So, now what? What are the risks of breast cancer and myocardial infarction among women receiving hormonal replacement therapy after menopause?

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The use of hormone therapy (HT) after menopause remains the object of controversy, as the first observational investigations had revealed significant reduction in mortality among therapy users compared with nonusers[1].

However, after the publication of Women's Health Initiative (WHI)[2], it was observed exactly the opposite, i.e., HT was associated with a higher rate of morbimortality regardless of age, which culminated with the recommendation that it should be prescribed only for short periods and only for menopausal symptoms[3,4].

Since then, many women have abruptly discontinued HT, resulting in a significant deterioration in quality of life[5].

Therefore, in an attempt to clarify the question of the effect of HT at different ages two meta-analyses were published involving randomized trials, of which results surprisingly found a reduction in cardiovascular events and mortality in younger women, but not in older women[5].

In 2009, Salpeter et al.[6] published an interesting article in The American Journal of Medicine dealing with the controversial issue of HT after menopause where they analyzed their impact on the cost and quality of life in two groups of women after menopause. For that purpose, a mathematical model evaluating the cost-effectiveness in different age groups was used. The results showed significant advances in the window of opportunity hypothesis for the use of HT because the study compared two groups of women, a younger post-menopausal (up to 59 years) and an older one (> 60 years). The mathematical model was based on the meta-analysis of randomized controlled clinical trials conducted until March 2008, and assessed the QALY (quality-adjusted-life years) that represents the cost-benefit of HT on the quality of life of women after menopause.

In conclusion, the study reported favorable cost-benefit of HT in the younger group, which did not occur in the older group; in fact, the young group had a gain of 1.49 QALYs, at a cost of US$ 2,438 (value < US$10,000 are considered to be significantly cost-effective). On the other hand, in the older group, the QALY gain was only 0.11, at a cost of US$ 27,953. Moreover, in the first nine years of treatment a worsening in quality of life of older women was observed, and only after this period an improvement was observed. In the young group, improvement in QALY was theoretically demonstrated with a treatment period that lasted up to 30 years.

These same authors have demonstrated in a meta-analysis of controlled clinical trials the occurrence of mortality decrease in younger women who used HT, with no benefit to the group who started HT later.

Thus, the results obtained in this study are consistent with those reported previously in observational designs – which had included younger women who started HT soon after menopause, that is, who showed improvement in quality of life and reduction in cardiac events. Moreover, it corroborates the results obtained from controlled clinical trials that assessed older women, such as the Women's Health Initiative, which showed no reduction in mortality.

Based on these studies, the Brazilian and International Guidelines have recommended to date the use of HT in women with menopausal symptoms, such as hot flashes, insomnia, vaginal dryness, from the stage of menopausal transition and discouraged its start many years after the age of menopause.

However, two recent studies regarding the risk of breast cancer have disclosed surprising results.

The first study, published in February 2011 by Beral et al.[7] of the Million Women Study (MWS) analyzed the relative risk (RR) of breast cancer in users and nonusers of HT in a United Kingdom population of 1,129,025 postmenopausal women by adjusted Cox's regression, based on prospective information. The authors observed that the relative risk of breast cancer in HT users was greater when initiated before or soon after menopause, than after a long period of time (p heterogeneity < 0.001 for both groups of HT users: estrogen with progestin and estrogen only). Among users of estrogen formulations only, the increased risk was slight or none when the steroid had been used for five or more years after menopause (RR = 1.05, 95% CI = 0.89 to 1.24), although when the use of estrogen alone was initiated before or within less than five years of menopause, the risk was significantly higher (RR = 1.43, 95% CI = 1.35 to 1.51).

A similar pattern was observed among users of combined estrogen with progestin (RR = 1.53, 95% CI = 1.38 to 1.70 and RR = 2.04, 95% CI = 1.95 to 2.14, respectively).

In patients 50-59 years of age, the yearly incidence rates

for breast cancer were 0.30% (95% CI = 0.29% to 0.31%) in non-users of HT and 0.43% (95% CI = 0.42% to 0.45%) and 0.61% (95% CI = 0.59% to 0.64%%), respectively, in users of estrogen alone and estrogen combined with progestin that had started HT before five years after menopause. From these results, the authors concluded that risk of breast cancer among HT users was higher in those using the combined estrogen-progestin therapy than in those who used estrogen-only formulations and that the start of the HT was associated before than in those who used estrogen-only formulations and that the start of the HT before or soon after the menopause onset was associated with a higher risk than if it had been started five years after menopause. These data indicate that the moment of HT start in relation to the menopause onset seems to be an important risk modulator associated with breast cancer.

