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Short Communication

Estrogen Withdrawal by Oophorectomy as Presumed Anticancer Means is a Major Medical Mistake

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Abstract

At the beginning of the 20th century, regression of breast cancers was achieved by surgical removal of ovaries in 30% of premenopausal cases. This therapeutic result led to the simplified, erroneous conclusion that estrogen deprivation by oophorectomy may be the appropriate cancer therapy. Nevertheless, clinical studies could not find convincing direct associations between serum sex hormone levels and breast cancer development among either pre- or postmenopausal cases. The principle of estrogen-induced cancer was also mistakenly supported by the local estrogen synthesis of the breast, which was supposed to help both the initiation and progression of cancers. Both estrogen deficiency and defective expression of estrogen receptors (ERs) may be the initiators of insufficient estrogen signaling and various human diseases, including breast cancer development. These different pathogenetic mechanisms may provide explanations for the extremely controversial results obtained by sexual hormone measurements in the serum of breast cancer cases. The pharmaceutical industry actively entered into the erroneous fight against estrogens by the development of ER blockers and inhibitors of estrogen synthesis, however, the therapeutic use of anti-estrogens remained unforeseeable and yielded toxic complications. The anticancer effect of estrogen withdrawal or other endocrine manipulations against estrogen signaling could not get above the "magic" 30%, as the majority of breast cancer patients are genetically not capable of appropriate compensatory actions. Long term health outcomes of bilateral surgical oophorectomy justify that in the majority of cases, the defect of hormonal and metabolic equilibrium leads to decreased cellular estrogen surveillance and increase in both morbidity and mortality.

INTRODUCTION

Correlations between the excess of female sexual steroids and breast cancer risk have been suspected for a long time. At the end of the 19th century, definite regression of advanced breast cancer was published in premenopausal patients following surgical oophorectomy [1]. In the UK, regression of breast cancers was achieved by surgical removal of ovaries in 30% of premenopausal cases [2]. This modest therapeutic result evoked great enthusiasm among physicians and led to the simplified, erroneous conclusion that estrogen deprivation by oophorectomy may be the appropriate cancer therapy.

These experiences mean the beginning of the unique, erroneous pathway of breast cancer care based on the presumably advantageous hypoestrogenism, which was thought to be a preventive and curative measure against mammary tumors [3]. Neither clinicians nor medical scientists realized that the living organism is not a static container and that abrupt withdrawal of a crucial mediator induces unpredictably strong compensatory mechanisms for survival, depending on the genetic proficiency of patients [3,4].

The struggle against estrogens presumed to have carcinogenic potential for the female breasts, was continued throughout the past century until now. The pharmaceutical industry actively entered into this fight by the development of estrogen receptor (ER) blockers and inhibitors of estrogen synthesis. Regretfully, the therapeutic use of antiestrogens remained unforeseeable and yielded toxic complications [5]. Moreover, the unique way of fighting against cancer could not increase the overall tumor free survival of patients with breast cancer.

Over the past decades, our understanding of ER physiology

in mammalians considerably widened, as we acquired deeper information's on the regulatory roles of ER-alpha and ER-beta in both the maintenance of somatic health and reproduction. ERs may act as a hub where physiologic molecular pathways converge and this allows maintaining the transcriptional activity of ERs in tune with all cellular functions [6].

At the same time, the correlations between estrogen supply and clinical pathologies including tumor development, exhibited many controversies. Increased estrogen concentrations did not show direct relationship with the risk of breast cancer initiation and progression [7]. Moreover, estrogen withdrawal could not consequently inhibit the progression or recurrence of mammary tumors [8]. These ambiguous data support that the regulation of ER transcriptional programs depends on fairly complex molecular pathways and may not be simply defined by either the high or low concentrations of estrogens [9,10].

