

· 综述 ·

Medical and psychosocial considerations in the treatment of young breast cancer patients

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Although advances in early detection and treatment have made breast cancer more a chronic illness rather than a death sentence, breast cancer remains a dreaded experience for women. A diagnosis of breast cancer can lead to serious psychosocial problems since this disease can have a devastating impact on women's sexual function and self-esteem. Despite the improvements in patient survival, it is necessary to examine and understand psychosocial quality of life (QOL) issues among breast cancer survivors. Indeed, younger breast cancer patients experience more severe emotional distress than older women, putting younger women at higher risk of psychosocial maladjustment^[1].

In theory, loss of a breast or poor breast appearance would be more distressing to younger than to older women, due to the association between youth and greater expectation of physical beauty. Potential infertility has a negative impact on a woman's self-conception as a sexual person. Systemic treatment disrupts sexual function by causing premature menopause, with estrogen loss leading to vaginal atrophy and androgen loss, which potentially decreases sexual desire and arousability. Easier access and increased awareness have resulted in higher rates of referral for genetic testing for hereditary breast cancer, especially in younger women, which may lead to an increase in psychological distress.

These age-related consequences of breast cancer require a greater understanding of the specific needs of younger women who are diagnosed with breast cancer and the unique challenges they experience. This review discusses the medical and psychological considerations applicable to breast cancer patients before treatment, especially in younger women requiring a more complex approach.

1 Body image

Body image is defined as the mental picture of

one's body and attitude about one's physical self, including feelings of femininity and attractiveness, health, wholeness, normal functioning and sexuality. As body image is more important to younger patients, it should be carefully considered. Physicians and surgeons should thoroughly discuss this issue with their patients preoperatively. Negative perceptions of body image among breast cancer survivors include dissatisfaction with appearance, perceived loss of femininity and body integrity, reluctance to look at oneself naked, feeling less sexually attractive, consciousness about appearance and dissatisfaction with surgical scars^[2]. Women with better perceptions of body image had higher self-confidence in coping with breast cancer^[3]. Moreover, self-perception of body image has been shown to correlate with QOL.

To date, no consensus has been reached on whether dissatisfaction with body image correlates with the type of surgery (i. e. mastectomy, breast conserving surgery or mastectomy followed by immediate reconstruction). Several studies reported that women who underwent a mastectomy were more likely to report body image dissatisfaction than those who underwent breast conserving treatment^[4], whereas other studies showed no correlation between surgery type and dissatisfaction with body image^[5]. More recent studies have tended to show correlations between more conservative surgery and better psychological outcomes, probably because of improvements in prognosis.

Type of surgery is based in part on the preferences of individuals, who must imagine the effects of surgery on their future life. However, predicting QOL and stigma following breast cancer surgery is challenging for newly diagnosed patients. An investigation of the correlation between a woman's preoperative prediction of the results of different types of breast cancer surgery and postoperative outcomes found that women inaccurately predicted postoperative QOL and stigma for all surgical options, particularly for mastectomy^[6]. Preoperatively, patients underestimated postoperative QOL and overestimated stigma related to mastectomy.

Since 2004, there have been reversals in the steady increase in breast conserving surgery rate and

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the steady decrease in mastectomy rate^[6-7]. One possible explanation for the increase in mastectomy rate may be increased education regarding reconstruction options^[8]. Women were found to be four times more likely to choose mastectomy when presented with options for breast reconstruction, with younger and more highly educated patients choosing mastectomy at higher rates than older and less educated patients^[9].

Early involvement of patients in surgical decision-making may be more informative and comprehensive for women considering surgery. Patient involvement has reduced depression and anxiety related to body image after mastectomy, as well as to diminish chronic pain and fatigue^[10].

2 Sexual problems

The increasing number of younger breast cancer survivors and the importance of sexual functioning promote the patients to understand the effects of breast cancer diagnosis and treatment on the time course of sexual problems and the factors contributing to these problems. Comparisons of young women with breast cancer and similarly aged healthy women found that breast cancer treatment substantially reduced sexual activity and increased body image and sexuality problems^[11]. For example, 67% of young women with breast cancer were sexually active compared with 74% to 81% of healthy young women^[11]. Furthermore, these sexual difficulties did not appear to be a short-term problem, since some women continued to experience sexual difficulties 5 – 10 years after diagnosis, including vaginal dryness, reduced frequency of sexual activity and reduced breast sensitivity^[2].

