Gynecological Endocrinology

ISSN: 0951-3590 (Print) 1473-0766 (Online) Journal homepage: https://www.tandfonline.com/loi/igye20

Hormonal contraception and risk of breast cancer: a critical look

Patricio Barriga, Paula Vanhauwaert & Arnaldo Porcile

To cite this article: Patricio Barriga, Paula Vanhauwaert & Arnaldo Porcile (2019): Hormonal contraception and risk of breast cancer: a critical look, Gynecological Endocrinology, DOI: 10.1080/09513590.2019.1576610

To link to this article: https://doi.org/10.1080/09513590.2019.1576610

Published online: 26 Feb 2019.

GYNECOLOGICAL ENDOCRINOLOGY
https://doi.org/10.1080/09513590.2019.1576610

Taylor & Francis
Taylor & Francis Group

REVIEW

Hormonal contraception and risk of breast cancer: a critical look

Patricio Barriga[a], Paula Vanhauwaert[b] and Arnaldo Porcile[c]

[a]School of Medicine, Finis Terrae University, Santiago, Chile;[b]Gynecologist, Clinica Alemana de Santiago, Santiago, Chile;[c]Faculty of Medicine, Universidad de Chile, Santiago, Chile.

ABSTRACT

Today health professionals are not only required to know medicine, but scientific reading, interpretation, and communication of new data. The new information about contraception and hormonal therapies must be analyzed by gynecologists to determine whether or not the new data are applicable to their patients and if it has an impact on their health. Recently a new study of hormonal contraceptives and the risk of breast cancer was published. In this study, the investigators found an elevation of the relative risk of breast cancers on the users *versus* the nonusers of hormonal contraception. After analyzing the publication and other data available, it is our opinion that it is a very low increase of the risk and its impact should be evaluated case by case, not forgetting to take into account the numerous beneficial effects that hormonal contraception have.

ARTICLE HISTORY
Received 11 June 2018
Accepted 13 December 2018
Published online 22 February 2019

KEYWORDS
Hormonal contraception; breast cancer; breast cancer risk

In the care of women, the health professional must make multiple decisions, for which analyzes the information from scientific publications in relation to these matters. In this way, he considers the risks and benefits of each action and work in the way that he considers most beneficial for his patient.

This analysis of information is not always easy, since articles often use epidemiological and statistical language, which must be translated and interpreted to determine if this or that effect, recently discovered, has an impact on the patient or not. Moreover, even in well-designed clinical studies, some authors have failed to show the real impact that their observations have for women [1,2] and the responsibility to detect this rests with clinicians.

Studies on the effects of the use of hormonal contraception (HC) or menopausal hormone therapies (MHT) are written in this language; this is how the need arises, for professionals dedicated to the care of women, to work not only in clinical aspects but also in the analysis, understanding and interpretation of statistical and epidemiological analyzes and in communicational aspects that allow to transmit their knowledge to his patients and the public.

In relation to the subject that brings us together, breast cancer is the main cancer in women worldwide and the most common cause of cancer mortality among women [3].

In 2017, a study was published that analyzes the possible relationship between breast cancer and contraceptives. This is a Danish observational study [4] that addresses the relationship between the risk of breast cancer and hormonal, combined and progestin-only formulations of contraception, including the newer.

This study describes an overall increase of approximately 20% in the relative risk of developing breast cancer when using hormonal contraceptives (HCs) of any type and states that this risk increases up to 38% when the use extends for 10 years or more. Finally, it argues that risk is maintained throughout the time of use of the HC. Once contraceptive is suspended, risk takes at least 10 years to return to the baseline risk of the user before starting.

Relative risks are statistical parameters that represent only that, an association of 'risk', and not a certainty. There are other known risk factors, in fact it is estimated that 21% of all deaths from breast cancer registered in the world are attributable to alcohol consumption, overweight and obesity, and lack of physical activity [5]. This relationship is more important in high-income countries (27%), where the most important factor is overweight and obesity. In low and middle income countries, the proportion of breast cancers attributable to these risk factors is estimated at 18% and the lack of physical activity is the most important determinant (10%). However, many women do not develop breast cancer, or it is investigated in early stages susceptible to curative treatment, if they comply with prevention strategies of each country.

It is not the first time that the association of the use of HC and breast cancer is studied. Several studies have addressed the issue and the results have been disparate.

A study published in 2006 [6] that considered prescriptions prior to 2010, described a slight increase in breast cancer, especially in those women who use them before the first term pregnancy.

In 2010, a study analyzed the risk of death from all causes in more than 46,000 female users *versus* non-users of HCs that were followed for 39 years. This one did not find difference in the risk of dying from breast cancer to these women [7].