Increasing incidence rate of breast cancer among postmenopausal cases contradicts the concept of estrogen-induced cancer

Considering the overall incidence of breast cancer, it is fairly low among young women (23.9%), whereas being much higher in older, postmenopausal cases with low baseline female hormone levels (76.1%) [11]. Moreover, clinical studies could not find convincing direct associations between serum sex hormone levels and breast cancer development among either pre- or postmenopausal cases [9].

In healthy postmenopausal women, serum estrogen levels are fairly decreased, whereas local estrogen concentrations in the breast are much higher, quite similarly to premenopausal levels [12]. The decrease in systemic estrogen supply may be locally counteracted by the increased aromatase activity of adipose fibrocytes and conversion of androgens to estrogens [13]. High aromatase activity and elevated local estrogen concentrations were particularly demonstrated at the invasive front of breast cancers, where the tumor-stromal interactions define the fate of cancer cells [14,15]. The principle of estrogen-induced cancer was mistakenly supported by local estrogen synthesis in the breast, which was supposed to help both the initiation and progression of cancers in spite of low postmenopausal serum estrogen concentrations [4].

Recent literary data suggest that increased in-breast aromatase activity and estrogen synthesis may have protective impact against breast cancer proliferation and spread [4,16]. In young premenopausal cases with breast cancer, clinical control and examination of removed tumor samples revealed that the absence of CYP19-aromatase activity carried a significantly high risk for local tumor recurrence and poor prognosis [17].

Multiparity decreases, while infertility and nulliparity increases the risk for breast cancer

In women, high reproductive capacity and multiparity are in inverse correlation with breast cancer risk, which fact represents the greatest challenge for scientists believing in estrogen induced cancer initiation and spread [4]. Good fertility is usually associated with excellent capacity to synthesize estrogens and pregnancy yields extremely elevated serum estrogen levels, while infertile and nulliparous women are hormonally challenged [18].

From the early 60's of the past century, parity associated protection against breast cancer was observed among women from all ethnic groups. The risk of developing breast cancer was strongly reduced in multiparous women as compared with nulliparous cases [19]. Animal experiments in rodents also justified that pregnancy before or soon after exposure to chemical carcinogens are highly protective against the induction of mammary malignancies [20]. Administration of pregnancy mimicking high doses of estradiol and progesterone before or after carcinogen treatment provided strong protection against the carcinogenesis in the mammary glands of rats and mice [21].

During healthy pregnancy, abundant ER expression in proliferating maternal and fetal structures up-regulates the syntheses of genome stabilizer BRCA protein, aromatase enzyme and estrogen synthesis. The auto-regulative circle of extreme increase in ER, BRCA protein and estrogen production ensures the safeguarding of abrupt cell proliferation and differentiation as well as all other cellular mechanisms [10]. High ER expression in all tissues of pregnant women may be maintained after the postpartum restoration of normal estrogen levels, which may ensure the upregulation of estrogen signaling and anticancer surveillance for a long time [18].

By contrast, in young women, disorders associated with infertility, such as polycystic ovarian syndrome, are in strong correlation with the increased risk of breast cancer [22]. The overall cancer risk among infertile women before in vitro fertilization (IVF) was found to be markedly increased in a large Swedish study [23]. Conversely, after IVF assisted childbirth, cancer risk was significantly decreased mainly due to a lower than expected risk for breast and cervical cancers [24]. Similarly, a conspicuous great reduction in breast cancer incidence was found among infertile women who underwent high dose estrogen treatment as ovulation induction therapy [25].

The grade of defect in estrogen signaling is directly associated with poorly differentiated, ER-negative breast cancer risk for women

The clinical and biologic significance of ER-protein expression in breast cancers has been equivocally established. Lack of ERs is a crucial indicator of poor prognosis and fatal outcome in patients with mammary cancers [11,26]. At the same time, the lack of progestin receptors (PRs) has no additive prognostic value in either ER-positive or ER-negative breast cancer cases [27]. Progestin is a female hormone having pivotal role in the secretion phase of endometrium and it is not an essential player in the overall regulation of cell proliferation.