Studies have shown that good body image is related to the resumption of sexual relations, whereas poor body image is associated with sexual dysfunction^[12]. Body image and sexual problems remained correlated, even after accounting for various physical and psychosocial factors^[13]. Other studies found that sexual problems in younger women were not related to sociodemographic factors or the type of breast cancer surgery^[4, 14]. Sexual problems soon after surgery and beyond the first year after treatment may be associated with other factors, including chemotherapy and reductions in perceived sexual attractiveness, which may result from treatment or reflect a generally negative self-image^[14]. Increased sexual problems among sexually active women were associated with being married, reporting vaginal dryness, poorer mental health, partner's difficulty understanding one's feelings, and more problems with body image.

In particular, the lower prevalence of sexual activity reported by Asian women may be due to

cultural difference between Asian and Euro-American regarding a woman's relationship with her partner and her role within the family. Asian women were more concerned about family harmony, whereas Euro-American women were more concerned about sexual intimacy with their partners^[15].

Although sexual functioning is an important QOL issue for women, it may be difficult for patients to initiate discussions, suggesting that clinicians should routinely raise the topic. A conceptual model was presented with proposing factors influencing sexual health, which included demographic and personal characteristics, medical variables, body image, partner relationship and health-related QOL^[16]. Oncologists can use this conceptual model to examine predictors of multiple domains of sexual problems among younger women diagnosed with breast cancer.

Surgery and radiotherapy can cause skin to become red, tender and irritated, although these effects may subside later. However, their partners do not know what is painful or how long this pain will continue, leading to longer sexual abstinence than required. Once couples begin to avoid sexual activity, they may continue to avoid sexual contact on an ongoing basis because of anxiety regarding their partner's withdrawal response. Interventions that increase understanding of these issues before and during treatment may be beneficial to both breast cancer patients and their spouses.

3 Interpersonal relationship

Young couples would likely face more relationship strain than older couples, since the latter have more mutual understanding and stability in relationship. A survey found that 41% of spouses of breast cancer patients experienced more than mild depression and 11% had obvious anxiety^[17]. Another study found that 88% of husbands of breast cancer patients experienced psychological and physical distress associated with their wives' cancer, including vague anxieties about the future, depressed mood, sleep disturbances and irritation^[18].

Despite these levels of distress experienced by breast cancer patients and their spouses, they did not show significantly elevated rates of divorce or separation^[19]. In one study, 42% of these couples stated that the diagnosis of breast cancer brought them closer, compared with 7% who felt more distant^[20]. Risk factors for poor adjustment included little social support from others, less marital satisfaction, a perceived increase in illness-related demands and having a partner on chemotherapy or with many role limitations^[21]. Interestingly, perceived deterioration of sexual relationship after surgery did not always lead to perceived deterioration

of their overall relationship^[22].

One of the major concerns for young families affected by breast cancer is its impact on their children. An extensive review found that parental cancer had a multifaceted impact on emotional, social, behavioral and cognitive aspects of child functioning. The most consistent variables appeared to be parental psychological functioning, marital satisfaction and family communication^[23]. A positive relationship between parents and children before diagnosis helped children adapt to the changes brought about by the illness^[24]. Open communication between parents and children led to more effective coping and strengthened parent-child relationship. Many children and adolescents reported that the illness led to the fact of spending more time with their parents and a sense of becoming closer to their families^[25]. These findings indicate that warm and supportive parenting may serve as a protective factor for these children and adolescents.

A literature review about children living with a parent with cancer found that parents are concerned about the best methods of talking about their advanced cancer with their children. These parents attempt to be good parents, maintain normalcy in their children's lives and be concerned about the emotional impact of cancer on children^[26]. Clinicians should encourage parents to communicate openly with their adolescents about the cancer treatment and consequences. In addition, it is imperative to provide parents with support and confidence in speaking with their adolescent children.

