SUBSEQUENT PREGNANCY AND PROGNOSIS IN BREAST CANCER SURVIVORS

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SUMMARY – An increase in the incidence of breast cancer in women aged <40 years in conjunction with a pronounced shift towards later childbearing has been reported in recent years. Because survival from breast cancer in women of childbearing age has significantly improved, they are often concerned whether subsequent pregnancy will alter their risk of disease recurrence. In the modern era, the prognosis of pregnancy-associated breast cancer is comparable to non-pregnancy-associated breast cancer and women can bear children after breast cancer treatment without compromising their survival. Therefore, they should not be discouraged from becoming pregnant, and currently the usual waiting time of at least 2 years after the diagnosis of breast cancer is recommended. However, a small, nonsignificant adverse effect of pregnancy on breast carcinoma prognosis among women who conceive within 12 months of breast cancer diagnosis and a higher risk of relapse in women younger than 35 up to 5 years of the diagnosis may be found. Fortunately, for women with localized disease, earlier conception up to six months after completing their treatment seems unlikely to reduce their survival. Ongoing and future prospective studies evaluating the risks associated with pregnancy in young breast cancer survivors are required.

Key words: *Breast neoplasms – complications; Female; Survivors; Pregnancy; Pregnancy complications, neoplastic; Risk factors*

Introduction

Breast cancer incidence increases with age, with the vast majority of women diagnosed after the age of 40. Nevertheless, approximately 7% of women with breast cancer are diagnosed before age 40, and this disease accounts for more than 40% of all cancers in women in this age group[1]. In women in developed countries, breast cancer is the most common cancer and 12% of breast cancer occur in women aged 20-34[2]. However, an increase in the incidence of breast cancer in women aged <40 has been reported in recent years in many western countries. The mean annual changes in the incidence for the calendar period 1995-2006 from all European cancer registries were 1.032 (95%CI=1.019-1.045) and 1.014 (95%CI=1.010-1.018) in women aged 20-29 and 30-39 at diagnosis, respectively[3]. In the USA, the incidence of breast cancer with distant involvement at diagnosis increased in 25- to 39-year-old women from 1.53 *per* 100,000 in 1976 to 2.90 *per* 100,000 in 2009. This is an absolute difference of 1.37 *per* 100,000, representing the mean compounded increase of 2.07% *per* year over the 34-year interval[4]. In Croatia in women aged 25-30, the incidence is only 0.57/100,000, which means that about 4 cases of breast cancer during pregnancy and 4 cases of pregnacies after completed treatment of breast cancer can be expected *per* year[5].

Many countries of the developed world have experienced a pronounced shift towards later childbearing in recent years. An increasing trend towards delay in

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childbearing from 30 to 40 years of age for different reasons, in addition to improved diagnostic and therapeutic methods is concordant with the increasing incidence of breast cancer in women that have not yet completed their family. It seems highly likely that in older women, the first full-term pregnancy increases the risk of breast cancer, whereas early age at full-term pregnancy appears to lower the risk. Although the definitive mechanism through which early pregnancy protects from breast cancer remains unclear, several hypotheses have been proposed, such as changes to the hormonal profile of parous women, differences in the estrogen responsiveness of the mammary gland, and the fact that a more differentiated mammary gland is less susceptible to carcinogens[6]. These age dependent relationships may be partly explained by the high proportion of estrogen receptor-negative tumors in younger women (<35 years), whereas delayed childbearing represents a risk factor for estrogen receptor-positive tumors among older premenopausal women[7]. An increased breast cancer risk with advancing maternal age at first childbirth is supported by a relative risk of 3.7 (95%CI: 1.30-10.5) in women with an estimated first median age of 41 years, compared with those with an estimated first birth age of 23 years[8]. In recent decades, considerable reduction in breast cancer-related death has been achieved with adjuvant therapies (chemotherapy, endocrine and targeted therapies, radiotherapy) but at the cost of significant long-term consequences, including infertility. Reproductive issues are of great importance to young women, in particular those that have not completed their families before breast cancer diagnosis[9]. There is the need to educate young patients regarding fertility issues at the moment of diagnosis[10]. Fortunately, pregnancy after breast cancer does not appear to confer poor prognosis. Moreover, a higher rate of pregnancy than expected was found after treatment, possibly due to newer treatments including fertility preservation and also possibly due to active fertility counseling programs[11]. In the past, women were counseled against pregnancy, based on the theory that elevated levels of estrogen and progesterone in pregnancy could increase the risk of breast cancer recurrence. However, current data show no increase in the risk of recurrence and no difference in survival in women who have children after breast cancer therapy as compared with women who choose not to become pregnant. As a result, breast cancer is no longer considered an absolute contraindication for subsequent pregnancies. A meta-analysis of 14 studies has confirmed that pregnancy in women with a history of breast cancer is safe and does not compromise their overall survival[12]. However, there is no information to estimate the impact of later pregnancies on the risk of recurrence in women with pregnancy-associated breast cancer. In a recent case report, the first description of a pregnancy-associated recurrence in a patient previously treated for pregnancy-associated breast cancer has been described[13].

