INTRODUCTION

Combined hormonal contraceptives (CHCs) are widely used across Europe [1] and in the United States (US) [2], with significant variations determined mainly by social and cultural background [3]. Indeed, several studies have shown that women have insufficient knowledge about the mechanisms of action of CHCs [4] and that they often under-recognise and misunderstand the main effects of these drugs on their general and reproductive health [5–7]. In this setting, healthcare providers (HCPs) play a significant role, as they should promote a shared decision-making process with each woman based on the potential health benefits of hormones use [8]. A recent northern Italian survey showed that CHC use is significantly associated with a satisfactory level of knowledge about the risks and benefits on the health and well-being of users; however, authors concluded that HCPs must be proactive in providing relevant information to help women choose their contraception and consider possible side effects [9]. Patients’ perceptions related to CHC use are even more complex when they are at increased genetic risk for breast and ovarian cancer development, as in the case of patients with germline BRCA1 or BRCA2 mutation [10]. The literature about CHC use and cancer development in BRCA mutation carriers is controversial: there is some evidence that CHC use may protect against ovarian cancer in patients with BRCA mutations [11–13], as reported in the general population [14]; recently, among BRCA1 mutation carriers, longer duration of oral CHC use has been found associated with a greater reduction in ovarian cancer risk [15]. On the other hand, whether epidemiological studies in the general population have documented a small increased risk of breast cancer associated with the use of CHC [16], conclusive results for BRCA1 mutation carriers are demanding; in this regard, recent studies have shown in BRCA mutation carriers a non-significant association between CHC use and breast cancer risk [17,18]; otherwise, other studies have reported a two-fold breast cancer risk in BRCA mutation carriers who started CHC use at a very young age [19,20]. Despite limitations of the data, as well as the need to consider other potential benefits and harms of CHC use, the actual recommendations suggest that there is insufficient evidence to recommend the use of these drugs as a chemoprevention strategy for reducing ovarian cancer risk in BRCA mutation carriers; otherwise, if women with BRCA mutation wish to use CHCs for contraception, there is no evidence to discourage their use [10,17].
The belief that CHC use might influence the risk of some diseases and cancers is particularly critical to address, as the use of these drugs is relatively common among patients with BRCA1 and BRCA2 mutation. Nevertheless, there are currently limited published studies evaluating the awareness of the effects of CHCs in women at high risk of developing breast and/or ovarian cancer, such as those with germline BRCA mutation. An Australian survey of 83 women [21] revealed that women with an increased familial risk of breast/ovarian cancer (excluding those with a confirmed BRCA mutation) received insufficient information related to CHC use and this was associated with their discontinuation or avoidance.

Therefore, the objective of this study is to evaluate the current knowledge on the benefits and risks of CHCs in women carrying BRCA mutations, also assessing their main concerns about taking these drugs, with a particular interest in the oncological implications, in comparison to women belonging to the general population.

Methods

Study design

This is a cross-sectional, observational study performed from January 2020 to April 2021 at two University Hospitals in services identifying families with increased hereditary cancer risk: Modena Family Cancer Clinic (MFCC), one of four hub centres of Emilia-Romagna, and the regional Liguria referral centre for hereditary cancers IRCCS Ospedale Policlinico San Martino. Consecutive healthy premenopausal women with a BRCA pathogenetic germline mutation were recruited without a history of breast cancer. A control group of age-matched women without this genetic mutation was obtained from a group of healthy premenopausal subjects with no previous oncological diseases and no personal and family history of breast/ovarian cancer evaluated for a routine gynecological examination at other gynecological services of the same hospitals between April 2021 and May 2021.

Evaluated variables

During the routine gynecological examinations, the following clinical data were collected: age, parity, number of vaginal or caesarean births, previous abortions, and previous gynecological surgeries (hysterectomy, mastectomy, quadrantectomy, risk-reducing mastectomy [RRM], risk-reducing salpingo-oophorectomy [RRSO]). Women who underwent a previous hysterectomy, mastectomy, quadrantectomy, risk-reducing mastectomy (RRM), risk-reducing salpingo-oophorectomy (RRSO) were excluded. After detailed counselling about the study, the women who chose to participate signed an informed consent form. Once included in the study, a single identical questionnaire was delivered to all study participants (with or without BRCA mutation) [Supplementary Table 1].