4 Fertility

Most anticancer treatments, including surgery, radiotherapy, chemotherapy, endocrine therapy and biologic therapy, have a substantial impact on gonadal function and may lead to loss of fertility. It was reported that 6%–9.5% of women with breast carcinoma are diagnosed before the age of 40 years, and infertility resulted from breast cancer treatment may be associated with psychosocial distress^[27]. Breast cancer survivors have lower pregnancy rates than age-matched healthy individuals^[28]. Access to fertility counseling is important to improve the prognosis of cancer patients and deal with social problems, evident in many countries, associated with delays in child-bearing.

American Society of Clinical Oncology recommends that younger cancer patients be referred for fertility counseling. In particular, these patients should be evaluated for risks of treatment-related infertility and all patients at risk of infertility and interested in fertility preservation should be referred to a specialist with expertise in fertility preservation methods.

About 48.3% of younger patients worried about whether pregnancy would affect their breast cancer, and 43.1% worried whether or not they could become pregnant if they wanted to. Previously, pregnancy after breast cancer was contraindicated due to the potentially negative impact of pregnancy on patient prognosis. However, women who became pregnant after breast cancer did not have a poorer prognosis^[29]. Moreover, no biological rationale or supporting evidence has determined an optimal time for these women to become pregnant. The experts recommend not becoming pregnant within 2 years after diagnosis in cases of early relapse^[30]. An ongoing prospective trial by Breast International Group and North American Breast Cancer Group is currently investigating the feasibility and impact of a temporary treatment interruption to allow conception in patients with endocrine responsive breast cancer^[31].

The incidence of anticancer-treatment-related ovarian failure in breast cancer patients mainly depends on chemotherapy regimen, the use of tamoxifen and the age of patients at diagnosis. This incidence rises with increasing age, 22%–61% in women <40 years and 61%–97% in women ≥40 years^[32].

There are two major mechanisms associated with chemotherapy induced ovarian toxicity: direct induction of follicles and oocyte apoptosis and vascular damage to ovaries^[33]. Alkylating agents, especially cyclophosphamide, are associated with a high risk of ovarian toxicity^[34], with carboplatin and cisplatin also having negative effects. In contrast, methotrexate and fluorouracil are associated with low risks of ovarian failure^[35].

Analysis of adjuvant endocrine therapy showed that tamoxifen alone was associated with a low risk of premature menopause, with the latter strictly dependent on age^[36]. In women >45 years, treatment with tamoxifen increased the risk of infertility by 10%^[36]. Temporary suppression of ovarian function and reversibility by analogs of luteinizing hormone (LHRHa) are also strongly associated with patient age, with resumption of the menstrual cycles expected in 90% of patients <40 years, but in only 70% of those >40 years^[36-37]. A meta-analysis on the role of LHRHa in preventing chemotherapy-induced premature ovarian failure (POF) found a relative risk (RR) of 0.40–0.46, showing that this strategy reduces the gonadal toxicity of cytotoxic therapy in premenopausal cancer patients. However, the groups of women who received chemotherapy alone and chemotherapy plus LHRHa had similar rates of resumed menses (RR: 1.31) and spontaneous pregnancy (RR: 0.96)^[38].

One study reported that 5% of young breast cancer patients experienced pregnancy and live birth

within 6 years of diagnosis^[2]. This loss of opportunity to have children is significant, not only for these women, but for their male partners. Moreover, both these women and their partners have little preparation for this change in family plans. Infertility problems result in broader relationship difficulties for couples. The main fertility preservation techniques currently available for young breast cancer patients include temporary ovarian suppression, embryo cryopreservation and cryopreservation of oocytes and ovarian tissue. Of the cryopreservation techniques tested, only cryopreservation of embryos and of mature oocytes have shown reliable results, whereas the cryopreservation of ovarian tissue, immature oocytes and oocytes matured *in vitro* are in early experimental phases^[39].

Oncologists should discuss with younger breast cancer patients about the possibility of fertility loss due to anticancer treatment and the available strategies to reduce these effects. Patients may make informed choices about fertility preservation strategies only after a proper discussion of their risks, success rates and costs. A pre-treatment active counseling resulted in a higher rate of pregnancy, indicating that an active approach to counseling makes a huge difference psychologically. A positive attitude towards pregnancy by physicians may also help reduce the fear of pregnancy after breast cancer and the resulting elective abortion rate^[40].