This paper reviews the literature regarding the influence of subsequent pregnancy on the prognosis in breast cancer survivors.

Survival of Patients with Pregnancy after Breast Cancer

Treatment of young women with breast cancer is usually the same as for older women. However, breast cancers in younger women are generally diagnosed at a later stage with more aggressive features and have inferior outcomes[14]. Therefore, young age represents an independent adverse prognostic factor for their survival in spite of more anthracycline-based adjuvant chemotherapy and hormonal therapy with tamoxifen in patients with positive lymph nodes and those with positive hormonal receptors[15]. However, recent advances in the field of adjuvant therapy in breast cancer have led to significant improvements in breast cancer survival. This has resulted in a progressive decline in breast cancer-related mortality, so that in 2010 there were estimated to be 400,000 breast cancer survivors under age 40 in the USA. Hence, enquiry into the feasibility of fertility preservation, subsequent pregnancy and breastfeeding is increasingly encountered[16]. Therefore, women of childbearing age with breast cancer are often concerned about whether they will become infertile after treatment, and in those who wish to bear children, whether a subsequent pregnancy will alter their risk of disease recurrence[17]. Concerns about premature menopause and infertility are common in younger women and have a role in the level of distress after treatment[18]. If a woman desires to bear children after her breast cancer treatment, she should be advised on fertility preservation options. Fertil-

ity preservation issues should be discussed within a multidisciplinary environment, including oncologists and fertility specialists, and these fertility procedures must be initiated as early as possible prior to starting systemic therapy. Young women should benefit from currently applied options, such as cryopreservation of embryos, oocytes, ovarian tissue and ejaculated or surgically retrieved sperms prior to treatment. However, this procedure requires *in vitro* fertilization and thus a participating male partner (or sperm donor). Oocyte and ovarian tissue cryopreservation are emerging options for women who do not have a male partner at diagnosis. However, most of these procedures are considered experimental, and there are limited data regarding the safety of such strategies. For this reason, they can only be contemplated after adequate counseling and should be limited to storage of gonadal tissue or whole gonads[14,19]. Among multiple strategies, controlled ovarian stimulation for embryo or oocyte cryopreservation is currently the best established method for fertility preservation. Current treatment protocols offer a minimal time delay until oncologic treatment is commenced. In urgent settings, random-start ovarian stimulation represents a new technique that provides significant advantage by decreasing the total time of the treatment, and because it may be started irrespective of the phase of the cycle without compromising oocyte yield and maturity before cancer treatment. However, in patients with estrogen-sensitive cancers, stimulation protocols using letrozole are currently preferred over tamoxifen regimens, and therefore it may be highly advisable to use letrozole with gonadotropins routinely as a safe, effective and novel protocol of ovulation induction[20]. Breast cancer survivors may be at risk of recurrent disease during subsequent pregnancy because they may be susceptible to the hormonal changes of pregnancy, stimulating growth of any remaining breast cancer cells or dormant micrometastases with subsequent pregnancies[17]. The influence of subsequent pregnancy on the prognosis of the disease is usually regarded through its effect on patient survival, observing survival rates or relative risks, and appearence of recurrence or distant metastases[21].

