

# **Chapter 2**

## **Special Issues in Younger Women with Breast Cancer**

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**Abstract** Although women less than 50 years old make up less than 25 % of the patient population with breast cancer in industrialized countries, they have unique clinical and psychosocial issues that must be addressed as part of their oncology care to ensure the best health and psychosocial outcomes after treatment. Preserving fertility is a major issue for many younger women who have either not had children or would like to have additional children after treatment. Dealing with the disruption of a cancer diagnosis at a young age is challenging physically, socially and emotionally, and the health care system does not always address these patients' concerns. Because younger women have the potential for a long life expectancy after cancer treatment, preventing and reducing the risk for late effects of cancer treatment is very important. We discuss these and a range of other issues throughout this chapter.

**Keywords** Younger women • Fertility • Psychosocial distress • Premature menopause • Hereditary breast cancer

### **Introduction**

In Western industrialized countries, breast cancer is primarily a disease of postmenopausal women, with incidence patterns showing a modest premenopausal peak in the fifth decade of life, but a much more substantial incidence peak in the seventh and eighth decades. For a woman who is age 30, the probability of developing breast cancer in the next 10 years is 0.44 % or 1 in 228, while at age 70 the 10

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**Table 2.1** Age-specific probabilities of developing invasive female breast cancer<sup>a</sup>

If current age is	The probability of developing breast cancer in the next 10 years is (in %)	Or 1 in:
20	0.06	1,732
30	0.44	228
40	1.45	69
50	2.31	43
60	3.49	29
70	3.84	26
Lifetime risk	12.29	8

Adapted from Desantis et al. (2014) with permission

<sup>a</sup>Among those free of cancer at the beginning of the age interval. Based on cases diagnosed between 2008 and 2010. Percentages and “1 in” numbers may not be numerically equivalent due to rounding. Probabilities derived using the National Cancer Institute DevCan software (version 6.7.0)

years probability is 3.84 % or 1 in 28 (Desantis et al. 2014) (Table 2.1). Thus, when cancer occurs in a very young woman it is a rare and unexpected event. She has no peers who have the disease, and she may be at a time in life where she has not completed her education or professional development, and may or may not be in a long-term partnered relationship. If she is without children, cancer treatment may substantially disrupt her childbearing plans; if she already is a parent, she may fear for her ability to successfully raise her children, and not leave them prematurely. For women who are in their 40s, cancer treatments may precipitate early menopause, and the disruptions of cancer treatments often add stresses to normal mid-life issues and career challenges.

Younger women are a heterogeneous group, at various developmental stages, and as such, their concerns and needs differ substantially from more mature women who have likely had friends who have experienced breast cancer, and for whom years of screening mammography and educational campaigns have alerted them to the possibility of breast cancer occurring. In this chapter, we will provide a description of the diverse characteristics of younger women with breast cancer, including the tumor and treatment variations, the reproductive consequences of treatments, the social and psychological sequelae, and their higher risk of mortality from breast cancer. We subsequently will examine the many research challenges and opportunities that management of this target population requires, including the tailoring of treatments to reduce the burden of long term toxicities, better management of psychological health, as well as better access to fertility preservation, health promotion and cancer prevention.

## Who Are the Younger Women with Breast Cancer?

Breast cancer in women younger than 50 makes up about 25 % of the incident breast cancer cases each year (Desantis et al. 2014) (see Table 2.2). Fewer numbers of incident cases occur if one uses earlier age cut-points, as noted previously. In a recent systematic review of the unique psychosocial needs of younger women with breast cancer, we used age 50 years as the cut-point for the review due to the paucity of

**Table 2.2** Estimated new female breast cancer cases and deaths by age, United States, 2013<sup>a</sup>

Age	In situ cases	Invasive cases	Deaths
<40	1,900	10,980	1,020
<50	15,650	48,910	4,780
50–64	26,770	84,210	11,970
65+	22,220	99,220	22,870
All ages	64,640	232,340	39,620