For both groups of women (with and without BRCA mutation), questionnaires collected data related to the type of CHC eventually used (oral, transdermal, vaginal ring), the brand name of the used product, use (current, past, never used) and the duration of use (months/years). Women were asked to evaluate how much, in their opinion, CHCs could affect the risk of developing certain types of cancer (breast, ovary, intestinal colorectal, lymphoma, uterine body, uterine cervix), diseases (venous thrombosis, breast cysts, cardiovascular diseases, anaemia, foetal malformations, infertility, ectopic pregnancy, sexually transmitted diseases) or symptoms (headache, weight gain, a decline of sexual desire, vaginal dryness, changed appetite, mood swings, abnormal menstrual bleeding, menstrual cramps, the appearance of pimples on the skin, depressed mood) using a Likert scale from −5 to +5. For cancers and diseases, the following scores were employed: −5 = reduces the risk of onset, 0 = neutral effect, +5 = increases the risk of onset and for symptoms −5 = improves with CHC use, 0 = neutral effect, +5 = worsens with CHC use [Supplementary Table 1].

The English translation of the questionnaires used in this study for women with and without BRCA mutations are reported in Supplementary Table 1. We employed the same questionnaires, which were used in other recent Italian studies [9,22,23] for enrolling premenopausal and postmenopausal women, which were validated in a previous pilot evaluation.

Ethics and statistics

The results of this study are part of a larger project named ‘Quality of (reproductive) life in women at increased risk for hereditary and/or ovarian cancer’, approved by the Ethics Committee Area Vasta Emilia Nord (Reference No. 515, 2019). Specific informed consent was obtained from each woman for the use of sensitive data for scientific purposes.

The answers to the questionnaires of women with and without BRCA mutation were analysed and compared. The prevalence in the two different study groups was calculated. Where necessary, the prevalence was compared using contingency tables. The within-group comparison was performed with the t-test for paired data and by the Mann-Whitney U test for normal and non-normal data distribution, respectively. The statistical analysis was performed using the statistical package StatView (v 5.01.98; SAS Institute Inc, Cary, NC). Correlations were considered significant at p-values < .05. The results of categorical variables are expressed in terms of frequency and percentage and those of continuous data in terms of mean ± standard deviation (SD).

Sample size calculation

Similarly to a previous study [22], assuming a pooled SD of 1 unit, the study would require a sample size of 63 women for each group (i.e., a total sample size of 126, assuming equal group sizes) to achieve a power of 80% and a level of significance of 5% (two-sided) for detecting a true difference in means of 0.5 units in Likert scale values between the groups.

Results

In total, 181 women were considered potentially eligible for the study; however, eleven women were excluded, as they were BRCA mutation carriers who had already
undergone RRSO (n = 3), had given incomplete answers to the questionnaire (n = 3), or withdrew consent to participate in the study (n = 5). Accordingly, 85 premenopausal healthy BRCA mutation carriers and a control group (n = 85) of similar age (p = .15) were included in our definitive analysis (mean age: 36.5 ± 8.3 years, range 20–49 years). The demographic characteristics of the two study populations are reported in Table 1. At the moment of study inclusion, 43/170 women (25.3%) in the whole group were present CHC users. Notably, present CHC users were more frequent in the control group (35.3% vs. 15.3%; p = .003) and in BRCA mutation we have found a higher prevalence of CHC never users (21.2% vs. 7%; p = .008) although in both groups there was a similar CHC time of use (48.0 (IQR: 7.5) vs. 24.0 (IQR: 5.8) months; p = .17).

**Knowledge of the effects of CHC use on the development of specific diseases and symptoms**

The answers to the questions ‘How much can CHCs increase or reduce the risk of developing these diseases?’ and ‘How much can CHCs improve or worsen these symptoms?’ are reported in Table 2 for the whole study group, in BRCA mutation carriers, and in control group separately.

Overall, the diseases that participants most perceived to be favoured by CHC use were venous thrombosis (1.5 ± 0.2), followed by cardiovascular (0.7 ± 0.1) and sexually transmitted diseases (0.4 ± 0.2). A protective role of CHCs was assumed for anaemia occurrence (–0.6 ± 0.1). These perceptions did not differ between mutation carriers and controls (Table 2).

Interestingly, all the participants had a negative perception about the risk of developing abnormal uterine bleeding (0.6 ± 0.2) and depressed mood (0.3 ± 0.1) during CHCs use. Otherwise, no positive or negative impact of CHCs was recognised in terms of weight increase (0.0 ± 0.2) and reduction of libido (0.0 ± 0.1). The most important beneficial recognised effects were reported for menstrual cramps (–0.6 ± 0.2) and, above all, for acne (–1.4 ± 0.2). These perceptions did not differ between BRCA mutation carriers and controls (Table 2).