Literary data erroneously support that young age is associated with a higher incidence rate of poorly differentiated, ER-negative breast cancers as compared with postmenopausal female cases [26]. Nevertheless, in healthy premenopausal women, overall breast cancer development is rare, as healthy ovulatory menstrual cycles are protective, and even a slightly or moderately defective estrogen synthesis may counteract cancer initiation [28].

In clinical studies, raw numbers show a close to twofold increase in ER-negative tumors and a much higher – almost fourfold – increase in ER-positive tumors with aging, while the percentage of ER-negative cancers exhibits a deceivingly decreasing trend [11]. The relatively higher percentage of surviving ER-negative mammary cancers among young cases may be attributed to the low incidence rate of more successfully eliminated ER-positive cancers rather than to an excessive inclination to the development of ER-negative tumors [18].

Many investigations mistakenly propose that parity associated increased estrogen concentration may differently or even quite inversely affect the risk of ER-positive and ER-negative cancers [29,30].

In multiparous women, good fertility-associated estrogen supply and increased ER expression strongly reduce the development of overall breast cancers [29]. Estrogens, being the specific ligand for ERs, may preferentially block the development and progression of ER-positive cancers; however, their killing capacity against ER-negative cancers is slower and weaker. In estrogen-rich milieu, a fairly decreased number and percentage of ER-positive tumors is associated with a moderately decreased number and an unchanged or deceivingly increased percentage of ER-negative breast cancers [18].

Conversely, in nulliparous women, the weakness of estrogen surveillance results in enhanced overall breast cancer risk. The insufficient estrogen supply has a defective killing capacity, even against the predominant, highly hormone-sensitive ER-positive breast cancer cells, resulting in an increased number and percentage of surviving ER-positive tumors. The survival possibility for hormonally weakly controlled ER-negative cancers may disproportionately improve and their raw number may be somewhat increased, while the relative number (percentage) decreases [18].

Either estrogen deficiency or estrogen resistance may be equally strong risk for breast cancer

Interplay between estrogen levels and ER expression has crucial role in the maintenance of appropriate estrogen signaling, which is the prerequisite of somatic and reproductive health in mammalians [4,10]. When estrogen signaling is jeopardized by genetic alterations and other endogenous or exogenous factors, the responses are defensive counteractions, such as increased ER expression and estrogen synthesis. The improvement of estrogen signaling up-regulates the machinery of genomic defense and ensures safe DNA replication [10].

Both estrogen deficiency and defective expression or activity of ERs may be the initiators of insufficient estrogen signaling and various human diseases, including breast cancer development [9,31]. These different pathogenetic mechanisms may provide explanations for the extremely controversial results obtained by sexual hormone measurements in the serum of breast cancer cases [9].

Defective estrogen synthesis induces accumulation of androgenic precursors and *estrogen deficiency*, but during these ongoing pathologic processes ER over expression may be more or less compensatory for the improvement of estrogen signaling [9,10]. Estrogen deficiency is the most important mechanism of the cancer risk in type 2 diabetes [18,28,32]. Conversely, when *estrogen resistance* means the onset of hormonal and metabolic disturbances attributed to defective ERs or low ER expression, the initial counteraction is hyperestrogenism, which may restore appropriate estrogen signaling [9]. Estrogen resistance is the causal factor of increased breast cancer risk in BRCA mutation carriers [10]. Compensatory mechanisms may transiently improve the damaged activity of estrogen surveillance; however, exhaustion of these processes leads to the breakdown of estrogen signaling and the development of various diseases, including cardiovascular diseases and malignancies.

Risks of artificial estrogen deficiency and estrogen resistance

In the early 70s, a synthetic estrogen receptor blocker, tamoxifen was introduced for the treatment of ER-positive breast cancers [33], with the purpose to achieve the erroneous aim: appropriate defense against presumably carcinogenic estrogen signaling. Tamoxifen treatment exhibited only 45-50% tumor response even in the targeted ER-positive tumors [34] and its therapeutic dose caused severe, frequently life-threatening toxic effects, including cardiovascular complications and malignancies [5].