In 2014 [8] another study that analyzed the risk of death after 36 years of follow-up in 121,000 female users *versus* non-users of contraceptives also found no significant difference of dying from breast cancer.

A Japanese study [9] that included more than 12,000 women between 20 and 69 years of age who underwent breast screening between 2007 and 2013, describes that after adjusting the data for parity, family history of breast cancer and breastfeeding,

CONTACT Patricio Barriga pbarriga@uft School of Medicine, Finis Terrae University, Santiago, Chile

premenopausal women who were using combined oral contraceptives (COC) at that time had fewer risks than non-users.

Other studies have shown a slightly increased risk of earlier diagnosis of breast cancer in women who carry mutations in the *BRCA1* and *BRCA2* genes for hereditary breast cancer when they start contraception before age 25, but there is also a decrease significant risk of ovarian cancer, which is increased in this group of women, as well as in the general population of women.

It is so, that the eligibility criteria for the use of contraceptives of WHO continues to classify the use of HCs in this population at risk as category 1, because the evidence does not suggest an increased risk of breast cancer among women with either family history of breast cancer or bearer of increased susceptibility genes for this, are modified by the use of COC [10].

It is important to keep in mind that breast cancer is rare in women under 40, regardless of whether or not they use HCs.

Also known is the fact that combined hormonal contraceptives (HCA) would be associated with a reduction in colon and endometrial cancer [11]. In the latter, progestogens with the Levonorgestrel Intrauterine Release System (IUS-LNG) have even shown special protection to proliferative disorders of the endometrium with atypia and that are precursors of endometrial adenocarcinoma [12,13].

The available scientific information is conclusive in pointing out that the use of CHC is associated with lasting protection, for decades, of a lower incidence of ovarian and uterine cancer, even after women stop using them. It is not risky to assume that CHC are associated with the prevention of more cancer than those that could be imputed to them.

Although the strength of Danish study focuses on the large cohort analyzed, which comprises 1.8 million women who are followed through the excellent national records, which include information on prescription drugs, breast cancer diagnoses, and some clinical characteristics of women, it also has limitations. Although the researchers provide information on clinical characteristics such as age, education, parity, and certain information about a family history of cancer, they do not include information about other known factors of breast cancer or other confounding factors; moreover, no reference is made to breast cancer screening, be it breast self-examination or mammography. Regarding the latter, breast cancer surveillance policies may be different for women who are in a medical record system and who receive prescribed hormonal treatments *versus* those who do not.

Besides, we must consider the very small absolute baseline risk of breast cancer in the population studied. These are women under 50 years old.

In this population, there were approximately 1.3 additional cases of breast cancer per 10,000 women per year who used HCs, equivalent to about one extra case of breast cancer per year for every 7690 users of HC.

For all the above, although the Danish work [4] constitutes a contribution to knowledge, the findings must be analyzed critically and with caution. The presence of some methodological limitations must be considered and the absolute risks for breast cancer that were identified are very low, in terms of clinical impact.

In general, meta analyzes [14–18] do not suggest an increase in total cancer or total mortality in women taking HCs, but rather highlight the little evidence to distinguish the effect of different formulations of COC. Patients tend to use more than one type of COC throughout their lives and there is a lack of studies that evaluate the 'accumulated dose' in life of the hormonal component of the contraceptives studied.

In addition, when prescribing a HC, both risks and benefits must be balanced. HC is a very effective form of contraception that allows women to control their fertility. Pregnancy and childbirth in themselves are not without risks. For example, during pregnancy there is an increased risk of thrombosis, particularly pulmonary embolism, and maternal mortality rates are appreciable. In developed countries, mortality rates average between 2 and 3 per 10,000 live births, and in low-income countries, rates are approximately 10 times higher [19].

The introduction of the 'contraceptive pill' more than 50 years ago, meant a reduction of unplanned pregnancies, better birth control and with it a reduction in the morbidity and mortality associated with pregnancy, childbirth, and puerperium, as well as a decrease in maternal mortality associated with unsafe abortion [20]. These effects also had an impact on the development of women beyond motherhood.

It is a challenge for researchers and epidemiologists to express in the best possible way the risks and benefits that can affect a population when it is operated for health reasons. As an example, in studies for MHT and risk of breast cancer, new statistical analyzes have shown that it is safe and with a very low clinical impact of events considered adverse [21].

It is concluded that new analyzes of this and other studies are needed using new complementary statistical methods [22–24] that allow clinicians to better evaluate the most recent formulations of contraceptives when users reach the age of highest incidence of breast cancer (40–60 years).

