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Mini Review

Melatonin and EMPT: Good News for Carriers of BRCA Mutations

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Abstract

Women who inherit certain types of mutations (harmful mutations) of BRCA (breast cancer susceptibility) genes are known to have an increased risk of cancer. Several options are available for managing this risk. They include enhanced screening, prophylactic surgery, and chemoprevention. In this article, we suggest that the recent discoveries concerning anti-cancer effects of melatonin, at the origin of the EMPT (estrogen-melatonin-progestagen therapy) formula for menopausal hormone replacement, are likely to tilt the balance of the current decision-making schemes towards less invasive and more patient-friendly strategies.

Keywords: *BRCA1; BRCA2; Breast Cancer; Ovarian Cancer; Melatonin; EMPT; Prophylactic Surgery; Chemoprevention; Hormone Replacement Therapy*

Abbreviations

BRCA: Breast Cancer Susceptibility; EMPT: Estradiol-Melatonin-Progestagen Therapy

Introduction

The breast cancer susceptibility genes *BRCA1* and *BRCA2* are human genes which encode two different tumor suppressor proteins BRCA1 and BRCA2, both involved in repairing DNA double-strand breaks but using distinct mechanisms of action [1]. BRCA1 and BRCA2 are normally expressed in different types of cells where they help repair damaged DNA or destroy the cells in which DNA cannot be repaired [2,3]. The two *BRCA* genes are expressed in both females and males, and mutations of either of them, leading to the insufficiency of the BRCA1 and/or BRCA2 proteins, make the human body susceptible to the development of different types of cancer. The risk of developing breast cancer by the age of 80 is about 72% for women who inherit a harmful *BRCA1* mutation and about 69% for those with a harmful *BRCA2* mutation [4] whereas only 12% of women in the general population develop this type of cancer during their lives [5]. As to the ovarian cancer, the risk associated with *BRCA1* mutations and *BRCA2* mutations is 44% and 17%, respectively [4], in contrast with only 1.3% in the general population [5]. Moreover, *BRCA1* and *BRCA2* mutations are associated, to a lesser extent, with an increased risk of other types of cancer, both in women and in men, such as fallopian tube [7,9], primary peritoneal [6,7], prostate [8], pancreatic [9], and colorectal [10] cancers.

Melatonin as an Alternative of Prophylactic Surgery in *BRCA* Mutation Carriers

Prophylactic surgery involves removing as much of the "at-risk" tissue as possible. It may include the removal of both breasts (bilateral prophylactic mastectomy) of both ovaries and fallopian tubes (bilateral prophylactic salpingo-oophorectomy), the fallopian tubes being included because ovarian cancers often originate there [5]. In spite of its invasive nature, prophylactic surgery does not provide a full protection against later cancer development, even though they confer substantial benefits [11,12]. In addition, bilateral salpingo-oophorectomy, when performed in young women, raises issues related with fertility preservation and hormone replacement therapy. Arguments for avoiding prophylactic surgery, as far as possible, are thus not lacking.

BRCA mutations affect the cellular mechanisms involved in the defense against DNA damage. Even though DNA damage is frequently associated with different types of cancer, a number of data suggest that carcinogenesis is often triggered upstream of the DNA damage, primarily by aberrations of cell signaling systems altering the cell's response to both extracellular and intracellular stimuli. Melatonin has been shown to suppress the invasive and metastatic potential of breast [13-15], ovarian [16], colon [17,18], liver [19] and lung [20] cancer cells through different signaling pathways largely unrelated either to DNA damage or to the function of the BRCA1 and BRCA2

proteins. In addition, melatonin counteracts the damage to DNA by mitigating the action of reactive oxygen and nitrogen species [21] and prevents accumulation of DNA damage through a p53-mediated mechanism [22]. Accordingly, preventive treatment with melatonin may stop the carcinogenetic process both upstream and downstream of the phases in which the action of the BRCA proteins is required. If this hypothesis is confirmed, the current attitude toward the use of prophylactic surgery in *BRCA* mutation carriers will need to be reconsidered, with more emphasis being given to chemoprevention, especially with the use of oral contraceptives.

It has been known since 2007 that oral contraceptives reduce the risk of ovarian cancer by about 50% both in the general population and in women with harmful *BRCA1* and *BRCA2* mutations [23]. With the inclusion of melatonin to control the risk of breast cancer, as proposed in the EMPT formula previously suggested for menopausal hormonal replacement therapy [24], this combined noninvasive chemoprevention may be considered as the first-choice approach, in combination with enhanced screening [5], in women in whom the *BRCA* mutations are not associated with mutations of other genes that increase breast and ovarian cancer risk, such as *PALB2*, TP3, CDH1, CHEK2, RAD51C, RAD51D, and STK11 [25]. Genetic testing for these other mutations is currently available as part of multigenic (panel) testing [5].

EMPT after prophylactic surgery in young women

Women who have undergone bilateral prophylactic salpingo-oophorectomy will spend the rest of their lives in the state of menopause, with all associated symptoms affecting the quality of life, but also with an increased risk of serious and potentially life threatening diseases associated with untreated menopause. It was demonstrated that 3.5 years after oophorectomy, *BRCA* mutation carriers experience a significant worsening of menopausal symptoms and a decline in sexual functioning, particularly when the surgery is performed prior to natural menopause [26].

According to a recently published prospective, longitudinal cohort study of bilaterally oophorectomized *BRCA1* mutation carriers from 80 participating centres in 17 countries, conducted between 1995 and 2017 with a mean follow-up of 7.6 years [27], estrogen-alone replacement did not increase the risk of breast cancer, whereas there was a slight trend towards a higher risk in women treated with estrogen plus progestagen. Similar to the replacement therapy suggested recently for naturally menopausal women [24], the inclusion of melatonin to estrogen and progestagen (the EMPT formula) is likely to inverse this trend.

Conclusion

New data concerning the anti-cancer effects of melatonin are likely to enable less invasive and more patient-friendly strategies for the management of women carrying harmful *BRCA1* and *BRCA2* mutations. Further study is needed to concretize the optimal preventive and therapeutic procedures for different genetic backgrounds and clinical scenarios.

Conflict of Interest

There is no conflict of interest in relation with this study.

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