Clinical data over decades have mistakenly suggested that tamoxifen is not, as originally designated, a pure antiestrogen, but rather it may be regarded as a selective estrogen receptor modulator (SERM), having variable agonistic and/or antagonistic activities on ERs at different sites [34]. Moreover, de novo or acquired resistance against tamoxifen treatment induces refractoriness or advanced growth of tumors being mistakenly evaluated as an aberrant estrogenic activity of the compound [8].

In reality, tamoxifen is a pure ER-blocker. Artificial ER-blockade without extreme compensatory actions highly endangers normal DNA replication in organs having cyclic proliferative activity, particularly in the endometrium. Crude inhibition of the activation of ER-regulated genes provokes intense counteractions in genetically proficient patients at all sites, including extreme increase in new ER and estrogen synthesis. In these cases, the apoptotic activity of up-regulated ER signaling results in transient tumor regression [3].

Aromatase inhibitors were also designed to inhibit estrogen signaling by blocking the biosynthesis of estrogens [35]. Aromatase inhibitors exhibited low rate of tumor response and estrogen loss induced high toxicity in the targeted postmenopausal breast cancer cases.

Estrogen withdrawal by aromatase inhibitors provokes ER-over expression even in tumor cells [36] and this acquired estrogen hypersensitivity helps the restoration of estrogen signaling and may transiently promote tumor regression [3]. Aromatase inhibition may block estrogen synthesis in mammary fibrous adipocytes as well; however, the compensatory activation of aromatase synthesis leads to high mammary estrogen concentration and good tumor response [17,37].

The anticancer effect of estrogen withdrawal or other chemical endocrine manipulations against estrogen signaling could not get above the "magic" 30%, as the majority of breast cancer patients are genetically not capable of extreme compensatory actions [3]. De novo or acquired apparent anti-estrogen resistance of breast tumors may be associated with the missing genetic capacity of patients for the appropriate up-regulation of estrogen signaling or with the exhaustion of defensive counteractions in cases previously showing good tumor response. The weaker the defensive counteraction against the drastic inhibition of estrogen signaling, the poorer is the prognosis of the disease. Anti-estrogens are strongly recommended for breast cancer prevention as well [38], in spite of the controversial results of their use in tumor therapy. In *BRCA1* mutation carriers, however, with high risk of familiar breast cancer, prophylactic anti-estrogen administration proved frequently to be ineffective or quite deteriorative [39].

Prophylactic oophorectomy as erroneous breast cancer prevention strategy in BRCA gene mutation carriers

Possibility of cancer prophylaxis in *BRCA*-mutation carrier women by oophorectomy seems to be highly paradoxical. In such patients, there is a permanent fight against the defective ER signaling by means of increased estrogen synthesis [10]. Nevertheless, in *BRCA*-mutation carriers, the brutalism of oophorectomy may be more promising, but not a good method for cancer prevention as compared to highly toxic anti-estrogen treatment. Removal of the ovaries does not provoke any further decrease in the low baseline level of ER expression as compared to the tamoxifen blockade of ERs. Moreover, the cessation of estrogen synthesis is restricted to the missing ovaries after their removal, while aromatase inhibitors block the activity of aromatase enzyme at all extraovarian sites. The shock of preterm menopause may transiently induce extreme extra-ovarian estrogen synthesis in *BRCA*-mutation carrier cases, but the possibility of delayed adaptation to the drastic changes is highly risky in terms of cancer initiation. Moreover, the initially provoked excessive extra-ovarian estrogen synthesis may calm down later and the patient remains defenseless [3].

