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Breast cancer risk of hormonal contraception: Counselling considering new evidence

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ABSTRACT

The possibility that the use of hormonal contraceptives may increase the risk of breast cancer has been raised since many years. In the past this hypothesis has been dismissed on the basis that available data were generally derived from "old" studies in which relatively high hormone doses had been used. The recent publication of two studies that analysed data from women receiving low-dose hormonal contraception and showed a statistically significant increase in breast cancer contradicts this reassuring belief.

The topic however is not settled, since different results were obtained in other studies and since hormonal contraception (HC) also has unquestionable positive effects such as a decrease in ovarian and in endometrial cancer.

The aim of the present paper is to provide evidence that may help gynaecologists and oncologists in discussing with their patients the use of HC.

Even if cancer phobia is a strong reason for not using or limiting HC, patients must be informed that notwithstanding the slightly increased breast cancer risk, the overall cancer risk may still be lower than non-users. Proper counselling may help the woman choose the most suitable contraception in the different phases of her life and on the basis of other conditions that may increase cancer risk such as overweight, smoking or family history.

1. Background

The combination of oestrogens and synthetic progestins are among the factors that may increase the risk of breast cancer (BC) and this has been proven, for example, in hormone-replacement treatment in postmenopausal women. A similar suggestion has been proposed for hormonal contraception since its introduction. Until recently this has been dismissed on the basis that data available were obtained from women treated with "old" formulations containing higher hormone dosages.

Two recently published Scandinavian studies (Busund et al., 2018; Morch et al., 2017) question this optimistic approach. Both studies were of adequate size, well performed and well analysed, and both found a significant increase in breast cancer incidence in women using oral contraception. These studies differ from previous analyses since they mostly included women treated with "modern" preparations composed of relatively low hormonal doses. It is important to note, however, that several studies reported different results. The aim of this paper is to discuss these results and to compare them with those of similar trials that provided different information.

Given the relevance of hormonal contraception and the sensations that just mentioning the word "cancer" may raise alert in most people, we think it is particularly important to provide oncologists and gynaecologists an update on the available data, to better counsel their patients.

2. Methods

Critical appraisal of the recent literaturewas performed using the following strategies.

2.1. Medline breast cancer risk of hormonal contraceptives

(("Contraceptives, Oral"[MAJR] OR "Contraceptives, Oral/ADVERSE EFFECTS"[MH] OR (contraceptive*[ti] AND (PILL[TI] OR pills[ti] OR oral[ti] OR hormonal[ti]))) AND (BREAST NEOPLASMS [MAJR] OR BREAST NEOPLASMS/EPIDEMIOLOGY[MH] OR BREAST neoplasms/etiology[mh] OR BREAST Neoplasms/chemically induced [MH] OR ((BREAST CANCER[TI] OR BREAST NEOPLASMS[MAJR])

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AND (RISK[TI] OR risk[mh] OR INDUCE*[TI]))))) AND (2017:2018[DP] OR REVIEW[PT] OR SYSTEMATIC[SB] OR epidemiology OR statistics)

2.2. Medline cancer risks and benefits of HC

((("Contraceptives, Oral"[MAJR] OR (contraceptive*[ti] AND (PILL [TI] OR pills[ti] OR oral[ti] OR hormonal[ti]))) AND (NEOPLASMS/EPIDEMIOLOGY[MH] OR neoplasms/etiology[mh] OR "Neoplasms/drug effects"[Mesh] OR "neoplasms/prevention and control"[mesh] OR Neoplasms/chemically induced[MH] OR ((CANCER[TI] OR NEOPLASMS[MAJR]) AND (RISK[TI] OR risk[mh] OR prevent*[ti] OR benefit*[ti] OR advantag*[ti] OR protecti*[ti]))))) AND (2016:2018[DP] OR REVIEW[PT] OR SYSTEMATIC[SB] OR epidemiology OR statistics)) NOT (RISK[TI] AND breast[ti])

3. Results

We will try to summarise the most relevant results of the trials on the relationship between HC and breast cancer that have been identified in the literature.

We start this analysis from the Danish study which has been recently published (Morch et al., 2017). This was a large, well conducted and well analysed study, but its results must be seen in the proper perspective and compared with data from equally relevant studies that obtained different results.

The authors collected data from all women in Denmark between 15 and 49 years of age who had not had cancer or venous thromboembolism and who had not received treatment for infertility (1.8 million women). These women were followed for an average of 10.9 years, for a total of 19.6 million person-years, to investigate a possible associations between the use of HC and the risk of invasive BC. The relative risk of BC among all current and recent users of HC was 1.20 (95% confidence interval [CI], 1.14–1.26). This risk was time dependent and increased from 1.09 (95% CI, 0.96–1.23) with less than 1 year of use to 1.38 (95% CI, 1.26–1.51) with more than 10 years of use (P = 0.002). After discontinuation of hormonal contraception, BC risk remained higher among women who had used hormonal contraceptives for 5 years or more than among women who had never used hormonal contraceptives. Risk estimates associated with current or recent use of various oral combination (oestrogen–progestin) contraceptives varied between 1.0 and 1.6. Women who currently or recently used the progestin-only intrauterine system also had a higher risk of breast cancer than women who had never used hormonal contraceptives (relative risk, 1.21; 95% CI, 1.11–1.33).

