The role of oral contraception use in the occurrence of breast cancer. A retrospective study of 405 patients

G. Iatrakis[1], C. Iavazzo[2], S. Zervoudis[3], A. Koumousidis[4], C. Sofoudis[2], T. Kalampokas[2], N. Salakos[2]

[1]Technological Educational Institute of Athens, School of Midwifery, Athens
[2]Family Planning Unit, 2nd Department of Obstetrics and Gynecology, Aretaieio Hospital, University of Athens Medical School, Athens
[3]LITO Hospital, department of Gynecological Oncology, Athens
[4]Department of Obstetrics and Gynecology, Tzaneio Hospital, Piraeus (Greece)

Summary

The investigation of potential predisposing factors of breast cancer, a disease accounting for almost one-third of malignancies in women, is necessary in order to reduce the incidence. *Materials and Method:* We interviewed 405 female patients who had been diagnosed with breast cancer and who also reported having used oral contraceptive pills before. They were categorized into two groups (group A < 7 years OC use and group B > 7 years OC use). *Results:* Statistical analysis revealed a small ($p < 0.02$) but significant increased risk of the disease to BRCA mutation carriers, as well as to the women with a significant medical or family history of breast, ovarian or colon cancer who had also previously used oral contraceptive pills for more than seven years. *Discussion:* Breast cancer seems to be positively dependent on prolonged oral contraceptive use. *Conclusion:* More research is needed to establish the hypothesis that the human genome is vulnerable to oral contraceptives.

Key words: Breast cancer; Risk factor; Oral contraceptives; BRCA mutation carriers; Prolonged use

Introduction

Breast cancer is a frequent disease, accounting for almost one-third of all malignancies in women, and a leading cause of death in the Western World [1]. Although overall cancer death rates in women between 1991 and 2005 decreased by 11.4%, with decreases in breast (37%) and colorectal (24%) cancer rates accounting for 60% of the total decrease [2], breast cancer still remains a plague which needs extended measures in order to be eliminated. Less than 1% of the disease appears in women under 25 years old, while in women more than 30 years old, a remarkable increase of the incidence is observed [3]. Most cases (80%) involve invasive ductal carcinoma, but lobular, medullary, mucinous and several other types of carcinomas may also be revealed on pathologoanatomic examination of the surgically extracted breast tumor [4]. Several predisposing factors of breast cancer have been discussed and recorded the last decades, with age, diet, alcohol consumption, obesity, several exogenous hormonal factors, e.g. oral contraceptives (OCs), medical and, finally family history prevailing in the field. Family history and mutations in the BRCA1 and BRCA2 genes are considered to be important correlates of lifetime risk, while genetic polymorphisms associated with estrogen synthesis and metabolism are currently under study (serum estrogen levels are higher in breast cancer cases than in controls) [5]. The aim of this study was to assess, using epidemiologic methods, the penetrance of genetic traits to OC users [6] treated for breast carcinoma, in relation to the duration of their overall contraceptive use. Since it is known that it is important to investigate and understand the potential predisposing factors of breast cancer to safely reduce its incidence, the study in question aspires to support and promote the efforts of our scientific community.

Materials and Methods

This study included 405 patients between 30 and 54 years of age, residents of the same metropolitan area, who were diagnosed with in situ or invasive breast cancer (ductal or lobular or other special type between January 2000 and December 2008 at the Department of Obstetrics and Gynecology, and reported to have used OCs for a variety of indications (contraception, ovarian cysts, etc.) during their lifetime. The patients filled out a questionnaire about their age, weight, menarche, several diet issues and alcohol consumption, childbirth and breastfeeding, family and medical history and the time and duration of OC use. Their answers were categorized into two groups - group A < 7 years total OC use (270 women) and group B > 7 years total OC use (135 women) and analyzed using statistics (chi-square test for evaluating the *null hypothesis* that *"the incidence of breast cancer is independent to prolonged oral contraceptive use"*). The questionnaire and the results, according to our population-in-control answers, are cited in Table 1.

Results

Distribution of the patients, according to their age and weight (obesity) was almost similar in the groups with no statistically significant differences. Diet and alcohol consumption also did not present any significant differences since Greek women tend, at large, to follow the Mediter-

Revised manuscript accepted for publication November 14, 2010

Table 1.

Measure	Question	OC use < 7 years 270 women (Group A)	OC use > 7 years 135 women (Group B)
Age	How old are you?	Mean age~ 47.3	Mean age ~48.1
Weight	How many kilos do you weigh?	~68 kilos on average	~72 kilos on average
Diet	Could you describe the main pattern of your everyday diet?	mainly mediterranean	mainly mediterranean
Alcohol consumption	How much alcohol do you usually consume?	3,7 glasses of wine or beer /week	3,4 glasses of wine or beer /week
Menarche	Could you report when your period first appeared?	~12.49	~12.76
Medical history	Have you ever suffered from breast, colon, endometrial, ovarian or any other type of cancer?	28 (10.37%)	25 (18.52%)
Family history	Had anyone in your family tree ever suffered from breast or ovarian cancer?	76 women had a close relative suffering from the disease (28.14%)	55 women had a close relative suffering from the disease (40.74%)
Childbirths	How many deliveries did you have in the past?	~1.407	~1.66
Breast-feeding	How many weeks overall (if any) did you breastfeed your child(ren)?	~14.5 weeks	~14.9 weeks

