the most notable findings from prominent, peer-reviewed research studies investigating the role of potential non-genetic determinants of breast cancer risk in female carriers of deleterious mutations of the BRCA1/2 gene. We focused on three major classes of proposed risk modifiers: reproductive factors, physical activity, and diet/body weight. While the research outlined in this review is a step forward in elucidating how lifestyle and environmental factors may interact to predict an individual's unique likelihood of breast cancer penetrance, it is clear, from a limited selection of relevant literature and remarkably inconsistent findings, that more research on the topic is necessary before any conclusions can be made unequivocally.

Limiting estrogen exposure has been proposed as a preventative strategy to reduce BRCA-related breast cancer risk in many studies [3,7,9,11,13,14], so the effect of reproductive factors on B.C. penetration is a common research question in the field. A number of discordant, yet significant findings provide insufficient evidence to hypothesize about the effects of oral contraceptive use on BRCA-related cancer, but highlight potential methodological limitations including different geographical inclusion criteria, sample size, and retrospective data collection methods [2,3,9,11]. Further, some studies found that ever having breastfed reduced early-onset B.C. risk, while others found no association between breastfeeding and cancer penetration [2,4,9,17]. The only reproductive factor that consistently implicates a protective effect is parity. Being parous versus nulliparous has been shown to reduce risk of breast cancer and delay breast cancer onset, with a reduction in risk for each additional full-term pregnancy [2,9,17]. To what extent parity reduces risk remains unclear and still indicates the need for future research with more standardized methodologies and larger sample sizes.

Similarly, the reported effects of physical activity, diet, and body size were all study-dependent and inconsistent. Some studies found that vigorous physical activity, high-quality/low calorie dietary intake, and adult weight loss each reduced risk of BRCA-related breast cancer, while others found that these associations were insignificant or different altogether [5-8,10,12-15,18]. A few noteworthy differences in these studies include various inclusion/exclusion criteria (i.e. geographical location, history of preventative surgeries, age, etc.) and methods of statistical analysis, particularly stratification for BRCA mutation type and menopausal status.

Overall, a variety of significant risk-mitigating findings for each of the aforementioned factors provides promising preliminary evidence of the potential to control non-genetic factors and ultimately reduce breast cancer penetration and mortality in the high-risk population of BRCA1/2 carriers. With that being said, striking inconsistencies and limitations among all of the studies deem it inappropriate for us to speculate about particular preventative strategies. It is evident that future research is necessary and these studies should be randomized trials that control for BRCA mutation type, age, menopausal status, and country of origin, among other confounding variables proposed in this review.

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