5 Premature menopause

Sudden menopause during breast cancer treatment may be particularly distressing for younger women. These unanticipated sets of changes can disrupt their sense of womanhood, as well as emphasizing the seriousness of their cancer.

Amenorrhea is a frequent consequence of breast cancer therapy in younger women. In many women, amenorrhea is temporary, with menses resuming in the months following the end of treatment. For some women, however, amenorrhea is permanent, heralding the onset of early menopause. These effects may be reversible over time, but it is hard to predict for individual women. Even if menses do resume, many breast cancer survivors are at increased risk of POF^[41]. Most women who remain amenorrheic for at least one year will not resume menstruation and will be considered to have experienced POF^[42]. Early menopause may also result from bilateral prophylactic oophorectomy for ovarian suppression or as a risk reduction strategy in women at high risk for ovarian cancer such as BRCA1/2 mutation carriers. Regardless of the reason, these women experience the physiological changes that frequently accompany menopause. While these experiences might be “normal” for women in their 50s, they may be extremely

depressing for women in their 20 s, 30 s and early 40 s and may negatively affect QOL. Not only are sexual concerns important for their own sake, but they appear to be related to broader aspects of well-being. Women and their partners should be made aware of these issues.

Fatigue and sleep disturbance may result from hot flashes and/or night sweats, and are associated with an increase in depressive symptoms in breast cancer women. In addition, women with POF are at increased risk for reduced bone mineral density (BMD) following adjuvant chemotherapy compared with premenopausal women. Bone loss can lead to osteopenia and osteoporosis if not treated, putting women at increased risk of fractures at an earlier age. This finding may have implications for long-term breast cancer survivors who may be at higher risk for osteopenia and osteoporosis.

Weight gain is frequent in women of all ages during and after breast cancer treatment. Among women who were pre-menopausal at diagnosis, those who become menopausal as a result of treatment seemed to experience more weight gain compared with women who remained premenopausal^[43]. Assessment of the physiological causes of weight gain related to adjuvant chemotherapy indicates that amenorrhea caused by adjuvant chemotherapy may precipitate fat accumulation and alterations in the distribution of fat^[44].

At present, it is unclear whether POF is a risk factor for other adverse outcomes, including decreases in cognitive function and cardiovascular health^[45].

6 Genetic counseling

Genetic testing is available to detect mutations in several genes associated with increased risk of breast cancer, including BRCA1, BRCA2, and PTEN genes. Increases in predictive genetic testing and genetic counseling may enhance the ability of mutation carriers to understand their risk of an inherited disorder, as well as their options dealing with these increased risks.

At present, many cancer centers offer genetic testing to younger breast cancer patients. Women diagnosed with breast cancer are offered genetic counseling and testing for germline mutations in BRCA1/2 if they have a strong family history and/or they meet other criteria associated with a mutation rate exceeding a predefined threshold, with age < 40 years being an important criterion. Genetic risk assessment is usually offered after completion of surgery and during adjuvant therapy, because of test results are usually not available until two months after blood drawing. Genetic counseling of these patients includes discussions of the increased risk of cancers in other organs, and the risk of other family members having the same mutations.

The incidence of another tumor developing in the treated breast is higher in women with than without BRCA mutations, and depends on the type of breast surgery. Mutation carriers were at significantly increased risks of local tumor recurrence following breast-conserving treatment than mastectomy at 10 (10.5% *vs* 3.5%) and 20 (30.2% *vs* 5.5%) years^[46]. Moreover, compared with non-carriers, BRCA1/2 mutation carriers had a substantially higher lifetime risk of contralateral breast cancer, which is age-dependent and can be as high as 68% if age at diagnosis of the first cancer was <40 years^[47].

These complexities in genetic risk information, and the caused considerable anxiety and distress may increase the psychological burden of these women, leading to specific counseling needs for affected women with a high perceived risk of developing a second breast cancer or ovarian cancer. Perception of high risk has been associated with a lack of motivation of patient decision-making and subsequent treatment, as well as resistance to standard education and counseling^[48].

Many studies have found that distress in women is greater if they are the first in their families to be tested for a BRCA gene mutation^[49]. The main reason that breast cancer patients undergo genetic testing was to alert their relatives to their own risk. However, affected women found it difficult to inform family members about their DNA test results. These findings indicate that women recently diagnosed with breast cancer, who are the first in their family to be tested for a BRCA gene mutation, are an extremely vulnerable group.

