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C. La Vecchia, L. A. Brinton, A. McTiernan

HORMONE REPLACEMENT THERAPY AND BREAST CANCER RISK: EPIDEMIOLOGY

Summary

The shape of incidence for breast and other female-hormone related neoplasms levells off after menopause, while the increase of most other common epithelial neoplasms steadily increases after menopause with a power of age. With reference to hormone related therapy (HRT) in menopause, most potential favourable and adverse effects on cancer risk of HRT are restricted to current users. On the basis of observational epidemiological data, the RR of breast cancer is moderately elevated in current and recent HRT users, and increases by about 2.3 % per year with longer duration of use, but the effect drops after cessation and largely, if not totally, disappears after about five years. Unopposed estrogen use is strongly related to endometrial cancer risk, but cyclic combined oestrogen-progestin treatment appears to largely or totally reduce this side effect, if progestin are used for at least 14 days per cycle. However, combined HRT may be associated with higher risk of breast cancer as compared to unopposed estrogens.

INTRODUCTION

Hormone replacement therapy (HRT) reduces climacteric symptoms, has favourable effects on bone metabolism and osteoporosis, and possibly on ischaemic heart disease and other cardiovascular diseases [1–3]. It may also reduce the risk of colorectal cancer [4]. Total mortality among women who use postmenopausal hormones is lower than among non-users, which probably to a large extent reflects favourable health characteristics of women who decide to use HRT [5, 6].

HRT, however, has also a number of adverse effects, the main ones being a promotional effect on endometrial cancer, and some elevation in the risk of breast cancer [4, 6, 7].

Most information on HRT and breast cancer comes from a reanalysis of individual data from 51 epidemiological studies, conducted in 21 countries and including 52,705 women with breast cancer and 108,411 controls [8]. This showed a 2.3 % (95 % confidence interval, CI, 1.1 to 3.6 %) increase in the relative risk (RR) of breast cancer for each year of HRT use. This corresponds to a RR of 1.35 (95 % CI 1.20 to 1.49) for current users who had used HRT for 5 years or more, and to a cumulative excess for women who began use of HRT at age 50 of approximately 2 cases/1000 women for 5-year users, 6 cases/1000 women for 10 year users, and 12 cases/1000 women for 15 year users.

This increase was comparable to the effect on breast cancer of later menopause, since among never-users of HRT the RR of breast cancer increased by 2.8 % (95 % CI 2.1 to 3.4 %) for each increasing year at menopause. This elevated risk, however, levelled off after stopping HRT use, with no material excess risk observed five or more years after stopping, as compared to never-users. The elevated risk associated to late menopause, in contrast, tended to persist for several years [9].

Use of HRT for a short time (i.e., < 5 years) to control menopausal symptoms is not related to any material increase in the risk of breast cancer [8, 10, 11]. The biologic mechanism underlying this association remains unclear. Changes in the composition of the breast tissue have been documented, with greater mammographic densities having been noted following hormone use [12]. Also of interest is whether genetic factors, including polymorphisms in hormone metabolizing genes, might be aetiologically involved.

COMBINATION OF ESTROGENS AND PROGESTINS

Another open question is the impact on breast cancer risk of the combination of estrogens and progestins, a therapy effective in reducing the excess endometrial cancer risk associated with estrogen use alone [13]. There are biological reasons to suspect an unfavourable effect of added progestins on breast carcinogenesis, since ovulatory cycles are related to breast cancer risk, and breast mitotic activity is higher during the luteal phase of the cycle (when progesterone levels are at their highest) [14, 15]. An early report of a Swedish cohort study [16] suggested that combined HRT may be more strongly related to breast cancer risk than estrogens alone, with a non-significantly elevated relative risk (RR) of 1.2 for ever-use and of 4.4 for more than six years use, based on 10 cases (and hence a wide confidence interval CI, 0.9 to 22.4). An update of the same study [17] confirmed these findings, showing RRs of 1.4 after 1–6 years and 1.7 after more than 6 years of use of combined preparations. The excess risk, however, appeared confined to recent users. Three other studies from Britain [18], Denmark [19] and Sweden [20] showed an association between combined HRT and breast cancer.

A report from the American Nurses Health Study cohort [21] confirmed some excess breast cancer risk among current long-term HRT users: the RRs were 1.3 (95 % CI 1.1 to 1.5) for conjugated estrogen users, 1.3 (95 % CI 1.0 to 1.7) for other estrogen users, and 1.4 (95 % CI 1.2 to 1.7) for estrogen plus progestin. A case-control study in Sweden, involving 3345 women with breast cancer, found a trend of increasing risk with duration of different types of combined estrogen-progestin use (RR = 2.4 for women treated for at least 10 years) [22].