However it is important to consider not only the statistical evaluation of this increase, but also its extent in terms of absolute numbers. In this study the absolute increase in risk was 13 extra cases per 100,000 person-years (95% CI, 10–16): one extra BC for every 7690 women using HC for 1 year.

The Norwegian Women and Cancer study (NOWAC) (Busund et al., 2018) is a prospective population-based cohort study that for the first time showed a significant association between progestin-only contraceptives (POC) and oestrogen receptor-positive (ER+) BC (HR = 1.59, 95% CI 1.09–2.32, p-trend = 0.03) or ER+/Progesterone Receptor positive (PR+) BC (HR = 1.63, 95% CI 1.07–2.48, ptrend = 0.05).

In this prospective population-based cohort study, BC risk was assessed in 74,862 premenopausal women using progestin-only (POC) or combined oral contraceptives (OC). POC use beyond five years was associated with ER+ (HR = 1.59, 95% CI 1.09–2.32, ptrend = 0.03) and ER+/PR + cancer (HR = 1.63, 95% CI 1.07–2.48, p trend = 0.05), and was not associated with ER- (p heterogeneity = 0.36) or ER-/PR- (p heterogeneity = 0.49) cancer. Combined OC use was associated with ER- and ER-/PR- cancer, but did not increase risk of ER + and ER+/PR + cancer. Current COC use gave different estimates for ER/PR-defined subtypes (p heterogeneity = 0.04). This study lacked the power to distinguish effects of POC use on subtype development and needs confirmatory trials as it is the first to show a significant associations between POC use and hormone receptor-positive breast cancer.

These two Northern European studies could discourage HC because they hasten the fear of BC, which appears to be a sufficient reason to reduce HC use while withholding its benefits. OC is associated with a reduced risk of different tumour types.

The 46,022 women who were recruited to the UK Royal College of General Practitioners' Oral Contraception Study (Iversen et al., 2017) in 1968 and 1969 were observed for up to 44 years. Ever use of HC was associated with reduced colorectal (incidence rate ratio, 0.81; 99% confidence interval, 0.66 − 0.99), endometrial (incidence rate ratio, 0.66; 99% confidence interval, 0.48 − 0.89), ovarian (incidence rate ratio, 0.67; 99% confidence interval, 0.50 − 0.89), and lymphatic and hematopoietic cancer (incidence rate ratio, 0.74; 99% confidence interval, 0.58 − 0.94). The increased risk of breast and cervical cancer that was seen in current and recent users appeared to be lost within approximately 5 years of stopping oral contraception, with no evidence of either cancer recurring at increased risk in ever users with time. There was no evidence of new cancer risks appearing later in life among women who had used HC. Thus, the overall balance of cancer risk among past users of HC was neutral with the increased risks counterbalanced by the endometrial, ovarian, and colorectal cancer benefits that persist more than 30 years.

An increase in the risk of breast cancer in women receiving HC had already been described in older studies: the Collaborative Group on Hormonal Factors in Breast Cancer (Collaborative Group on Epidemiological Studies of Ovarian Cancer et al., 2008) reported a relative risk of 1.24 (95% confidence interval [CI], 1.15–1.33) and a similar increase was described in the Nurses' Health Studies (Romieu et al., 1989) and by Hunter et al. (Hunter et al., 2010).

Another meta-analysis (Kahlenborn et al., 2006) found that HC use was associated with 29% higher breast cancer risk in parous women (OR 1.29, 95% CI, 1.20–1.40), 24% higher risk in nulliparous women (OR 1.24, 95% CI 0.92–1.67) and 19% higher risk in women younger than 50 years (OR 1.19, 95% CI 1.09–1.29). In parous women who used OCs before their first full-term pregnancy, risk for breast cancer increased by 44% (OR 1.44, 95% CI 1.28–1.62), and by 52% if OC use lasted for four or more years (OR 1.52, 95% CI 1.26–1.82).The relative risk of BC progressively disappeared within 10 years of HC discontinuation or was mainly confined to the use before the first pregnancy.

In a recent study (Lovett et al., 2017) examining variation in hormonal exposure across seven combined oral contraceptive (COC) formulations, exposure of ethinil estradiol was not different from the physiological, while exposure from OC progestins ranged from one sixtieth to 8-fold median endogenous progesterone over 28 days.

Some trials have studied the occurrence of different subtypes of BC: triple-negative breast cancer (TNBC) is a unique subtype of breast cancer resistant to endocrine and targeted therapy, that usually relapses early, progresses rapidly and is associated with a poor prognosis. In a meta-analysis (Li et al., 2017) women who use HC have a greater risk of TNBC compared with women who do not (OR = 1.31, 95% CI = 1.18–1.45; Z = 5.26, P < 0.00001), further confirmed by the case-control comparison using the healthy population as the control arm (OR = 1.21, 95% CI = 1.01–1.46; Z = 2.04, P = 0.04).