Long term health outcomes of bilateral oophorectomy

The proportion of hysterectomies accompanied by prophylactic oophorectomy in the United States showed an increasing trend, from 29% in 1979 to 45% in 2004 [40]. The Mayo Clinic Cohort Study showed that surgical ovarian loss has a long-term harmful impact on women's health, particularly for those who underwent oophorectomy before their natural menopause. Bilateral oophorectomy increased overall mortality in women before age 45 years; hazard ratio (HR]) was 1.67. The increased mortality was especially high among those women who did not use hormone replacement therapy (HRT) up to the age of 45 years (HR=1.93) [41].

The incidence of ischemic heart disease was highly increased among women who underwent bilateral oophorectomy before age 40 years (HR=8.7) as compared with cases oophorectomized after age 45 years [42]. Women, who underwent bilateral oophorectomy before age 50 years and did not use HRT had an increased risk of stroke as well (HR=2.19) [43].

In the Mayo Clinic Cohort Study of Oophorectomy and Ageing, women oophorectomized before the onset of menopause had an increased risk of cognitive impairment or dementia as compared with control cases (HR=1.33). Women who underwent oophorectomy before age 43 years had the greatest risk (HR=1.74) [44].

Oophorectomy in premenopausal, young women is a well-established risk factor for osteoporosis. Surgical removal of ovaries even in postmenopausal cases may cause increased risk for osteoporotic fractures [45].

Certain tumors exhibit increased incidence rate in women who underwent hysterectomy with oophorectomy. Both lung cancer incidence and mortality were increased in oophorectomized women as compared with those who had ovarian conservation [43]. High prevalence of oral cancer [46] and renal cell carcinoma [47] was also observed among women who underwent hysterectomy and oophorectomy. In a population–based cohort study, women had a conspicuously increased risk of so called "estrogen related" cancers of breast, uterus and ovary despite the oophorectomy [41].

CONCLUSION

The results of clinical examinations suggest that either oophorectomy or anti-estrogen treatment may not improve the expectations for disease free survival, but in the majority of cases deteriorates hormonal and metabolic equilibrium leading to decreased cellular estrogen surveillance and increase in both morbidity and mortality.

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REFERENCES

1. Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. Lancet. 1896; 2: 104-107.
2. Boyd S. On oophorectomy in cancer of the breast. BMJ. 1900; 2: 1161-1187.
3. Suba Z. The pitfall of the transient, inconsistent anticancer capacity of antiestrogens and the mechanism of apparent antiestrogen resistance. Drug Des Devel Ther. 2015; 9: 4341-4353.
4. Suba Z. Causal therapy of breast cancer irrelevant of age, tumor stage and ER-status: stimulation of estrogen signaling coupled with breast conserving surgery. Recent Pat Anticancer Drug Discov. 2016 Apr 15. [Epub ahead of print].
5. Braithwaite RS, Chlebowski RT, Lau J, George S, Hess R, Col NF. Meta-analysis of vascular and neoplastic events associated with tamoxifen. J Gen Intern Med. 2003; 18: 937-947.
6. Maggi A. Liganded and unliganded activation of estrogen receptor and hormone replacement therapies. Biochim Biophys Acta. 2011; 1812: 1054-1060.
7. Kaaks R, Berrino F, Key T, Rinaldi S, Dossus L, Biessy C, et al. Serum sex steroids in premenopausal women and breast cancer risk within the European Prospective Investigation into Cancer and Nutrition (EPIC).

J Natl Cancer Inst. 2005; 97: 755-765.

8. Larionov AA, Miller WR. Challenges in defining predictive markers for response to endocrine therapy in breast cancer. Future Oncol. 2009; 5: 1415-1428.

9. Suba Z. Diverse pathomechanisms leading to the breakdown of cellular estrogen surveillance and breast cancer development: new therapeutic strategies. Drug Design Devel Ther. 2014; 8: 1381-1390.

10. Suba Z. DNA stabilization by the upregulation of estrogen signaling in BRCA gene mutation carriers. Drug Des Devel Ther. 2015; 9: 2663-2675.