Adapted from Desantis et al. (2014) with permission

Source Total estimated cases are based on 1995–2009 incidence rates from 49 states as reported by the North American Association for Central Cancer Registries. Total estimated deaths are based on data from the US mortality data, 1995–2009, National Center for Health Statistics, Centers for Disease Control and Prevention

<sup>a</sup>Rounded to nearest 10

literature focused solely on very young women (Howard-Anderson et al. 2012). 45 years is probably a more appropriate age to use as a cut point for linking to other studies of young adults with cancer, which use 39 years as the upper age limit (Brinton et al. 2008; Tricoli et al. 2011). However, in detailed interviews with younger women with breast cancer, classification of “young” was more often associated with life stage and challenges, rather than chronological age (Dunn and Steginga 2000). While there is no official definition of “young breast cancer patient” we will focus on the diversity of clinical and psychosocial features of women with breast cancer who are less than 50 years at diagnosis. However, a CDC program and federal legislation that has called attention to this group of patients using an age of less than 45 years at diagnosis ([http://www.cdc.gov/cancer/breast/young\\_women/index.htm](http://www.cdc.gov/cancer/breast/young_women/index.htm)) Although we acknowledge that younger men may be affected by breast cancer, this is such a small group, for which even less is known, that we confine our discussion to women.

The complexity of discussing this special population relates foremost to the diversity of life stage of development interacting with chronological age. The experience of the rare young woman diagnosed with breast cancer while in college is extremely different from the mother of teenage children who is in her early 40s. However, within these several decades of risk that these two women mark, the emotional, educational, professional and reproductive issues may be similar and be independent of chronological age. The ability to accept the cancer diagnosis, complete treatment, remain adherent to endocrine therapy if required, and continue with education or work, may be more tied to emotional maturity and financial resources, which may or may not be related to chronological age. Also, younger women with breast cancer have a higher likelihood of hereditary breast cancer, where knowledge of the potential risk for the disease is known (i.e., by family history if not by established mutation); however, many women diagnosed at a young age may first learn of having a germ line mutation for breast cancer at the time of cancer diagnosis, without prior knowledge of the disease in any relatives, especially if this is passed through the paternal line. The rate of germ line mutations of *BRCA1* are considerably higher in younger women than in older women, and *TP53* mutations may also be responsible for breast cancer in these

**Table 2.3** Predicted probabilities of a *BRCA1* mutation based on age and tumor characteristics

Age (years)	All histologies (%)	ER-negative and high-grade tumors (%)
<30	8	35
31–34	5	26.5
35–39	2	6.6
40–44	1.5	3.7
45–49	1	2.5
50–59	0.3	0.9

ER Estrogen receptor

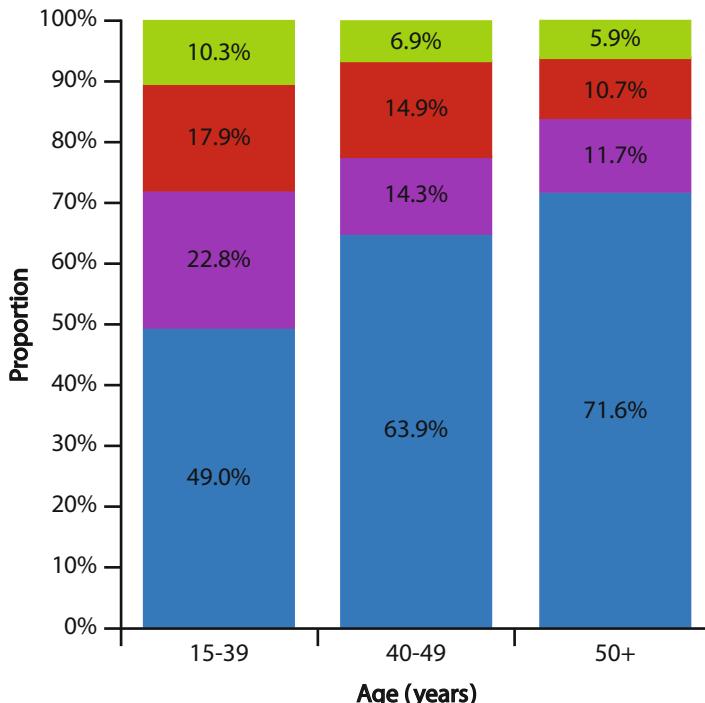
Adapted from Gabriel and Domchek (2010) with permission