Current combined HC users for more than 5 years and ages 20–39 years in a recent case-control study had an increased risk for oestrogen-receptor negative (ER^-) and triple-negative breast cancer (ER^-: OR 3.5, 95% CI 1.9–9.0; triple-negative: OR 3.7, 95% CI 1.2–11.8) (Beaber et al., 2014).

A systematic review (Gierisch et al., 2013) of 44 breast, 12 cervical, 11 colorectal, and 9 endometrial cancer studies concluded that breast cancer incidence was slightly, borderline, significantly increased in users (OR, 1.08; CI, 1.00–1.17). In a sensitivity analysis of only U.S.-based studies, effect sizes were smaller and no longer statistically significant (OR, 1.03; CI, 0.93–1.14).

Concerning women at high risk for BC, such as those carrying a mutation in genes BRCA1 and/or BRCA2, they may have a small increase in the risk of BC (Brohet et al., 2007) counterbalanced by the reduction in the risk (≤ 54%) of ovarian cancer (OC) in these individuals (Cibula et al., 2010).

A retrospective cohort study (Grandi et al., 2017) reviewed data from 2527 women (4.5% BRCA mutation carriers, 72.2% high risk, and 23.3% intermediate risk using the Modena criteria and the Tyrer-Cuzick model). The use of HC was not associated with an increased risk of breast cancer (cumulative hazard: never used, 0.17; HC users, 0.20; P = .998), regardless of the duration of use (cumulative hazard: never used, 0.17, used < 5 years, 0.20; used 5–10 years, 0.14; used > 10 years, 0.25; P = .414). This was confirmed for the different risk groups when interacted in a Cox proportional hazard regression model. The ethinyl estradiol (EE) dose did not influence the risk of BC (cumulative hazard, 2.37; 95% confidence interval, 0.53–10.1; never used, 0.18; EE < 20 μg used, 0.04; EE ≥ 20 μg used, 0.16; P = .259). The types of progestins used might influence the risk, with some, such as gestodene (P = .028) and cyproterone acetate (P = .031), associated with an even greater reduced risk.

The formulation of HC seems to play a relevant role, especially when medicated IUD are compared with oral administration. The associations between the levonorgestrel-only oral formulation and the levonorgestrel-releasing intrauterine device (LNG -IUD) and breast-cancer risk were positive in the study by Morch, but not in other trials.

A post-marketing survey in a sample of 17,360 Finnish women aged 30–54 years using LNG–IUD (Backman et al., 2005) found no difference in breast cancer incidence in this cohort compared to the age-specific incidence in the average Finnish female population of same age as derived from the Finnish Cancer registry. There was no indication of a difference in breast cancer incidence between LNG–IUD users and average Finnish female population in any age group. Within the limitations of this study, the results are compatible with the absence of an elevated breast cancer risk in LNG–IUD users.

A large case-control study (Dinger et al., 2011) found no increased risk for breast cancer associated with LNG–IUD compared to copper IUDs. It included a total of 5113 cases (women ≤50 years of age) and 20,452 matched controls in Finland and Germany matched by year of birth and area of residence. No increased risk for breast cancer was found in ever users, or current users. Use of LNG–IUD was not associated with a higher risk of invasive breast cancer with regional or distant metastases. Thus, no indications for tumor promotion or tumour induction were found in this study.

In 2014, Soini et al. (2014) published the results of a database study on cancer incidence and LNG-IUS use, including incidence of breast cancer, in Finnish population. The standardized incidence ratio (SIR) for endometrial, ovarian, pancreatic, and lung cancers were statistically significantly lower in LNG–IUD users, compared to the general female population. While for breast cancer there was a slightly increased SRI among Finnish women aged 30–49 years who used for LNG-IUS for menorrhagia. The authors themselves remarked that the breast cancer results "should be interpreted with caution in light of the limitations of the study."

A case-control analysis was performed on data from Finnish participants of a cross-sectional 'Women's Health and Use of Hormones' survey (WHH survey) looking at use of external hormones and breast cancer risk (Heikkinen et al., 2016). 5927 women with a history of breast cancer identified via the Finnish Cancer Registry, and 19,633 controls identified via the Finnish Central Population Register. LNG IUD users below 50 years of age do not show an increased risk for breast cancer in line with the results of the study published by in 2011 (Dinger et al., 2011).