11. Hartley MC, McKinley BP, Rogers EA, Kalbaugh CA, Messich HS, Blackhurst DW, et al. Differential expression of prognostic factors and effect on survival in young (< or =40) breast cancer patients: a case-control study. Am Surg. 2006; 72: 1189-1194.

12. Van Landeghem AA, Poortman J, Nabuurs M, Thijssen JHH. Endogenous concentration and subcellular distribution of estrogens in normal and malignant human breast tissue. Cancer Res. 1985; 45: 2900-2906.

13. Bulun SE, Chen D, Moy I, Brooks DC, Zhao H. Aromatase, breast cancer and obesity: a complex interaction. Trends Endocrinol Metab. 2012; 23: 83-89.

14. Suzuki T, Miki Y, Akahira J, Moriya T, Ohuchi N, Sasano H. Aromatase in human breast carcinoma as a key regulator of intratumoral sex steroid concentrations. Endocr J. 2008; 55: 455-463.

15. Sasano H, Miki Y, Nagasaki S, Suzuki T. In situ estrogen production and its regulation in human breast carcinoma: From endocrinology to intracrinology. Pathol Int. 2009; 59: 777-789.

16. Suba Z. Circulating and local estrogen concentrations are protective against breast cancer in obese women. In: Rahman A, Zaman K, editors. Topics in Anti-Cancer Research. Bentham Science Publishers, online. 2015; 4: 3-42.

17. Bollet MA, Savignoni A, De Koning L, Tran-Perennou C, Barbaroux C, Degeorges A, et al. Tumor aromatase expression as a prognostic factor for local control in young breast cancer patients after breast-conserving treatment. Breast Cancer Res. 2009; 11: 54.

18. Suba Z. Triple-negative breast cancer risk in women is defined by the defect of estrogen signaling: preventive and therapeutic implications. Onco Targets Ther. 2014; 7: 147-164.

19. Britt K, Ashworth A, Smalley M. Pregnancy and the risk of breast cancer. Endocr Relat Cancer. 2007; 14: 907-933.

20. Rajkumar L, Guzman RC, Yang J, Thordarson G, Talamantes F, Nandi S. Prevention of mammary carcinogenesis by short-term estrogen and progestin treatments. Breast Cancer Res. 2004; 6: 31-37.

21. Jerry DJ. Roles for estrogen and progesterone in breast cancer prevention. Breast Cancer Res. 2007; 9: 102.

22. Papaioannou S, Tzafettas J. Anovulation with or without PCO, hyperandrogenaemia and hyperinsulinaemia as promoters of endometrial and breast cancer. Best Pract Res Clin Obstet Gynaecol. 2010; 24: 19-27.

23. Cetin I, Cozzi V, Antonazzo P. Infertility as a cancer risk factor - a review. Placenta. 2008; 29: 169-177.

24. Källén B, Finnström O, Lindam A, Nilsson E, Nygren KG, Olausson PO. Malignancies among women who gave birth after in vitro fertilization. Hum Reprod. 2011; 26: 253-258.

25. Terry KL, Willett WC, Rich-Edwards JW, Michels KB. A prospective study of infertility due to ovulatory disorders, ovulation induction, and incidence of breast cancer. Arch Intern Med. 2006; 166: 2484-2489.

26. Talley LI, Grizzle WE, Waterbor JW, Brown D, Weiss H, Frost AR. Hormone receptors and proliferation in breast carcinomas of equivalent histologic grades in pre- and postmenopausal women. Int J Cancer. 2002; 98: 118-27.

27. Hefti MM, Hu R, Knoblauch NW, Collins LC, Haibe-Kains B, Tamimi RM, et al. Estrogen receptor negative/progesterone receptor positive breast cancer is not a reproducible subtype. Breast Cancer Res. 2013; 15: 68.