ranean diet. The mean age of menarche was ~12.58 years old with no statistically significant differences between group A (~12.49) and group B (~12.76). Moreover, the mean number of childbirths and the overall duration of the lifetime breastfeeding were similar in both groups. On the other hand, according to their family history, 76 women (28.14%) in group A had a close relative (first- or second-degree, possibly BRCA mutation carriers) with a positive medical history for breast or ovarian cancer, while 55 (40.74%) in group B reported the above. Moreover, 25 patients of group B (18.52%) and 28 patients of group A (10.37%) reported a positive medical history of either a previous breast or another type of cancer (endometrial, ovarian, colon). Assessment and statistical analysis led us to the conclusion that there is a small ($p < 0.02$ for possible BRCA mutation carriers/$p < 0.05$ for patients with a history of previous cancer) but significantly increased risk of the disease in BRCA mutation carriers (mainly $p < 0.02$), as well as to the women with a certain medical or family history of breast, ovarian or colon cancer ($p < 0.05$), who have additionally used OCs for more than seven years in their lifetime.

Discussion

The matter as to whether OCs are potential risk factors for breast carcinoma or not remains controversial today. Many scientists support the belief that the risk of common exposure to OCs increases in women with other risk factors [7], whereas others claim that modern data do not suggest an increased risk for breast carcinoma in OC users [8]. Our study shows that there was a small but clinically significant increased risk for the disease mainly in OC users with possible BRCA1/2 mutations as well as in users with a previous positive medical history of cancer.

The term *"possible BRCA1/2 carriers"* is used in our study to emphasize the fact that the method/criteria we followed in order to consider some patients as carriers of the deleterious mutations in the BRCA1 or BRCA2 genes are not a product of an accurate laboratory testing (e.g., through methods of chromatography) but a conclusion reached applying specific patterns (a clinical outcome derived directly from their family history). These patterns include two first-degree relatives with breast cancer, one of whom received the diagnosis at age 50-years-old or younger; a combination of three or more first- or second-degree relatives with breast cancer regardless of age at diagnosis; a combination of both breast and ovarian cancer among first- and second-degree relatives; a first-degree relative with bilateral breast cancer; a combination of two or more first- or second-degree relatives with ovarian cancer regardless of age at diagnosis; a first- or second-degree relative with both breast and ovarian cancer at any age; and a history of breast cancer in a male relative [9]. Moreover, as women with none of these family history patterns have a low probability of having a deleterious mutation in BRCA1 or BRCA2 genes [9], women with some of these family history patterns can therefore be categorized as possible BRCA 1/2 carriers. We noticed that the correlation between the duration of previous OC use in possible BRCA 1/2 carriers and their proportion in each group (A or B) was positive and statistically differentiated ($p < 0.02$). The above epidemiological information can be used to evaluate the effect of OC use on women with inherited breast cancer: the prolonged use of OCs might provoke an earlier appearance of the inherited type of disease. Although no statistically significant change of the micronucleus frequency in lymphocytes of peripheral blood has been recorded in patients who took low dose OCs after a period of six consecutive menstrual cycles (micronucleus test is a method used in discovering of chromosome aberrations (genotoxicity) in the cells exposed to effects of chemical mutagens) [10], long-term studies should be performed in women/OC users and carriers of BRCA 1/2 genes to establish the chromosomal changes, if any, in their cells; changes that could explain the above-mentioned finding.

A similar but weaker bond seems to exist between the positive medical history of a previous breast, colon, endometrial, ovarian or any other type of cancer and the

duration of OC use in women suffering from breast cancer. Again the above information leads us to the hypothesis that human genes in these patients are vulnerable to exogenous contraceptives. This possible susceptibility ($p < 0.05$) of the genome to OCs could be explained through the fragile profile of the genotype and phenotype of these patients. Extended research could prove the scientific quality of our above statement in the future.

Unfortunately, although we tried to record, study, and control any potential risk factors that could affect and alter our results, leading us to false outcomes, the field in question is multidimensional and even a homogeneous population like the one we studied, can have differences that could be substantial and major, changing the results and altering our scientific opinion towards the null hypothesis. Keeping the above in mind, although we consider that it is too risky to express the idea that "prolonged use of OCs can cause chromosomal aberrations in women who are not carriers of any specific oncogenes", we support the belief that prolonged use of OCs can cause chromosomal aberrations, leading to breast malignancies in women susceptible to cancerous mutation genomes.

Conclusion

The null hypothesis is rejected since breast cancer seems to be positively dependent on prolonged OC use. The human genome appears to be vulnerable to exogenous hormones in OCs, but more research is needed to establish this finding in the future.

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Address reprint requests to:
C. IAVAZZO, M.D.
38, Seizani Str.
Nea Ionia, Athens (Greece) 14231
e-mail: christosiavazzo@hotmail.com