A case-control study (Lyytinen et al., 2010) on hormonal therapy as a risk for breast cancer was carried out using data from the Finnish population register. Cases (n = 9956) were women at the age of 50–62 years diagnosed with invasive breast cancer between 1995–2007, and the matched controls were women of same age. The adjusted OR for invasive breast cancer in postmenopausal women using LNG–IUD was 1.53 (95%CI 1.33–1.75), and for LNG -IUD + estrogen replacement therapy (ERT) was 2.07 (95%CI: 1.78–2.41), both statistically significant. However, the study has important limitations which prevent meaningful conclusions based on the presented results: the study could not control for important confounders such as age at menarche, age at menopause, body weight, family history of breast cancer, or socio-economic status. Women at higher risk may have been preferentially prescribed this method, leading to a selection bias. Authors state that "Chance of prescription bias of LNG-IUS may have contributed to the excess risk for breast cancer in our study." There was a high degree of under-estimation of LNG IUS exposure in the study population. The study did not control for the fact that women who have used LNG–IUD after the diagnosis of breast cancer (e.g. continued use of a previously inserted device after diagnosis, or started the use of LNG–IUD for endometrial protection during tamoxifen therapy) would have inevitably been classified as "exposed cases". Thus, such use could have caused an overestimation of breast cancer risk.

Finally, this study was conducted on women of peri-menopausal age, and therefore has limited implications on the risk of BC caused by HC.

4. Discussion

In this part we will analyse data already listed in detail in the "result" section and we will provide an appraisal of evidence especially when results of the different studies are non-consistent or even contradictory.

4.1. Summary of new data about breast cancer effect of hormonal contraceptives

New data about breast cancer risk of hormonal contraception are in line with what was previously known but need to be analysed and put in contest to appropriately counsel patients (Hunter, 2017). These are the main subjects of discussion.

4.2. A slight increase in breast cancer in hormonal contraception users is biologically plausible

Both oestrogen and progesterone have a stimulatory effect on cell proliferation in the breast, potentially via breast tumour stem cells (Finlay-Schultz and Sartorius, 2015).

Natural oestrogens (estrone and estradiol) are reported to be mutagenic and carcinogenic through a genotoxic mechanism–formation of depurinating oestrogen-DNA adducts by the reaction of catechol oestrogen quinones with DNA (Cavalieri and Rogan, 2014).

The International Agency for Research on Cancer IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2007) in 2007 concluded that there was sufficient evidence to establish the carcinogenicity of combined oral oestrogen–progestin contraceptives in humans, with an increased risk of breast cancer limited to women who were currently using or had recently used them.

4.3. The magnitude of risk found in newer studies is in agreement with the older ones

The magnitude of the relative risk of the association between the current use of HC and BC is well established and not changed. The relative risk of 1.2 in the current analysis by Morch study (Morch et al., 2017) is the same reported by the Collaborative Group on Hormonal Factors in Breast Cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 1996) where the risk of BC was 1.24 and similar of previous prospective studies such as the Nurses' Health Studies (Hunter et al., 2010; Romieu et al., 1989).

In the meta-analysis published by Kahlenborn et al. (2006) HC use was associated with an increase in breast cancer that varied according to parity status. The increase in risk however progressively disappeared within 10 years of HC discontinuation or was mainly confined to the use before the first pregnancy.

4.4. Newer hormonal contraceptives with a lower estrogen to progestogen potency seem to have the same breast cancer risk as older products

The really innovative finding in the study by Morch et al. (2017) is that there is an increase in BC even with contemporary formulations of HC, and the increase is similar to what had been described for older formulations. Previous data were based on the use of often higher oestrogen dose formulations and most progestins used tended to be more androgenic. Oestrogen potency has declined but progestogen effect, which contributes most to contraceptive efficacy, has not been reduced as much. These data seem to indicate an important or maybe even prevalent role of the progestogen component of HC on BC risk. In a recent study (Lovett et al., 2017) examining variation in hormonal exposure across seven combined oral contraceptive (COC) formulations, exposure of ethinyl estradiol was not different from the physiological range, while exposure from OC progestins ranged from one sixtieth to 8-fold median endogenous progesterone over 28 days.

The most important subgroup analyses in the study by Morch et al. (2017) involved the risks associated with the various formulations used, particularly different progestins. Although there are some differences in the relative risks, all the confidence intervals overlap the consensus estimate of 1.20. Thus, these results seem to suggest that no particular preparation is free of risk. Notably, the associations between the levonorgestrel-only oral formulation and the levonorgestrel-releasing intrauterine device (IUD) and breast-cancer risk were positive.

4.5. Different HC seem to have a different effect on the various BC subtypes

Breast cancer actually encompasses diverse subtypes with very different clinical behaviour: oestro-progestin contraceptives seem to increase the risk of ER and PR negative breast cancers, while progestogen only formulations may increase ER and PR positive BC.

Triple-negative breast cancer (TNBC) is a unique subtype of breast cancer resistant to endocrine and targeted therapy, usually relapses early, progresses rapidly and is associated with a poor prognosis. Li et al. (2017) showed that HC may increase the risk of TNBC and similar results were obtained in a case-control study not only for TNBC but more generally for ER-BC (Beaber et al., 2014). In the Norwegian Women and Cancer study (NOWAC) (Busund et al., 2018) combined HC use was associated with ER- and ER-/PR- cancer, but POC use beyond five years was associated with an increase in ER + but not with ER- cancers.