### Table 1. Demographic characteristics of the study population.

| BRCA mutation carriers | Control group | p value |
|------------------------|---------------|---------|
| (n = 85)               | (n = 85)      |         |
| Mutation type          |               |         |
| BRCA1: 40 (47.0%) /    |               |         |
| BRCA2: 45 (53.0%) /    |               |         |
| Age (years; mean ± SD) |               |         |
| 37.4 ± 7.5             | 35.5 ± 9.0    | .15     |
| Nulliparous (n, %)     |               |         |
| 45/85 (52.9%) /        | 54/85 (63.5%) | .16     |
| CHC use (n, %)         |               |         |
| Present users          |               |         |
| 13 (15.3%)             | 30 (35.3%)    | .003    |
| Past users             |               |         |
| 62 (72.9%)             | 61 (71.8%)    | .86     |
| Vaginal Ring           |               |         |
| 3 (3.5%)               | 8 (9.4%)      |         |
| Pill                   |               |         |
| 10 (11.8%)             | 22 (25.9%)    |         |
| Vaginal Ring           |               |         |
| 7 (8.2%)               | 8 (9.4%)      |         |
| Patch                  |               |         |
| 1 (1.2%)               | 1 (1.2%)      |         |
| Never                  |               |         |
| 18 (21.2%)             | 6 (7%)        | .008    |
| Duration of use (months; median IQR) | 24.0 (IQR: 5.8) | 48.0 (IQR: 7.5) | .17 |

CHC: combined hormonal contraceptives.

### Table 2. Likert scale from –5 to +5 (mean ± standard Error) in descending order for the questions ‘How much can CHCs increase or reduce the risk of developing these diseases?’ and ‘How much can CHCs improve or worsen these symptoms?’ in the whole study group, in BRCA mutation carriers, and in control group, respectively.

| Evidence from the current literature | Total group (n = 170) | BRCA mutation carriers (n = 85) | Control group (n = 85) | p value |
|-------------------------------------|----------------------|---------------------------------|------------------------|---------|
| How much CHCs can increase or reduce the risk of developing these diseases? |     |     |     |
| Venous thrombosis                   | Increased risk [24]  | 1.5 ± 0.2                        | 1.5 ± 0.2              | 1.6 ± 0.3 | .91 |
| Cardiovascular diseases             | Increased risk [25]  | 0.7 ± 0.1                        | 0.7 ± 0.2              | 0.8 ± 0.2 | .76 |
| Sexually transmitted diseases       | Increased risk [26]  | 0.4 ± 0.2                        | 0.6 ± 0.2              | 0.2 ± 0.3 | .25 |
| Breast cysts                        | Increased risk [27]  | 0.3 ± 0.2                        | 0.5 ± 0.2              | 0.1 ± 0.2 | .25 |
| Infertility                         | Neutral effects [27] | 0.0 ± 0.1                        | –0.1 ± 0.2             | 0.0 ± 0.2 | .68 |
| Foetal malformations                | Neutral effects [27] | 0.0 ± 0.1                        | 0.2 ± 0.1              | –0.2 ± 0.2 | .13 |
| Ectopic pregnancy                   | Reduced risk [27,28] | –0.1 ± 0.1                       | 0.0 ± 0.1              | –0.2 ± 0.2 | .32 |
| Anaemia                             | Reduced risk [29]    | –0.6 ± 0.1                       | –0.4 ± 0.2             | –0.8 ± 0.1 | .42 |
| How much can CHCs improve or worsen these symptoms? |     |     |     |
| Abnormal uterine bleeding           | Improvement [29]     | 0.6 ± 0.2                        | 0.6 ± 0.2              | 0.5 ± 0.3 | .66 |
| Depressed mood                      | Worsening [30]       | 0.3 ± 0.1                        | 0.2 ± 0.2              | 0.4 ± 0.2 | .40 |
| Mood swings                         | Worsening [30]       | 0.3 ± 0.2                        | 0.5 ± 0.2              | 0.1 ± 0.3 | .29 |
| Headache                            | Uncertain [31]       | 0.3 ± 0.2                        | 0.3 ± 0.2              | 0.4 ± 0.3 | .75 |
| Increased appetite                  | Uncertain [32]       | 0.2 ± 0.1                        | 0.4 ± 0.2              | 0.0 ± 0.2 | .12 |
| Weight increase                     | Uncertain [32]       | 0.0 ± 0.2                        | 0.3 ± 0.3              | –0.2 ± 0.3 | .32 |
| Reduction of libido                 | Worsening [33]       | 0.0 ± 0.2                        | 0.1 ± 0.2              | –0.1 ± 0.2 | .41 |
| Vaginal dryness                     | Improvement [33]     | –0.2 ± 0.2                       | 0.0 ± 0.2              | –0.4 ± 0.3 | .13 |
| Menstrual cramps                    | Improvement [27]     | –0.6 ± 0.2                       | –0.4 ± 0.2             | –0.8 ± 0.3 | .25 |
| Acne                                | Improvement [27]     | –1.4 ± 0.2                       | –1.2 ± 0.2             | –1.5 ± 0.3 | .36 |