Barriers to genetic counseling among patients who declined genetic testing include concerns about health insurability, cost, emotional impact, the lack of perceived benefit and time commitment. Anxiety and the anticipation of negative emotional reactions to the test results have also been identified as important reasons to decline genetic testing^[50].

Clinicians need to be aware of the possibly high psychological distress faced by recently diagnosed breast cancer patients who take part in genetic testing and counseling. Patients diagnosed less than 1 year earlier, as well as those at high risk for a second breast cancer or ovarian cancer may require additional counseling to manage high levels of distress and assist in their decision-making process.

7 Conclusion

This review focused on the medical and psychosocial impacts of newly diagnosed breast cancer on younger women. These women have specific needs, requiring consideration and interventions by specialists to deal with distress associated with body image and sexual problems,

interpersonal relationships (especially the impact on their children), infertility, premature menopause and genetic counseling. Young women experience unique challenges, such as how to tell their partners and when and how to address potential awkwardness in sexual behaviors, and when to address fertility issues. Thus, a wide range of important psychosocial issues should be addressed to optimize QOL of younger breast cancer patients and their partners. Special consideration should be given to the above-mentioned factors as women adapt to cope with breast cancer diagnosis.

Many younger women are promising in their professional careers or at their career peak. Moreover, they are at different stages of family and personal development; with children at home, or contemplating having additional children, etc. A sophisticated and planned approach for younger breast cancer patients could result in successful breast cancer management and minimize the social ripple effect.

References

- [1] Schag CA, Ganz PA, Polinsky ML, et al. Characteristics of women at risk for psychosocial distress in the year after breast cancer [J]. *J Clin Oncol*, 1993, 11(4): 783-793.
- [2] Ganz PA, Greendale GA, Petersen L, et al. Breast cancer in younger women: reproductive and late health effects of treatment [J]. *J Clin Oncol*, 2003, 21(22): 4184-4193.
- [3] Pikler V, Winterowd C. Racial and body image differences in coping for women diagnosed with breast cancer [J]. *Health Psychol*, 2003, 22(6): 632-637.
- [4] Arora NK, Gustafson DH, Hawkins RP, et al. Impact of surgery and chemotherapy on the quality of life of younger women with breast carcinoma: a prospective study [J]. *Cancer*, 2001, 92(5): 1288-1298.
- [5] Goldberg JA, Scott RN, Davidson PM, et al. Psychological morbidity in the first year after breast surgery [J]. *Eur J Surg Oncol*, 1992, 18(4): 327-331.
- [6] Waljee JF, Ubel PA, Atisha DM, et al. The choice for breast cancer surgery: can women accurately predict postoperative quality of life and disease-related stigma? [J]. *Ann Surg Oncol*, 2011, 18(9): 2477-2482.
- [7] John EM, Miron A, Gong G, et al. Prevalence of pathogenic BRCA1 mutation carriers in 5 US racial/ethnic groups [J]. *JAMA*, 2007, 298(24): 2869-2876.
- [8] Alderman AK, Hawley ST, Waljee J, et al. Understanding the impact of breast reconstruction on the surgical decision-making process for breast cancer [J]. *Cancer*, 2008, 112(3): 489-494.
- [9] Janz NK, Mujahid M, Lantz PM, et al. Population-based study of the relationship of treatment and sociodemographics on quality of life for early stage breast cancer [J]. *Qual Life Res*, 2005, 14(6): 1467-1479.
- [10] Kalaitzi C, Papadopoulos VP, Michas K, et al. Combined brief psychosexual intervention after mastectomy: effects on sexuality, body image, and psychological well-being [J]. *J Surg Oncol*, 2007, 96(3): 235-240.
- [11] Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors [J]. *JAMA*, 1999, 281(6): 537-544.
- [12] Ganz PA, Kwan L, Stanton AL, et al. Quality of life at the end of primary treatment of breast cancer: first results from the moving beyond cancer randomized trial [J]. *J Natl Cancer Inst*, 2004, 96(5): 376-387.
- [13] Fobair P, Stewart SL, Chang S, et al. Body image and sexual