4.6. Different formulations of HC may have different effects

Levonorgestrel-releasing intrauterine devices (LNG -IUD) are used both for contraception and to control endometrial polyps and bleeding. Results may therefore differ according to the indication and to the age of women.

A large case-control study (Dinger et al., 2011) found no increased risk for breast cancer associated with LNG–IUD compared to copper IUDs. Similar results were obtained by a database study (Soini et al., 2014): the standardized incidence ratio (SIR) for endometrial, ovarian, pancreatic, and lung cancers were lower in LNG–IUD users, compared to the general female population. An increase in breast cancer was a only observed among women aged 30–49 years who used LNG-IUS for menorrhagia. The study authors themselves urge that the breast cancer results “should be interpreted with caution in light of the limitations of the study”. No increase was seen in a case-control study on Finnish women (Heikkinen et al., 2016): LNG IUD users below 50 years of age did not show any increase in breast cancer, and this confirmed previous data published in 2011 (Dinger et al., 2011).

In a case-control study (Lyytinen et al., 2010) on hormonal therapy as a risk for breast cancer the OR for invasive breast cancer in post-menopausal women using LNG–IUD was 1.53 (95%CI 1.33–1.75), and for LNG -IUD + estrogen replacement therapy (ERT) was 2.07 (95%CI: 1.78–2.41), both statistically significant. This however seems to have limited importance in the present analysis which focuses on HC and therefore on younger, premenopausal women.

In peri-menopausal women, LNG-IUS was not associated with an increased total risk of BC, although in the subgroup of women in their early 40′s, it was associated with a slightly increased risk for invasive tumors (Siegelmann-Danieli et al., 2018). No difference in BC incidence was observed in 17,360 Finnish women aged 30–54 years using LNG–IUD (Backman et al., 2005).

Concerning the oral formulation of LNG and breast-cancer risk there was a positive association in the study by Morch, but this is not confirmed by other data.

4.7. Duration response effects of HC on BC is confirmed but risk persistence beyond five years is not conclusive

In the study by Morch et al. (2017) the duration–response association of HC on BC was observed and significant among women younger than 35 years of age and among nulliparous women. There was a suggestion that risk may persist more than 5 years after discontinuation of HC among women who had used HC for at least 5 years, but this should be regarded as preliminary. The increased risk would not have been significant with adjustment for multiple comparisons involving different categories of duration and time since last use.

It therefore appears that the excessive risk will diminish with time and will go back to baseline: this will happen after 5 years for shorter use of HC and after 10 years for women using HC for a longer time.

4.8. Surveillance bias could partly explain new results too

The increase of breast cancer may be partly contributed to by the increased number of visits to healthcare providers observed in users of HC in comparison with non-users of contraception. This may be associated with more careful cancer screening and therefore diagnosis, although the authors argue that this would not fully explain the association.

4.9. The study by Morch found that hormonal contraceptives are associated with only one extra breast cancer for every 7690 users a year

The relative risk of breast cancer in the Danish study (Morch et al., 2017) was 20% higher among women who currently or recently used contemporary hormonal contraceptives than among women who had never used them. However, for counselling purposes absolute numbers are better understood: the absolute increases in breast cancer risk in the above-mentioned study was small, only one extra breast cancer for every 7690 women using HC for one year.

This is particularly true for younger women: under 35 years of age the excess of BC was 2 cases in 100.000/year (Peachman, 2018).

4.10. Other recent studies and meta analyses found an overall neutral breast cancer risk

The Centers for Disease Control and Prevention (CDC) case–control study reported by Marchbanks et al. (2002) showed no significant increase in BC risk. The age range of women involved in that study was quite wide (35–64 years) and the upper bound of the 95% confidence interval for current users of 1.3 includes the relative risk of 1.20 in the study by Morch et al. (2017).

A Systematic Review (Gierisch et al., 2013) of 44 breast, 12 cervical,

11 colorectal, and 9 endometrial cancer studies concluded that breast cancer incidence was slightly increased in users (OR, 1.08) but less than in Morch study (1.20). In a sensitivity analysis of only U.S.-based studies, effect sizes were smaller and no longer statistically significant (OR, 1.03; CI, 0.93–1.14). On the basis of the point estimates of the meta-analyses, the approximate increase in estimated lifetime absolute risk of breast cancer from ever use of oral contraceptives is 0.89% (NNH, 113). In this systematic review, contrary to Morch study, no time-dependent relationship was found as a function of duration of use: 1–12 months (OR, 0.95; CI, 0.83–1.09); 13–60 months (OR, 1.03; CI, 0.92–1.15); 61–120 months (OR, 1.01; CI, 0.90–1.13); and > 120 months (OR, 1.04; CI, 0.93–1.17). Heterogeneity was significant (t = 5.84, 19 DF, P < 0.0001).