A column about evidence from the current literature (with a specific reference) has been added.
Discussion

Main results

The results of the present study aim to strengthen counselling activity related to CHC use, especially in women at high oncological genetic risk, such as BRCA mutation carriers. In fact, acting on false myths and trying to overcome unjustified worries are two of the most important tasks critical for the therapeutic prescription process today, particularly in women at higher risk of developing cancer.

Our findings clearly show that the perceptions of BRCA mutation carriers do not differ from those of the general population concerning the knowledge of the impact of CHC use on the risk of the developing symptoms, often consisting of commonly experienced side effects during hormonal therapy (i.e., weight increase, reduction of libido); furthermore, both groups share a similar level of knowledge related to the extra-contraceptive positive impacts of CHC use on dysmenorrhoea and acne. The perception of the development of specific diseases (i.e., venous thrombosis, cardiovascular disease) did not also differ between BRCA carriers and the control group. On the other hand, that related to the long-term oncological impact of CHCs, particularly on gynecological cancers (breast, uterine cervix, uterine body, and ovarian cancers) and colorectal cancer risk, significantly differed.

Data of our study show that the majority of BRCA mutation carriers tend to ignore the protective role of CHCs in the pathogenesis of ovarian, uterine, and colorectal cancers. On the other hand, BRCA mutation carriers recognised an increased risk of developing breast and cervical cancer due to CHC administration, although, it cannot be excluded that their negative perception could have been overestimated, as it was significantly more elevated than that of the control group.

Overall, investigating time and effort in teaching the correct key messages could potentially increase CHC use in women with high oncological genetic risk, such as BRCA mutation.

Interpretation

Communicating cancer risk information is relevant for many HCPs; in particular, it has a critical role during specialist counselling of patients carrying BRCA mutations. Moreover, information about the various risks can be important in motivating each woman to engage in long-term treatments, such as CHC use. Nevertheless, a reliable epidemiological assessment of any association of CHC use with cancer incidence requires a large sample size and careful evaluation of all potential sources of appreciable bias.

Our data indicate that current myths and taboos regarding side effects and long-term consequences of CHC use on women's health need to be fully addressed, investing time and effort in clinical practice.

Poor knowledge about the positive effects of hormonal treatments on the risk of some cancers was demonstrated. Women carrying BRCA mutations are still not aware of the protective action of CHCs against ovarian, endometrial, and colorectal cancer, similarly to findings obtained in previous studies [9,21–23,38]. This low level of awareness is particularly surprising for ovarian cancer, given that the lifetime risk (by the age of 70 years) of this neoplasia in women with a proven BRCA mutation is very high (approximately 40% in BRCA1 mutation carriers and 18% in BRCA2 mutation carriers) [39]. Notably, while in the control group there was a perception of a protective role of CHC use on the risk of ovarian cancer, BRCA mutation carriers wrongly attributed a slightly increased risk of this cancer-associated with their use. Our study found comparable results for endometrial cancer and colorectal cancer, for which the protective role of CHC therapy was only correctly recognised by healthy women.

On the other hand, BRCA mutation carriers had a more negative perception of the risk of developing breast cancer due to using CHCs than the control group. Nevertheless, several patients with a BRCA mutation in our study were able to identify the potentially increased breast cancer risk associated with CHC use, and their family history may influence their decision not to use CHCs; however, data from the current literature suggest that CHC use in the general population is associated with an increased risk of breast cancer of just 1.3 (95% CI 1.0–1.6) extra cases per 10,000 person-years in comparison to women who have never used CHCs [40]. Therefore, it can be argued that the perception of developing breast cancer due to CHCs could have been overestimated by BRCA carriers in comparison to healthy controls. Nevertheless, it is not completely clear who underestimates and who overestimates the risk (BRCA mutation carriers or control women?).