It is essential to bear in mind that before the decision to use HC, this must be preceded by careful counseling, evaluating the benefits *versus* the risks of the different methods of contraception, including the other options that do not involve hormonal contraception, so that they can opt in informed way to the method that best suits to their wishes and needs.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Patricio Barriga http://orcid.org/0000-0002-3494-7556

References

[1] Bassuk SS, Manson JE. Oral contraceptives and menopausal hormone therapy: relative and attributable risk of cardiovascular disease, cancer, and other health outcomes. Ann Epidemiol. 2015;25:193–200.
[2] Manson JE ,Aragaki AK, Rossouw JE. Menopausal hormone therapy and long-term all-cause and cause-specific mortality the women's health initiative randomized trials. JAMA. 2017;318:927–38.
[3] Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. CA Cancer J Clin. 2005;55:10–30.
[4] Mørch LS, Skovlund CW, Hannaford PC, et al. Contemporary hormonal contraception and the risk of breast cancer. N Engl J Med. 2017;377:2228–2239.
[5] Danaei G, Vander Hoorn S, Lopez AD, et al. Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. Lancet. 2005;366(9499):1784–1793.
[6] Kahlenborn C, Modugno F, Potter DM, et al. Uso de anticonceptivos orales como factor de riesgo de cáncer de mama premenopáusico: un metaanálisis. Mayo Clin Proc. 2006;81:1290–1302.
[7] Hannaford PC, Iversen L, Macfarlane TV, et al. Mortality among contraceptive pill users: cohort evidence from Royal college of general practitioners' oral contraception study. BMJ. 2010;340:c927.

[8] Charlton BM, Rich-Edwards JW, Colditz GA, et al. Oral contraceptive use and mortality after 36 years of follow-up in the nurses' health study: prospective cohort study. BMJ. 2014;349:g6356.
[9] Ichida M, Kataoka A, Tsushima R, Taguchi T. No increase in breast cancer risk in Japanese women taking oral contraceptives: a case-control study investigating reproductive, menstrual and familial risk factors for breast cancer. Asian Pac J Cancer Prevent. 2015;16: 3685–3690.
[10] Gaffield ML, Kiarie J. WHO medical eligibility criteria update. Contraception. 2016;94(3):175. September (ref. 271 to 293).
[11] Charlton BM. contraceptive use and mortality after 36 years of follow up interested nurse health study: prospective cohort study. Br Med J. 2014;349:6356.
[12] Luo L, Luo B, Zheng Y, et al. Levonorgestrel-releasing intrauterine system for atypical endometrial hyperplasia. Cochrane Database Syst Rev. 2013;CD009458.pub2.
[13] Dominick S, Hickey M, Chin J, et al. Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen. Cochrane Database Syst Rev. 2015;CD007245.
[14] Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies. Lancet. 1996; 347:1713–1727.
[15] Hankinson SE, Colditz GA, Manson JE, et al. A prospective study of oral contraceptive use and risk of breast cancer (Nurses Health Study, United States). Cancer Causes Control. 1997;8:65–72.
[16] Marchbanks PA, McDonald JA, Wilson HG, et al. Oral contraceptives and the risk of breast cancer. N Engl J Med. 2002;346:2025–2032.
[17] Kumle M, Weiderpass E, Braaten T, et al. Use of oral contraceptives and breast cancer risk: the Norwegian-Swedish women's lifestyle and health cohort study. Cancer Epidemiol Biomarkers Prev. 2002;11: 1375–1381.
[18] Dumeaux V, Alsaker E, Lund E. Breast cancer and specific types of oral contraceptives: a large Norwegian cohort study. Int J Cancer. 2003;105:844–850.
[19] Molina RL, Pace LE. A renewed focus on maternal health in the United States. N Engl J Med. 2017;377:1705–1707.
[20] Aedo S, Cavada G, Blumel JE, et al. Women's health initiative estrogen plus progestin clinical trial: a study that does not allow establishing relevant clinical risks. Menopause. 2015;22:1317–1322.
[21] Singh S, Wulf D, Hussain R, et al. Abortion Worldwide: A Decade of Uneven Progress, New York: Guttmacher Institute; 2009. Available from: https://www.guttmacher.org/report/abortion-worldwide-decade-uneven-progress.
[22] Royston P, Parmar MK. The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt. Statist Med. 2011;30: 2409–2421.
[23] Royston P, Parmar MK. Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. BMC Med Res Methodol. 2013;13:152.
[24] Rothman KJ, Greenland S. Causation and causal inference in epidemiology. Am J Public Health. 2005;95:S144–S150.