A time-dependent relationship as a function of time since last oral contraceptive use, with higher risk associated with more recent use of oral contraceptives and ORs that approach 1 (no effect) by ≥20 years of use: 0–5 years (OR, 1.21; CI, 1.04–1.41); 5–10 years (OR, 1.17; CI, 0.98–1.38); 10–20 years (OR, 1.13; CI, 0.97–1.31); > 20 years (OR, 1.02; CI, 0.88–1.18). Heterogeneity was significant (σ = 0.12; t = 4.95, 11 DF, P = 0.0004).

The strength of evidence for the effect of ever oral contraceptive use on breast cancer incidence was moderate in the review by Gierisch et al. (2013). Most studies were of good or fair quality, exhibited consistent findings, and confidence interval for summary estimate were precise. All included studies were observational and the strength of evidence was low for both duration of use and time since last use for risk of breast cancer incidence, with a high level of heterogeneity across studies.

4.11. HC seems not to increase breast cancer even in women at a higher baseline risk

Hormonal contraceptive use does not increase the risk of BC in a population of women with a family history (first- or second-degree relatives), so much that in fifth edition of the Medical Eligibility Criteria for Contraceptive Use the WHO expert working group determined that the use of HC should not be restricted for such higher BC risk women (World Health Organization, 2015).

Those with a documented genetic mutation such as and BRCA2 have a possible and controversial, small increase in the risk of BC (Brohet et al., 2007) counterbalanced by the reduction in the increased risk (≤54%) of ovarian cancer (OC) in these individuals (Cibula et al., 2010).

A retrospective cohort study (Grandi et al., 2017) reviewed data from 2527 women. The use of HC was not associated with an increased risk of breast cancer (cumulative hazard: never used, 0.17; HC users, 0.20; P = .998), regardless of the duration of use. This was confirmed for the different risk groups when interacted in a Cox proportional hazard regression model. The ethinyl estradiol (EE) dose did not influence the risk of BC while the type of progestins might influence the risk, with some, such as gestodene (P = .028) and cyproterone acetate (P = .031), associated with an even greater reduction in risk.

The same applies to older premenopausal women that have an age-related higher risk of breast cancer which is not increased by HC (Tepper et al., 2018)

4.12. No solid data can help choosing the safest hormonal contraception

Most of the HC studied contain ethinyl estradiol and only recently some of them use estradiol. The progestogens used are so different in mineralocorticoid, glucocorticoid and androgenic effect that a differential breast cancer effect is expected. Breast tissue produces estrogens and this is a further possible mechanism by which HC can change BC risk. According to *in vitro* data, oestrogen production by breast tissue seems to be reduced with some progestogens (Del Pup et al., 2014), but the clinical significance of this is not known. So it is not possible to help clinicians identify the best product.

In the study by Morch et al. (2017) various formulations used, particularly of different progestins, had some differences in the relative risks, but all the confidence intervals overlapped the overall estimate of 1.20. Randomized comparative clinical data are not available, so it is not yet possible to draw conclusions on which are the safer estrogen or progestogen components of HC in terms of BC risk.

4.13. It is still controversial if levonorgestrel IUD is associated with breast cancer risk

The associations between the levonorgestrel-only oral formulation and the levonorgestrel-releasing intrauterine device (LNG-IUD) and breast-cancer risk were positive in the study by Morch, but this is not confirmed by other data.

A post-marketing survey in a sample of 17,360 Finnish women aged 30–54 years using LNG–IUD (Backman et al., 2005) found no difference compared to the average Finnish female population of similar age and there was no indication of a difference in breast cancer incidence in any age group. Within the limitations of this study, the results are compatible with the absence of an elevated breast cancer risk in LNG–IUD users.

A large case-control study (Dinger et al., 2011) found no increased risk for breast cancer associated with LNG–IUD compared to copper IUDs. In 2014, Soini et al. (2014) published the results of a database study on cancer incidence and LNG–IUD use, including incidence of breast cancer. The standardized incidence ratio (SIR) for endometrial, ovarian, pancreatic, and lung cancers were statistically significantly lower in LNG–IUD users, compared to the general female population. While for breast cancer there was a slightly increased SRI among Finnish women aged 30–49 years who used for LNG–IUD for menorrhagia. The study authors themselves urge that the breast cancer results "should be interpreted with caution in light of the limitations of the study."

A publication by Heikkinen et al. (2016) describes a case-control analysis. LNG–IUD users below 50 years of age did not show an increased risk for breast cancer in line with the results of the study published by Dinger et al. in 2011 (Dinger et al., 2011).

In peri-menopausal women, LNG–UD was not associated with an increased total risk of BC, although in the subgroup of women in their early 40′s, it was associated with a slightly increased risk for invasive tumors (Siegelmann-Danieli et al., 2018).

4.14. Lifestyle improvements can reduce breast cancer risk counterbalancing hormonal contraception breast effects

There are some conditions that may increase BC risk in young women. Lifestyle improvements can reduce BC risk counterbalancing the effects of HC on breast cancer risk. As an example, obese women have a greater risk of premenopausal triple negative breast cancer (TNBC) than non-obese women (Pierobon and Frankenfeld, 2013). In the pre-menopausal group OR was 1.43 (95% CI: 1.23–1.65). So the already mentioned possible increase in triple negative breast cancer (TNBC) risk by HC could be reduced and counterbalanced by normalizing body weight in premenopause. This is very important considering the worse prognosis of TNBC and the overall multiple health benefits.