women (Gabriel and Domchek 2010) (Table 2.3). Increasingly, breast cancer gene panels are being used to assess these younger women, and in the future, we may have a better explanation for the occurrence of cancer at such a young age. Also, among these women may be survivors of a prior childhood cancer in which radiation treatment to the thorax or total body was included (Moskowitz et al. 2014). Such women are also among the younger breast cancer patients and survivors.

One of the other challenges among younger women is the co-occurrence of breast cancer and pregnancy—largely due to the later age of marriage and childbearing among well-educated women (Litton et al. 2013; Partridge et al. 2004; Theriault and Litton 2013). Deferring pregnancy until an older age is a recent phenomenon in Western industrialized countries. These breast cancers may be diagnosed during pregnancy or in the first years after childbirth. Large tumors and delays in diagnosis are common due to the natural changes that occur in the breast as part of pregnancy and lactation. Clearly, these cancers are already present in the breast prior to the pregnancy, but come to clinical recognition with the stimulation of hormones during pregnancy. The increased challenge of delivering antineoplastic treatments during pregnancy, as well as the high risk management of the mother and fetus, can add to the stress of the cancer diagnosis and treatment for young women. And of course, for most young women of reproductive age who are diagnosed with breast cancer, the concerns about preserving fertility may influence decision-making about treatments, (Ruddy et al. 2014) including finding clinicians to provide these services in a timely manner, as well as having the financial resources to pay for these services.

## Is Breast Cancer Biologically Different in Younger Women?

Genetic and genomic discoveries during the past 15 years have allowed us to subtype breast cancer molecularly and develop classifications that are useful with regard to biology and therapy. Survival outcomes for women younger than 35 have been historically poor (Keegan et al. 2013), although most of the improvements related to introduction of adjuvant chemotherapy were most apparent in younger women. For some time, it has been known that the frequency distribution of hormone receptor positive breast cancer is lower in younger women than post-menopausal women, but



**Fig. 2.1** Proportion of breast cancer subtypes among California women by age group, 2005–2009. Hormone receptor (HR) positive and human epidermal growth factor receptor 2 (HER2) negative (blue), HR+/HER2+ (red), HR-/HER2+ (green), and triple negative (purple). Adapted from Keegan et al. 2012 with permission

recent gene expression studies have more extensively characterized the distribution of hormone receptor positive, triple negative, double negative and HER2 positive tumors (Keegan et al. 2012) (Fig. 2.1). Also, some of these subtypes vary by race/ethnicity, most notably the high proportion of triple negative and basal cell phenotypes in African American and Latino women, as well as the higher rates of incident breast cancer in African American women before age 40 compared to other ethnic groups (Brinton et al. 2008). In addition, the higher rate of incident stage IV metastatic breast cancer among younger age women compared to older women complicates the initial treatment and management (Johnson et al. 2013).

## Treatment of Breast Cancer in Younger Women

All of the age and life stage variables described earlier will influence the treatment of young women, beyond the tumor stage and biological features, which would be the dominant consideration in older women. If the younger woman carries a

deleterious *BRCA1/2* mutation, she may opt for bilateral mastectomy at the time of initial surgery, even though breast conservation could be considered. The young woman's treatment decision-making may also be influenced by her marital status and whether she has completed childbearing. In addition, we see some women opting for very aggressive chemotherapy regimens, even in the setting of small tumors with favorable characteristics, due to their desire to stay alive to raise children or pursue other meaningful goals. Other younger women may avoid treatments because they fear their toxicity, such as infertility. Because younger women often have more advanced stage disease at diagnosis, they will more likely be subjected to post-mastectomy or axillary radiation, which may contribute to the burden of survivorship symptoms. In our experience, younger women opt for disability during treatment more frequently than older women. The experience can be physically and emotionally overwhelming.