Differently from control, BRCA mutation carriers correctly recognised a higher risk of developing uterine cervix cancer due to CHCs. However, it is important to remember the exceedingly small negative CHCs impact on the absolute risk of cancer of this cancer. For this reason, it cannot be excluded that in this group of patients there could be an overestimation of the perception of developing uterine cervix cancer.

### Table 3. Likert scale from −5 to +5 (mean±standard Error) in descending order for the question: ‘How much can CHCs increase or reduce the risk of developing these cancers?’ in the whole study group, in BRCA mutation carriers, and in control group, separately.

| Cancer Type                  | Total group (n = 170) | BRCA mutation carriers (n = 85) | Control group (n = 85) | p     |
|------------------------------|----------------------|--------------------------------|-----------------------|-------|
| Breast cancer                | 0.8 ± 0.2            | 1.2 ± 0.2                      | 0.2 ± 0.2             | 0.008 |
| Uterine cervix cancer        | 0.4 ± 0.2            | 0.5 ± 0.2                      | –0.3 ± 0.2            | 0.07  |
| Lymphoma                     | 0.1 ± 0.1            | 0.4 ± 0.2                      | 0.0 ± 0.1             | 0.7   |
| Uterine body cancer          | 0.0 ± 0.2            | 0.4 ± 0.2                      | –0.4 ± 0.2            | 0.01  |
| Colorectal cancer            | 0.0 ± 0.1            | 0.2 ± 0.2                      | –0.3 ± 0.2            | 0.02  |
| Ovarian cancer               | –0.2 ± 0.2           | 0.1 ± 0.3                      | –0.7 ± 0.3            | 0.01  |

A column about evidence from the current literature (with a specific reference) has been added.
Overall, BRCA mutation carriers seem to have an altered perception of the impact of hormones in the pathogenesis of gynecological cancers (including breast cancer). Supporting this, both groups had a neutral not statistically different perception of the risk of developing lymphoma in the case of CHC administration; in fact, the current literature reports that this cancer localisation is not likely influenced by CHC use [35].

Knowledge of the effects of CHC on the development of specific diseases and symptoms was not different between the two study groups. The highest concern of the whole study population was related to the onset of venous thrombosis; however, it cannot be excluded that this may represent an overestimation of the risk, as it has been previously reported that CHCs can be responsible for approximately only eight extra cases of venous thrombosis per 10,000 person-years [24].

Considering these results, attitudes towards HCPs may contribute significantly to women’s knowledge of the impact of CHCs on the development of cancer, specific diseases, and symptoms. The ability of HCPs to share conclusive information with potential users, especially in populations with familial risk, is of extreme importance. Moreover, as demonstrated in our multivariate analyses, a greater specific education level of the participants could be associated with a higher level of knowledge of the benefits and risks related to CHC use, leading to more widespread use in this specific high-risk population. This data is consistent with previous studies performed on the general population [7,41–43].

Exhaustive information should be given to BRCA mutation carriers so that they can make informed decisions about the health consequences of CHC use. The data presented in the study also suggest that a specific information leaflet summarising the major benefits and risks of long-term CHC use in the context of hereditary cancer would be valuable for women at higher cancer risk and the doctors who care for them.

**Study limitations**

There were several limitations to this study, including its cross-sectional design and the representativeness of the sample, which was not a randomly selected population. Recruiting participants directly from the family cancer clinics and other gynecological hospital services may have biased the sample due to the inclusion of participants with relatively high health awareness and those who are better motivated to co-operate with HCPs in screening initiatives. Moreover, our sample size calculation indicated that this study was able to recognise a true difference of 0.5 units in Likert scale values between the two groups. However, the sample size is not large enough to enable the detection of any negligible differences of less than 0.5 points between the groups. Lastly, the Likert scale used in the questionnaires is limited by the fact that it is not ideal for comparing the size (strength) of any perceived associations with the strength of the known association (current literature) between CHC use and specific symptoms, diseases, and cancers. The advantages of this study are the presence of a control group without the BRCA mutation, the in-depth questions of the questionnaires, and the availability of a wide range of data from participants. Moreover, the age distributions of the two included groups were similar.

**Conclusions**

The results of our study show that the perceptions of BRCA mutation carriers do not differ from those of the general population concerning the knowledge of the impact of CHC use on the risk of developing symptoms and disease. On the other hand, their perceptions are significantly different in relation to the long-term oncological effects of CHCs, particularly on breast, uterine cervix, uterine body, colorectal, and ovarian cancer risk during long-term use. Therefore, detailed counselling, particularly regarding oncological issues, is essential to facilitate a shared decision about possible CHC use in BRCA mutation carriers.

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