Exposure to sunlight or vitamin D supplement may play an important role cancer diseases too (Trummer et al., 2016). Higher blood 25(OH) vitamin D levels are associated with a reduced breast cancer risk and mortality (Chen et al., 2013; Kim and Je, 2014; Yin et al., 2013) and this suggestion could help counterbalancing BC HC induced risk and have multiple health benefits as well. Vitamin D receptor (VDR) controls the expression of genes that regulate breast cell proliferation, differentiation, and apoptosis. Vitamin D deficiency is associated with poor breast cancer prognostic features (de Sousa Almeida-Filho et al., 2017) as insufficient and deficient level of vitamin D were significantly associated with negative oestrogen receptor (OR 3.77 CI

95% 1.76–8.09 and OR 3.99 CI 95% 1.83–8.68), high Ki-67 (OR 2.50, CI 95% 1.35–4.63, and OR 2.62, CI 95% 1.40–4.98), and positive axillary lymph node status (OR 1.59, CI 95% 1.03–2.33, and OR 1.58, CI 95% 1.02–2.92) respectively. In a case control study (Sofi et al., 2018) women with serum 25(OH)D levels less than 20 ng/ml had higher odds of having BC [2.4 (1.2–5.1)] and those with calcium levels less than 10.5 mg/dl had an even higher risk [3.7 (1.5–8.8)].

4.15. The use of oral contraceptives is associated with substantial reductions in the risks of endometrial cancers

A systematic review Gierisch et al. (2013) showed that endometrial cancer is reduced by HC use (OR, 0.57; CI, 0.43–0.77) even if heterogeneity was significant ($Q = 26.11$, 6 DF, $P < 0.001$). Only one study was conducted with patients from the United States and reported a somewhat greater protective effect than summary estimates for all studies (OR, 0.34; CI, 0.25–0.47). On the basis of the point estimates of the meta-analyses, the approximate decrease in absolute risk of endometrial cancer is 1.77% (NNT 60).

The reduction in endometrial cancer is strong and acknowledged in all literature (Mueck et al., 2010). LNG–IUD particularly reduces endometrial cancer risk so much that it is used to treat atypical endometrial hyperplasia and early cancer in women desiring to preserve the uterus.

4.16. The use of oral contraceptives is associated with substantial reductions in the risks of tubal and ovarian cancers

According to the Collaborative Group on Epidemiological Studies of Ovarian Cancer (Collaborative Group on Epidemiological Studies of Ovarian Cancer et al., 2008). The longer women used oral contraceptives, the greater the reduction in ovarian cancer risk ($p < 0.0001$). This reduction in risk persisted for more than 30 years after oral contraceptive use had ceased but became somewhat attenuated over time-the proportional risk reductions per 5 years of use were 29% (95% CI 23–34%) for use that had ceased less than 10 years previously, 19% (14–24%) for use that had ceased 10–19 years previously, and 15% (9–21%) for use that had ceased 20–29 years previously. Ten years use of oral contraceptives was estimated to reduce ovarian cancer incidence before age 75 from 1.2 to 0.8 per 100 users and mortality from 0.7 to 0.5 per 100. For every 5000 woman-years of use, about two ovarian cancers and one death from the disease before age 75 are prevented.

Ovarian cancer incidence was significantly reduced in HC users (OR [odds ratio], 0.73; 95% CI 0.66 to 0.81), with greater reductions seen with longer duration of use (Havrilesky et al., 2013).

4.17. The global cancer effect of HC seems neutral or slightly protective

HC use increases risk of breast cancer but reduces risk of ovarian, endometrial, and colorectal cancer in the most relevant studies (Cibula et al., 2010; Gierisch et al., 2013; Havrilesky et al., 2013). Cancer outcomes associated with ever vs. never use of oral contraceptives in the Royal College of General Practitioner's Oral Contraception Study among 46,000 U.K. women (mean age, 29) who were followed for up to 36 years (1968–2004) confirms an overall OR = 0.88 (0.83 − 0.94) (Iversen et al., 2017). Bassuk and Manson (2015) calculated that the net effect of the use of HC for 5 years or longer is associated with a slight reduction in the total risk of cancer. Data from the recent literature are summarized in Table 2. Results are difficult to compare as they come from different sources, populations and HC use but they are all reassuring.

HC could increase the risk for cervical cancer (Iversen et al., 2017) the associations observed may be due to the fact that sexually active women are more likely not to use barrier methods, having intercourses and are also more likely to contract human papilloma viruses (HPV) that causes cervical cancer. An increased risk of cervical cancer that was seen only in current and recent users appeared to be lost within approximately 5 years of stopping oral contraception, as for breast cancer. While the protective effects on endometrial, ovarian and colorectal cancer last much longer.