An interesting fact that was commented in the editorial accompanying the study, which refers to the fact that the risk of breast cancer in both groups of HT users has been attenuated by overweight and obesity, a result that had already been observed in other studies. However, when the incidence rates, rather than the relative risk were calculated, it became clear that this attenuation is apparent and was driven by higher incidence of breast cancer in HT non-users with adiposity. In fact, among the non-users but not among users of hormone therapy, incidence of breast cancer was higher with increasing adiposity. Thus, the proportional increase in breast cancer risk among hormone users was lower in those who were overweight and obese than among women within normal weight range. Elevation in blood concentrations of endogenous estrogens, by increasing the body mass index among HT non-users, explains, albeit not completely, the higher risk of breast cancer after menopause with increasing adiposity. As blood concentrations of endogenous estrogen usually increase with adiposity in women after menopause, it seems plausible that hormone therapy could alter the exposure to sex hormones to a greater extent in normal weighed women than in obese ones. In fact, among obese women users of estrogen only, the incidence rates of breast cancer did not differ statistically from non-users.

Epidemiological evidence consistently show that the risk of breast cancer among HT users returns to that of non-users, as soon as they cease their use. The observed decline in incidence rates of breast cancer in the United States and in many other countries after 2002, following the reduction in the prevalence of HT use provides independent support for the epidemiological data.

Obesity and the interval between the menopause onset and HT start appear to be important factors, so in the WHI[2], 80% of the participants were overweight or obese and approximately 90% were randomized to hormone therapy lasting five or more years after menopause. Among the estrogen users, the Million Women Study found little or no increased risk of breast cancer in overweight or obese women who started hormone therapy five or more years after menopause (RR = 0.91, 95% CI = 0.73 to 1.14), consistent with the results of WHI (RR = 0.77, 95% CI = 0.59 to 1.01). The values for users of estrogen-progestin (RR = 1.39, 95% CI = 1.18 to 1.64) were also consistent with the results of WHI (RR = 1.26, 95% CI = 1, 00 to 1.59).

Moreover, in the MWS incidence rates of breast cancer associated with estrogen plus progestin in users starting five or more years after menopause were similar to those observed in WHI (0.46% a year vs. 0.43% a year) and 0.3% a year in non-users of HT, both in MWS and WHI. However, incidence rates of breast cancer in MWS were higher among users of estrogen-progestin that started the association before five years after menopause (0.61% a year). This result was not a random one, as the vast majority of women had been randomly assigned to using estrogen after five years of menopause. Thus, the results of randomized trials of hormone therapy in relation to breast cancer risk such as the WHI may not apply to women who started hormone therapy close to the time of menopause onset.

The second study, published in 2011 by Lacroix et al.[8] of the WHI, evaluated after 10.7 years users of conjugated equine estrogen (CEE) submitted to hysterectomy, regarding the risk of coronary heart disease, invasive breast cancer, stroke, deep vein thrombosis (DVT), colorectal cancer, hip fractures and death. It should be recalled that this arm of WHI in hysterectomized women was suspended after 7.1 years of follow-up due to higher stroke risk, in spite of its low probability to alter the risk benefit of HT use. The results of this arm, after intervention, had not yet been published and refer to a population of 10,739 hysterectomized women 50 to 79 years and users of a dose of 0.625 mg CEE/day. The follow-up of this study continued until August 2009, with 7,645 surviving participants (78%).

The results obtained, regarding the annual risk after the intervention, among CEE users compared with the placebo group were respectively: for coronary artery disease [0.64% vs. 0.67% (HR 0.97, 95% CI, 0.75-1.25)]; breast cancer [0.26% vs. 0.34% (HR 0.75, 95% CI, 0.51 - 1:09)] and stroke [0.36% vs. 0.41% (HR 0.89, 95% CI, 0.64-1.24)], with the risk of DVT still not high after the intervention [0.17% vs. 0.27% (HR 0.63, 95% CI, 0.410.98)], the risk of hip fracture after the intervention was lower [0.36% vs. 0.28% (HR, 1.27, 95% CI, 0.88-1.82)] and the risk of total mortality did not show any difference [1.47% vs. 1.48% (HR, 1.00, 95% CI, 0.84-1.18)].

It is noteworthy the fact that, throughout the follow-up period, the incidence of breast cancer was persistently lower in the CEE group when compared with placebo, i.e., it was respectively 0.27% vs. 0.35% (HR 0.77, 95% CI, 0.62-0.95). Additionally, all other observed results

were more favorable in younger women (50 to 59 years) than in older ones (70 to 79 years) such as in coronary artery disease (p = 0.05 for the interaction), myocardial infarction (p = 0.007 for interaction), colorectal cancer (p = 0.04 for interaction), total mortality (p = 0.04 for interaction) and the overall index for chronic diseases (p = 0.009 for interaction). Thus, the authors concluded in a general analysis of the results that the use of CEE by hysterectomized women after menopause followed by 10.7 years and having used CEE for a mean of 5.9 years did not result in an increase or decrease in the risk of coronary artery disease, DVT, stroke, hip fracture, colorectal cancer or total mortality, whereas the breast cancer risk remained decreased.