- problems in young women with breast cancer [J]. *Psychooncology*, 2006, 15(7): 579-594.
- [14] Burwell SR, Case LD, Kaelin C, et al. Sexual problems in younger women after breast cancer surgery [J]. *J Clin Oncol*, 2006, 24(18): 2815-2821.
 - [15] Kagawa-Singer M, Wellisch DK. Breast cancer patients' perceptions of their husbands' support in a cross-cultural context [J]. *Psychooncology*, 2003, 12(1): 24-37.
 - [16] Ganz PA, Desmond KA, Belin TR, et al. Predictors of sexual health in women after a breast cancer diagnosis [J]. *J Clin Oncol*, 1999, 17(8): 2371-2380.
 - [17] Inoue S, Saeki T, Mantani T, et al. Factors related to patient's mental adjustment to breast cancer: patient characteristics and family functioning [J]. *Support Care Cancer*, 2003, 11(3): 178-184.
 - [18] Takahashi M. Psychosocial distress among young breast cancer survivors: implications for healthcare providers [J]. *Breast Cancer*, 2014, 21(6): 664-669.
 - [19] Dorval M, Maunsell E, Taylor-Brown J, et al. Marital stability after breast cancer [J]. *J Natl Cancer Inst*, 1999, 91(1): 54-59.
 - [20] Dorval M, Guay S, Mondor M, et al. Couples who get closer after breast cancer: frequency and predictors in a prospective investigation [J]. *J Clin Oncol*, 2005, 23(15): 3588-3596.
 - [21] Northouse LL, Peters-Golden H. Cancer and the family: strategies to assist spouses [J]. *Semin Oncol Nurs*, 1993, 9(2): 74-82.
 - [22] Takahashi M, Kai I. Sexuality after breast cancer treatment: changes and coping strategies among Japanese survivors [J]. *Soc Sci Med*, 2005, 61(6): 1278-1290.
 - [23] Visser A, Huizinga GA, van der Graaf WT, et al. The impact of parental cancer on children and the family: a review of the literature [J]. *Cancer Treat Rev*, 2004, 30(8): 683-694.
 - [24] Christ GH, Siegel K, Sperber D. Impact of parental terminal cancer on adolescents [J]. *Am J Orthopsychiatry*, 1994, 64(4): 604-613.
 - [25] Kennedy VL, Lloyd-Williams M. How children cope when a parent has advanced cancer [J]. *Psychooncology*, 2009, 18(8): 886-892.
 - [26] Phillips F. Adolescents living with a parent with advanced cancer: a review of the literature [J]. *Psychooncology*, 2014, 23(12): 1323-1339.
 - [27] Reh AE, Lu L, Weinerman R, et al. Treatment outcomes and quality-of-life assessment in a university-based fertility preservation program: results of a registry of female cancer patients at 2 years [J]. *J Assist Reprod Genet*, 2011, 28(7): 635-641.
 - [28] Stensheim H, Cvancarova M, Møller B, et al. Pregnancy after adolescent and adult cancer: a population-based matched cohort study [J]. *Int J Cancer*, 2011, 129(5): 1225-1236.
 - [29] Azim HA Jr, Kroman N, Paesmans M, et al. Prognostic impact of pregnancy after breast cancer according to estrogen receptor status: a multicenter retrospective study [J]. *J Clin Oncol*, 2013, 31(1): 73-79.
 - [30] Cardoso F, Loibl S, Pagani O, et al. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer [J]. *Eur J Cancer*, 2012, 48(18): 3355-3377.
 - [31] Pagani O, Partridge A, Korde L, et al. Pregnancy after breast cancer: if you wish, ma'am [J]. *Breast Cancer Res Treat*, 2011, 129(2): 309-317.
 - [32] Del Mastro L, Venturini M, Sertoli MR, et al. Amenorrhea induced by adjuvant chemotherapy in early breast cancer patients: prognostic role and clinical implications [J]. *Breast Cancer Res Treat*, 1997, 43(2): 183-190.
 - [33] Oktem O, Oktay K. Quantitative assessment of the impact of chemotherapy on ovarian follicle reserve and stromal function [J]. *Cancer*, 2007, 110(10): 2222-2229.