HC could also increase risk for hepatic adenomas and liver cancer, in women at low risk for HBV infection. High risk of bias and /or small numbers preclude precise effect estimates so cervical and liver cancer are not included in Table 2 and they are supposed not to change significantly in the overall global cancer estimates.

4.18. Younger HC users without contraindications have a beneficial global benefit to risk ratio

An important subject to discuss at the end of counseling is the reassuring neutral to slightly protective global cancer risk of HC and the global health benefits to risks ratio that should be tailored according to each individual situation and described in simple terms (Del Pup and Becorpi, 2018).

Women younger than 35 years may be scared of breast cancer but have a very low baseline risk. If using HC their absolute increase in risk, according to Morch data, is only 2 additional breast cancer diagnoses for every100000 women per year.

Current HC use risk is not an oncological, but mostly a thrombotic issue. HC increases venous thromboembolism and ischemic stroke, but that risk is negligible if HC is properly used and avoided when contraindicated. Age and lifestyle heavily impact on the risk benefit ratio. HC has important quality of life and health benefits that shoud be considered during counselling. They prevent unwanted pregnancies and confer noncontraceptive benefits, including treatment of menstrual cycle irregularity, heavy menstrual bleeding, premenstrual syndrome, perimenopausal vasomotor symptoms, and acne or hirsutism.

5. Counselling strategies to put breast cancer risk in perspective

The fear of BC risk after hormonal contraceptives can be discussed with potential users using these evidence based arguments, according to the literature review, summarized in Table 1.

A complete knowledge of results published in the literature is essential in order to give a correct information. Advantages and risks associated with HC should be carefully discussed with every woman: in

Table 1
Topics to guide counselling about breast cancer (BC) effect of hormonal contraceptives (HC).

A slight increase in breast cancer in HC users is biologically plausible
The magnitude of risk found in newer studies is low and in agreement with the older ones
Newer hormonal contraceptives with a lower estrogen to progestogen potency seem to have the same BC risk as older products
Different preparations seem to have a different effect on the various breast cancer subtypes
Duration response effects of HC on BC is confirmed but risk persistence beyond five years is not conclusive
Surveillance bias could partly explain new results too
The study by Morch found that HC is associated with only one extra breast cancer for every 7690 users a year
Other recent studies and meta analyses found an overall neutral BC risk
HC seems not to increase BC even in women at a higher baseline risk
No solid data can help choosing safest HC in terms of breast cancer risk
It is still controversial if levonorgestrel intrauterine systems are associated with BC risk
Lifestyle improvements can reduce BC risk counterbalancing the effects of HC
The use of oral contraceptives is associated with substantial reductions in the risks of endometrial cancers
The use of oral contraceptives is associated with substantial reductions in the risks of tubal and ovarian cancers
The global cancer effect of HC seems neutral or slightly protective
Younger HC users without contraindications have a beneficial global risk /benefit ratio

Table 2
Summary of main cancers risk in hormonal contraception: a quantitative guide to counseling.

	Summary of main studies OR (95% CI)	Royal Practitioner 2007 OR (95% CI)	Royal Pratictioner 2017 OR (95% CI)	Attributable risk (+) or Preventive fraction (−) %	NNH (+) or NNT (−)	absolute risk of cancer %
Breast	1.08 (1.00–1.17)	0.98 (0.87–1.10)	1.04 (0.91–1.17)	+3	113	0.89
Endometrium	0.57 (0.43–0.77)	0.58 (0.42–0.79)	0.66 (0.48–0.89)	−34.3	−60	1.77
Ovarian	0.73 (0.66–0.81)	0.54 (0.40–0.71)	0.67 (0.50–0.89)	−33.6	NA	0.54
Colorectal	0.86 (0.79–0.95)	0.72 (0.58–0.90)	0.81 (0.66–0.99)	−19.1	−132	0.76
Global cancer risk		0.88 (0.83–0.94)	0.96 (0.90, 1.03)	−4.2		−2.18
References	1–3	4	5	5		1-3, 6

References:
1 (Cibula et al., 2010).
2 (Gierisch et al., 2013).
3 (Havrilesky et al., 2013).
4 (Hannaford et al., 2007).
5 (Iversen et al., 2017).
6 (Bassuk and Manson, 2015).
NNT (number needed to treat) and NNH (number needed to harm) from Gierisch 2013. NA= not assessed.

some studies there is an increase in BC (statistically significant but numerically very small) but this is not evident in all studies. On the other hand HC reduces the risk of ovarian cancer (which has a much higher lethality than breast cancer) and of endometrial cancer. Furthermore this discussion may be a favourable situation to encourage women to adopt lifestyle behaviours (stop smoking, doing physical activity, losing weight) that may not only reduce breast cancer risk but also have a protective effect toward many other neoplastic and non-neoplastic diseases.

Conflict of interest

The authors declare that they have no conflict of interest related to the subject of the present paper.

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