In non-population based studies employing case-matching methodology, which have provided more data to allow analysis of 5- and 10-year survival rates, there appears to be a survival advantage in the group of cases in comparison with controls. This survival superiority presented in survival rates is also observed in those patients with negative lymph nodes, and compares favorably with patients with positive lymph nodes in both case control studies and case series. The literature in any earlier or later published series indicates that subsequent pregnancy in women with breast cancer does not decrease their survival. Moreover, survival rates in breast cancer patients who have subsequently become pregnant are good, often the same and sometimes even better than in patients without subsequent pregnancy[12,16]. In an earlier study by Mignot *et al.*[22], it was demonstrated that there was no significant difference in survival curves because the 10-year survival rate in patients who conceived after breast cancer treatment was 71% (90% in those with nodes - cancer and 71% in those with nodes + cancer, with no significant difference between the cases and controls in each group). Clark and Chua[23] report that subsequent pregnancies taking place at least one year and preferably two years after treatment for breast cancer do not affect patient survival. Moreover, subsequent pregnancy may confer an improved prognosis. Lethaby *et al.*[24] also found no significant differences in survival between the women who had pregnancies subsequent to diagnosis of breast cancer and breast cancer patients who did not conceive. Gelber *et al.*[25] report that subsequent pregnancy does not adversely affect the prognosis of early-stage breast cancer because overall 5- and 10-year survival percentages measured among patients who became pregnant were 92% and 86%, respectively, and survival in the matched comparison group was 85% at 5 years and 74% at 10 years The superior survival rate may merely reflect a healthy patient selection bias, but it is also consistent with an antitumor effect of pregnancy. In a study by Largillier *et al.*[26], it was found that pregnancy subsequent to breast cancer therapy resulted in a 77% decrease of death in women younger than 35.

The population-based studies tried to avoid the recollection bias prevalent in the retrospective studies, but perhaps they added bias in the choice of control subjects for matching. These studies in addition to retrospective studies have shown that subsequent pregnancy results in an improvement of survival with favorable relative risks between 0.2 (0.1-0.5) and 0.8

(0.3-2.3). In a study by Sankila *et al.*[27], it was found that controls had a 4.8-fold risk of death compared with those who delivered after a diagnosis of breast cancer. Their interpretation of this result was a "healthy mother effect" (i.e. that only women who feel healthy give birth and those who are affected by the disease do not). Von Schoultz *et al.*[28] found that the relative hazard for women who became pregnant after diagnosis of breast cancer in comparison with women without subsequent pregnancy was 0.48, which suggested a possible decreased risk of distant dissemination. Kroman *et al.*[29] report that women who had full-term pregnancy after breast-cancer treatment had a non-significantly reduced risk of death (relative risk 0.55) compared with women who had no full-term pregnancy. In a study by Velentgas *et al.*[30], the age-adjusted relative risk of death associated with any subsequent pregnancy was 0.8. Although the findings of the study were based on a small number of deaths, they do not suggest that pregnancy after a diagnosis of breast carcinoma has an adverse effect on survival. Mueller *et al.*[31] found that women with child births occurring 10 months or more after diagnosis had a significantly decreased risk of dying (relative risk = 0.54), compared with women without subsequent child births. It has been suggested that the results of the study may provide some reassurance to young women with breast carcinoma that subsequent childbearing is unlikely to increase their risk of mortality. Blakely *et al.*[32] report that the incidence of disease recurrence was 23% in women who experienced pregnancy and 54% in women who did not. The hazard ratio for disease recurrence in patients with post-treatment pregnancy was 0. In a repeated study by Kroman *et al.*[33], it was found that women who had full-term pregnancy subsequent to breast cancer treatment had a reduced risk of dying (relative risk 0.73), compared with other women with breast cancer. In line with their previous study, but based on more than twice the patient material, they found no evidence that pregnancy after treatment of breast cancer had negative influence on the prognosis. Kranick *et al.*[34] report that in women with and without subsequent pregnancy, neither the risk of recurrence nor death differed significantly by subsequent pregnancy history during an average 12-year follow up (adjusted hazard ratio recurrence 1.2; adjusted hazard ratio death 1.0). In a recent study, Litton[35] found that for breast cancer survivors, there does not appear to be an increased risk of death associated with subsequent pregnancies when compared with breast cancer patients who did not have subsequent pregnancies. A meta-analysis by Azim *et al.*[12] suggested the pregnancy after a diagnosis of breast cancer to be associated with improved survival when compared to breast cancer patients that did not have pregnancy after their diagnosis. The women who became pregnant following breast cancer diagnosis had a 41% reduced risk of death compared to women who did not become pregnant. Hence, breast cancer survivors should not be denied the opportunity of future conception.