 - [34] Fisher B, Dignam J, Mamounas EP, et al. Sequential methotrexate and fluorouracil for the treatment of node-negative breast cancer patients with estrogen receptor-negative tumors: eight-year results from National Surgical Adjuvant Breast and Bowel Project (NSABP) B-13 and first report of findings from NSABP B-19 comparing methotrexate and fluorouracil with conventional cyclophosphamide, methotrexate, and fluorouracil [J]. *J Clin Oncol*, 1996, 14(7): 1982-1992.
 - [35] Ganz PA, Land SR, Geyer CE Jr, et al. Menstrual history and quality-of-life outcomes in women with node-positive breast cancer treated with adjuvant therapy on the NSABP B-30 trial [J]. *J Clin Oncol*, 2011, 29(9): 1110-1116.
 - [36] Goodwin PJ, Ennis M, Pritchard KI, et al. Risk of menopause during the first year after breast cancer diagnosis [J]. *J Clin Oncol*, 1999, 17(8): 2365-2370.
 - [37] Del Mastro L, Catzeddu T, Venturini M. Infertility and pregnancy after breast cancer: current knowledge and future perspectives [J]. *Cancer Treat Rev*, 2006, 32(6): 417-422.
 - [38] Yang B, Shi W, Yang J, et al. Concurrent treatment with gonadotropin-releasing hormone agonists for chemotherapy-induced ovarian damage in premenopausal women with breast cancer: a meta-analysis of randomized controlled trials [J]. *Breast*, 2013, 22(2): 150-157.
 - [39] Lambertini M, Anserini P, Levaggi A, et al. Fertility counseling of young breast cancer patients [J]. *J Thorac Dis*, 2013, 5 Suppl 1: S68-80.
 - [40] Rippy EE, Karat IF, Kissin MW. Pregnancy after breast cancer: the importance of active counselling and planning [J]. *Breast*, 2009, 18(6): 345-350.
 - [41] Partridge A, Gelber S, Gelber RD, et al. Age of menopause among women who remain premenopausal following treatment for early breast cancer: long-term results from International Breast Cancer Study Group Trials V and VI [J]. *Eur J Cancer*, 2007, 43(11): 1646-1653.
 - [42] Partridge AH, Ruddy KJ. Fertility and adjuvant treatment in young women with breast cancer [J]. *Breast*, 2007, 16 Suppl 2: S175-181.
 - [43] Goodwin PJ, Ennis M, Pritchard KI, et al. Adjuvant treatment and onset of menopause predict weight gain after breast cancer diagnosis [J]. *J Clin Oncol*, 1999, 17(1): 120-129.
 - [44] Del Rio G, Zironi S, Valeriani L, et al. Weight gain in women with breast cancer treated with adjuvant cyclophosphamide, methotrexate and 5-fluorouracil. Analysis of resting energy expenditure and body composition [J]. *Breast Cancer Res Treat*, 2002, 73(3): 267-273.
 - [45] Vearcombe KJ, Pachana NA. Is cognitive functioning detrimentally affected after early, induced menopause? [J]. *Menopause*, 2009, 16(1): 188-198.
 - [46] Pierce LJ, Phillips KA, Griffith KA, et al. Local therapy in BRCA1 and BRCA2 mutation carriers with operable breast cancer: comparison of breast conservation and mastectomy [J]. *Breast Cancer Res Treat*, 2010, 121(2): 389-398.
 - [47] Evans DG, Moran A, Hartley R, et al. Long-term outcomes of breast cancer in women aged 30 years or younger, based on family history, pathology and BRCA1/BRCA2/TP53 status [J]. *Br J Cancer*, 2010, 102(7): 1091-1098.
 - [48] Bleiker EM, Hahn DE, Aaronson NK. Psychosocial issues in cancer genetics--current status and future directions [J]. *Acta Oncol*, 2003, 42(4): 276-286.
 - [49] Loader S, Shields CG, Rowley PT. Impact of genetic testing for breast-ovarian cancer susceptibility [J]. *Genet Test*, 2004, 8(1): 1-12.
 - [50] Geer KP, Ropka ME, Cohn WF, et al. Factors influencing patients' decisions to decline cancer genetic counseling services [J]. *J Genet Couns*, 2001, 10(1): 25-40.

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