However, in an analysis by age range the authors observed that in regard to the risk of myocardial infarction, colon cancer and all causes of mortality among younger CEE users (50 to 59 years at baseline) showed much more favorable results than in the older ones (70 to 79 years).

Undeniably, the most significant result refers to the outcomes of coronary heart disease, where the risk of myocardial infarction decreased by 40% to 50% in CEE users than in the placebo group of the same age, but was higher in women aged 70 to 79 years. Thus, in absolute numbers, for each 10,000 users-year of CEE aged between 50 and 59 years there was a reduction of 12 cases of heart attacks, 13 deaths and 18 adverse events, differently from women between 70 and 79 years, where for every 10,000 CEE users there was an increase of 16 heart attacks, 19 deaths and 48 adverse events (p-values for interaction with age were statistically significant).

These results add further support to the so-called "window of opportunity" (timing hypothesis) regarding the prescription of HT. However, it is unclear whether these results concerning the reduction in the risk of invasive breast cancer can be applied to all menopausal women, as well as to users of estradiol or other estrogen formulations, and whether this reduction persists after a longer usage.

It appears that these two studies may have a big impact and possibly change the opinion of the American Heart Association, the United States Preventive Services Task Force, and the Brazilian Society of Cardiology. The latter together with the Brazilian Society of Climacterium have issued recommendations advising against the use of HT with the isolated objective of preventing cardiovascular events, because until then, the indication for HT was restricted to menopausal symptom control in relatively young women (or a few years after menopause). Also still recommended is the restricted use to a few years, a fact that had also been confirmed by a Cochrane systematic review of 19 clinical trials involving 41,904 women.

Therefore, the study of LaCroix[8] confirmed recent evidence from controlled clinical trials that had already shown HT benefits in younger women (between 50 and 59 years), such as a reduction in cardiac events and coronary calcification. The study also stresses the need for more controlled investigations, such as the Kronos Early Estrogen Prevention Study (KEEPS) started in 2005 and scheduled to end this year and which main objective was precisely to evaluate in healthy younger women (between 42 and 58 years), the impact of HT on the carotid intima-media thickness and coronary calcium content.

Final considerations

Currently with the available scientific knowledge, HT is indicated for the treatment of hot flashes and genital atrophy attenuation, but not for primary or secondary prevention of cardiovascular disease. However, regarding the recent menopause period, there is evidence that HT could reduce the progression of atherosclerosis and the incidence of myocardial infarction, but not of stroke; the WHI finished study clearly demonstrates that conjugated equine estrogen users aged between 50 and 59 years showed significant reduction in risk of myocardial infarction, without increasing the risk of stroke and breast cancer.

These findings, although relevant, must be critically considered in the overall healthcare of women during menopause, taking into account the fact that HT represents only one of the interventions and, when indicated, should always be combined with changes in lifestyle, such as regular exercises, balanced diet and elimination of smoking, among others.

References

1. Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MJ. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. Ann Intern Med 2000;133(12):933-41.
2. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288(3):321-33.
3. Majumdar SR, Alamasi EA, Stafford RS. Promotion and prescribing of hormone therapy after report of harm by the Women's Health Initiative. JAMA 2004; 292(16):1983-8.
4. Salpeter SR, Walsh JM, Greyber E, Ormiston TM, Salpeter EE. Mortality associated with hormone replacement therapy in younger and older women: a metaanalysis. J Gen Intern Med 2004;19(7):791-804.
5. Salpeter SR, Walsh JM, Greyber E, Salpeter EE. Brief report: coronary heart disease events associated with hormone therapy in younger and older women. A meta-analysis. J Gen Intern Med 2006;21(4):363-6.
6. Salpeter SR, Buckley NS, Liu H, Salpeter EE. The cost-effectiveness of hormone therapy in younger and older postmenopausal women. Am J Med 2009;122(1):42-52.
7. Beral V, Reeves G, Bull D, Green J, for the Million Women Study Collaborators. Breast Cancer Risk in Relation to the Interval Between Menopause and Starting Hormone Therapy. J Natl Cancer Inst 2011;103(4):296-305.
8. LaCroix AZ, Chlebowski RT, Manson JE, Aragaki AK, Johnson KC, Martin L et al. WHI Investigators. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. JAMA 2011;305(13):1305-14.