Excluding the effects of pregnancy after breast cancer on survival rates and relative risks, other outcome measures include recurrence and incidence of distant metastases. Sutton *et al.*[36] found a recurrence rate of 28% in the pregnancy group and 46% in the non-pregnant group. With regard to distant metastasis, von Schoulz *et al.*[28] report a rate of 8% among all patients who became pregnant, compared with a rate of 24% among patients without subsequent pregnancy. Similarly, Malamos *et al.*[37] report a 14% rate of local recurrence in the pregnant group and 39% in the non-pregnant group. Kajouharova *et al.*[38] found an incidence of distant metastases of 15% among all patients who became pregnant subsequent to surgery for breast carcinoma. Therefore, it is evident that pregnancy may not have an adverse effect on the incidence of recurrence or poor survival in patients previously treated for breast cancer.

Interval from Diagnosis of Breast Cancer to Pregnancy

The optimal time to delay pregnancy following diagnosis and treatment of breast cancer is unknown and it is an important issue for all patients considering pregnancy. The definition of this time interval is variable because some studies use the period from the time of diagnosis to the time of delivery, which excludes abortions, whilst others use the time from diagnosis of breast cancer to diagnosis of pregnancy, which will then include all abortions[21]. The risk of relapse and the time to recurrence is related to many factors including the stage, grade and nodal status, as well as the hormone receptor status[39]. From ear-

lier to current studies, the usual practice recommends waiting for at least 2 years between diagnosis of early breast cancer and pregnancy, as most recurrences will develop in this time[26]. Previous reports suggest that women who survive breast cancer and subsequently conceive have at least equivalent, if not better, survival than similar women matched for age and stage of cancer who do not subsequently conceive[25,39]. Saphner *et al.*[40] have reported that the risk of recurrence was greatest (13.3%) in the interval between year 1 and 2 after surgery. This risk then decreased consistently, and beyond 5 years averaged at about 4.3% *per* year in women with hormone receptor positive breast cancer. However, patients with hormone receptor negative tumors had a higher hazard of recurrence in years 0-5, which then decreased over time, whereas the hazard of recurrence for women with hormone receptor positive cancers was relatively constant in the first 5 years after diagnosis and from years 5 to 12. Gelber *et al.*[25] report a better survival rate in those women who had subsequent pregnancy (overall 5-year survival rate of 92% *versus* 85% in cases *versus* controls), even though 43% of cases completed pregnancy within 1 year of diagnosis. Although in a recent study by Litton[35], there does not appear to be an increased risk of death associated with subsequent pregnancies for breast cancer survivors when compared with controls, waiting for at least 2 years is recommended because it may convey a protective effect. Kranick *et al.*[34] in their study found that neither the risk of recurrence nor death differed significantly by subsequent pregnancy history during an average 12-year follow up. Although the number of cases was limited, subgroup analyses indicated a small, nonsignificant adverse effect among women who conceived within 12 months of diagnosis. On the other hand, Largillier *et al.*[26] found a high risk of relapse in women aged under 35. Therefore, it may be preferable to postpone pregnancy in these patients beyond 5 years after breast cancer therapy. However, Ives *et al.*[41] do not support the current medical advice given to all premenopausal women with a diagnosis of breast cancer to wait for 2 years before attempting to conceive. This recommendation may be valid only for women who are receiving treatment or have systemic disease at diagnosis. On the other hand, for women with localized disease, conception as early as six months after completing their treatment is unlikely to reduce survival. The results reflect the clinical recommendation that women delay pregnancy for two years after diagnosis and suggest that women who have good prognosis need not wait for two years to become pregnant.

It is advisable that pregnancy be avoided during active treatment of breast cancer and several years after, so appropriate, acceptable and effective contraception is a priority. Those who have completed their childbearing should be advised about permanent sterilization. However, in cases when childbearing has not been completed, the use of natural family planning and barrier contraceptives is recommended to prevent undesired pregnancy while the risk of relapse is present[42].

Hypothesis on Survival

The good survival rate consistently observed in reviews, often the same or better for patients who become pregnant subsequent to a diagnosis of breast cancer than in patients with no subsequent pregnancy, may in part be due to the bias of retrospective studies. One possible explanation for this supposed survival advantage is the 'healthy mother effect,' as women who feel healthy may be more likely to conceive, leading to selection bias[27]. However, there are also biological theories as to why pregnancy may protect against relapse, such as alloimmunization against breast cancer cells. It is postulated that breast carcinoma cells and fetal cells share common antigens, representing a basis for isoimmunization that occurs during pregnancy. The fetal antigen hypothesis has confirmed the presence of a tumor-specific antigen, MUC1, on both fetal and breast cancer tissues. Multiparous women also generate anti-MUC1 major histocompatibility complex-restricted cytotoxic T cell cytolytic activity against MUC1-bearing tumor cell lines[43]. Because the mammary gland is exposed to the highest physiological concentrations of estradiol and progesterone during full-term pregnancy, it is possible that these elevated levels of hormones induce cytotoxic effects and protection from mammary cancer[44]. If a woman has full-term pregnancy and has not already had a prior initiation event, then the pregnancy would be expected to leave the breast tissue more differentiated and less susceptible to carcinogenic influences at long