28. Suba Z. Circulatory estrogen level protects against breast cancer in obese women. Recent Pat Anticancer Drug Discov. 2013; 8: 154-167.

29. Phipps AI, Malone KE, Porter PL, Daling JR, Li CI. Reproductive and hormonal risk factors for postmenopausal luminal, HER-2-overexpressing, and triple-negative breast cancer. Cancer. 2008; 113: 1521-1526.

30. Ma H, Wang Y, Sullivan-Halley J, Weiss L, Marchbanks PA, Spirtas R, et al. Use of four biomarkers to evaluate the risk of breast cancer subtypes in the women's contraceptive and reproductive experiences study. Cancer Res. 2010; 70: 575-587.

31. Suba Z. Defective estrogen signaling is the highest risk for breast cancer. Int J Cancer Res Prev. 2015; 8: 209-225.

32. Suba Z. Low estrogen exposure and/or defective estrogen signaling induces disturbances in glucose uptake and energy expenditure. J Diabet Metab. 2013; 4: 272-281.

33. Jordan VC, Dowse LJ. Tamoxifen as an anti-tumour agent: effect on oestrogen binding. J Endocrinol. 1976; 68: 297-303.

34. Hayes DF. Tamoxifen: Dr. Jekyll and Mr. Hyde? J Natl Cancer Inst. 2004; 96: 895-897.

35. Dixon JM. Endocrine resistance in breast cancer. New J Science. 2014; 27.

36. Santen RJ, Song RX, Zhang Z, Kumar R, Jeng M-H, Masamura A, et al. Long-term estradiol deprivation in breast cancer cells up-regulates growth factor signaling and enhances estrogen sensitivity. Endocr Relat Cancer. 2005; 12: 61-73.

37. Miller WR, O'Neill J. The importance of local synthesis of estrogen within the breast. Steroids. 1987; 50: 537-548.

38. Colditz GA, Bohlke K. Priorities for the primary prevention of breast cancer. CA Cancer J Clin. 2014; 64: 186-194.

39. Gorski JJ, Kennedy RD, Hosey AM, Harkin DP. The complex relationship between BRCA1 and ERalpha in hereditary breast cancer. Clin Cancer Res. 2009; 15: 1514-1518.

40. Lowder JL, Oliphant SS, Ghetti C, Burrows LJ, Meyn LA, Balk J. Prophylactic bilateral oophorectomy or removal of remaining ovary at the time of hysterectomy in the United States, 1979-2004. Am J Obstet Gynecol. 2010; 202: 538.

41. Rocca WA, Grossardt BR, de Andrade M, Malkasian GD, Melton LJ. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. Lancet Oncol. 2006; 7: 821-828.

42. Løkkegaard E, Jovanovic Z, Heitmann BL, Keiding N, Ottesen B, Pedersen AT. The association between early menopause and risk of ischaemic heart disease: influence of Hormone Therapy. Maturitas. 2006; 53: 226-233.

43. Parker WH, Jacoby V, Shoupe D. Effect of bilateral oophorectomy on women's long term health. Women's Health (Lond Engl). 2009; 5: 565-

576.

44. Rocca WA, Grossardt BR, Maraganore DM. The long-term effects of oophorectomy on cognitive and motor aging are age dependent. Neurodegener Dis. 2008; 5: 257-260.

45. Melton LJ 3rd, Khosla S, Malkasian GD, Achenbach SJ, Oberg AL, Riggs BL. Fracture risk after bilateral oophorectomy in elderly women. J Bone Miner Res. 2003; 18: 900-905.

46. Suba Z. Gender-related hormonal risk factors for oral cancer. Pathol Oncol Res. 2007; 13: 195-202.

47. Gago-Dominguez M, Castelao JE, Yuan JM, Ross RK, Yu MC. Increased risk of renal cell carcinoma subsequent to hysterectomy. Cancer Epidemiol Biomarkers Prev. 1999; 8: 999-1003.

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