A report on 46,355 participants followed for a mean of 10.2 years in the Breast Cancer Detection and Demonstration Project showed that women who had used combined estrogen and progesterone had a 40 % increased incidence rate (RR = 1.4, 95 % CI = 1.1 to 1.8) of developing breast cancer compared with never-users [23]. Furthermore, the risk from combined therapy was greater than that observed with unopposed estrogen (20 % increase in risk, 95 % CI = 1.0 to 1.4). The increased risk was limited to use within the prior four years; women who had used HRT in the past but stopped did not have an increased risk for breast cancer. The increased risk was also largely confined to women with a body mass index of 24.4 or less, which indicates that there could be a threshold effect of HRT, since heavier women are likely to have a higher average level of endogenous estrogen that in itself increases risk.

Likewise, a population-based case-control study of 1897 postmenopausal cases and 1637 postmenopausal population controls from Los Angeles County [24] found a RR of 1.06 (95 % CI 0.97 to 1.15) for each 5 years of estrogen replacement therapy use, but of 1.24 (95 % CI 1.07 to 1.45) for combined estrogen-progestin treatment, thus suggesting that addition of a progestin to HRT enhances the risk of breast cancer relative to estrogen use alone. The excess risk for combined therapy may be around 5 % per year, as compared with 2.3 % for estrogen alone. The data of various studies are inconsistent with reference to sequential *versus* continuous therapy.

The reanalysis of individual data from 51 studies [8], moreover, found a similar excess breast cancer risk for women using estrogens alone and combined estrogen-progestin treatment, and no marked differences in relation to hormone types or doses of HRT preparations, although little information was available about long duration of use of any specific preparation.

Epidemiological evidence

A case-control study from Washington state [25] suggested that combined HRT increases the risk of lobular, but not ductal breast carcinoma, but the findings are inconclusive due to the small number of exposed cases.

Another major issue is the time-risk relation after stopping HRT. The effect of steroid hormones is thought to be on the later stages of carcinogenesis (i.e. they are promoters) [26]; consequently, the increased breast cancer risk associated with HRT declines within a few years after stopping use.

Although the absence of a long-term cumulative risk is reassuring, a 20 to 30 % excess risk of breast cancer in women aged 50 to 65 years – when HRT use is most frequent – has to be weighed against the benefits of HRT on the bone and perhaps on the cardiovascular system, since the incidence of breast cancer in the sixth decade of life is high [27, 28].

There are no data from clinical trials on the HRT-breast cancer association, but the Postmenopause Estrogen/Progestin Intervention (PEPI) trial reported that increased mammographic density was observed in 3.5 % of the estrogen-only group, but in 16 to 23 % of the different estrogen/progestin schedules [29].

Implication for survival

Although hormone replacement therapy has been associated with an increased incidence of breast cancer, use appears to lead to lower mortality from breast cancer or improved prognosis in some [11, 20, 30–32], although not all [4, 33], studies. Although some of this effect may be due to increased breast cancer surveillance among hormone users, a favourable biologic effect of hormone use on the biologic characteristics of breast tumours cannot be dismissed [32, 34].

In the American Cancer Society Cancer Prevention Study II, breast cancer mortality did not increase with estrogen use overall and no excess risk was observed for thin or heavy women [35].

Although a diagnosis of breast cancer has been conventionally viewed as a contraindication for subsequent HRT use, this notion is being questioned by given data showing favourable effects of HRT on breast cancer prognosis [36]. Although the few studies that have addressed this issue seem to indicate no adverse effects of HRT usage among breast cancer survivors, sample sizes have been limited [37].

Conclusion

The evidence from observational epidemiological studies indicates that the risk of breast cancer is elevated among women using HRT, increases with longer duration of use, is reduced after cessation of use and levels off about five years after stopping use. Recommendations for prolonged HRT use must be considered on an individual basis, taking into account the presence of other risk factors for breast cancer, such as family history of breast cancer or a personal history of benign breast disease.

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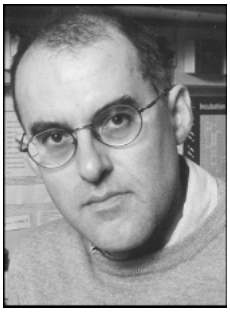

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