term[45]. In women with BRCA1 or 2 gene mutations, the risks of pregnancy are not well established. Observational studies suggest that BRCA1 mutation carriers who have their first child at 30 years or older may have a reduced personal risk of breast cancer. However, the opposite effect has been observed in BRCA2 mutation carriers where late first pregnancies (over 30 years) are linked with an increased risk of breast cancer[46]. In a recent multi-center cohort study in 12,084 women with a BRCA1 or BRCA2 mutation, there were 128 case subjects who were diagnosed with breast cancer while pregnant or who became pregnant after the diagnosis of breast cancer. It was found that pregnancy concurrent with or after a diagnosis of breast cancer does not appear to adversely affect survival among BRCA1/2 mutation carriers[47]. Therefore, young breast cancer patients who have not completed their family should not be discouraged from becoming pregnant when they wish to, since there is no adverse effect of pregnancy on survival. Although fertility may be impaired by chemotherapy, births seem to sustain no adverse effects, while breastfeeding appears to be feasible and safe[48]. In addition, it has recently been found that microchimerism may be highly relevant to later cancer development. Detection of male microchimerism was strongly associated with a reduced risk of developing breast cancer and also an increased risk of developing colon cancer. Lower concentrations of Y chromosome from previous pregnancies with a male fetus have been found in women with breast cancer (40%) as compared with cancer-free women (70%). Therefore, lower concentrations of microchimerism may predate cancer diagnosis, and higher levels may indicate a possible beneficial effect on breast cancer development[49].

Conclusions

There is a wide perception that subsequent pregnancy may worsen the prognosis of young breast cancer survivors. In many earlier and current studies, it has been found that pregnancy is not associated with an increased risk of disease recurrence or poorer survival in patients previously treated for breast carcinoma. Therefore, young breast cancer patients who have not completed their family should not be discouraged from becoming pregnant, and the current usual waiting time of at least 2 years after the diagnosis of breast cancer is recommended. However, a small, adverse effect of pregnancy on breast carcinoma prognosis among women who conceive within 12 months of breast cancer diagnosis and a higher risk of relapse in women aged less than 35 for up to 5 years may be found. Fortunately, for women with localized disease, earlier conception up to six months after completing their treatment seems unlikely to reduce their survival. Ongoing and future prospective studies evaluating the risks associated with pregnancy for young breast cancer survivors are required.

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Sažetak

KASNIJA TRUDNOĆA I PROGNOZA KOD PREŽIVJELIH OD RAKA DOJKE

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U posljednje vrijeme izvješćuje se o sve većoj pojavnosti raka dojke skupa s izraženijim odgađanjem rađanja kod žena mlađih od 40 godina. Budući da se preživljenje žena generativne dobi zbog raka dojke značajno poboljšalo, one su često zabrinute hoće li kasnija trudnoća doprinijeti opasnosti od recidiva bolesti. U današnje vrijeme prognoza raka dojke u trudnoći je usporediva s rakom dojke koji nije u svezi s trudnoćom i žene mogu rađati djecu nakon liječenja raka dojke bez ugrožavanja njihovog preživljavanja. Stoga žene ne treba obeshrabriti u želji za trudnoćom, a uobičajene su preporuke da se pričeka s trudnoćom najmanje 2 godine nakon postavljene dijagnoze. Ipak, malen i neznakovit nepovoljan učinak trudnoće na rak dojke može se naći među ženama koje zanesu unutar 12 mjeseci od dijagnoze raka dojke, a veća opasnost od recidiva kod žena mlađih od 35 godina do čak 5 godina nakon dijagnoze. Srećom, kod žena s lokaliziranom bolešću izgleda manje vjerojatno da bi ranija trudnoća do čak 5 mjeseci nakon završenog liječenja ugrozila njihovo preživljavanje. Potrebna su daljnja istraživanja koja će procijenti rizike u svezi s trudnoćom kod mlađih osoba preživjelih od raka dojke.

Ključne riječi: *Rak dojke – komplikacije; Ženska osoba; Preživjele osobe; Trudnoća; Trudnoća, komplikacije tumora*