The psychosocial challenges of getting young women through treatment may be considerable. As alluded to earlier, the emotional and financial resources needed to cope with treatments which often last more than a year, are substantial. Finally, adherence to endocrine therapy is a particularly challenging problem, as often chemotherapy has induced transient or permanent amenorrhea, and the addition of tamoxifen increases the likelihood of greater vasomotor symptoms (Ganz et al. 2011), as well as sexual dysfunction in some. Several studies document a relationship between younger age and nonadherence to endocrine therapy. Factors such as low social support, a perceived lack of understanding of endocrine therapy and lack of the opportunity to ask questions at diagnosis, and a greater number of menopausal symptoms are associated with nonadherence [e.g., (Cluze et al. 2012)].

Premature menopause and infertility are a frequent consequence of treatments in young women, and prolonged treatments may also interfere with the timing of subsequent childbearing. Specifically, the 5 years of endocrine therapy with tamoxifen may make it difficult to fit in a pregnancy, especially if a woman is in her late 30s. Although recent data do not suggest increased risk for breast cancer recurrence with childbearing, (Azim et al. 2012, 2013) this is still a major concern for some women. This is especially an issue for women with DCIS for whom treatment decisions may be quite difficult. We discuss fertility and reproductive concerns in greater detail in the Chap. 10. Premature menopause may lead to other health consequences such as weight gain and menopause-related symptoms.

## Risk of Mortality and Late Effects from Breast Cancer and Its Treatments

Breast cancer is the leading cause of death among women 40–59 years (Siegel et al. 2014) so that fear of recurrence and death from cancer is a reality for younger women with breast cancer. This is in spite of the significant advances in treatment with chemotherapy and targeted therapies. Many of the women living for long periods of time with metastatic breast cancer are younger women

(see Chap. 15 on metastatic breast cancer survivors). Younger women are also at greatest risk for experiencing the long-term and late effects of cancer treatment, similar to childhood cancer survivors, as they have a long time horizon of survival in which these long-term and late effects may occur. For example, fractures from early osteoporosis, cardiac failure, and second cancers (breast and non-breast) can occur. The extent to which the breast cancer treatments received as a young woman may accelerate various aspects of organ aging is uncertain at this time. Clearly, some of the manifestations of cognitive difficulties may portend accelerated brain aging, and both structural and functional brain changes have been observed in breast cancer survivors several decades later (Koppelmans et al. 2012a, b). Thus, younger women need to be viewed as a high-risk population at risk for future health events, and should be considered for systematic cancer prevention and control interventions. This is particularly true for *BRCA1/2* carriers in whom second cancers of the breast and Fallopian tubes/ovaries can be prevented or their risk reduced.

## Quality of Life, Psychological, and Behavioral Concerns

Breast cancer has a more negative impact on quality of life among younger women, particularly in the psychosocial and emotional domains (Cimprich et al. 2002; Ganz et al. 2003; Howard-Anderson et al. 2012; Mor et al. 1994). Younger women with breast cancer report worse mental health-related quality of life than both age-matched women without breast cancer and older women with breast cancer (Howard-Anderson et al. 2012). Younger women also report elevated levels of distress and depressive symptoms following cancer diagnosis, which may persist into survivorship (Avis et al. 2012, 2013). Higher levels of depressive symptoms in younger women are due to a variety of factors, including more aggressive treatment (though differences remain after controlling for type of treatment), a lower sense of peace and meaning in life, and particularly greater illness intrusiveness (Avis et al. 2012, 2013). Indeed, younger women report higher levels of illness intrusiveness in all domains of life, including health, diet, work, recreation, financial situation, relationships, and sex life, which are closely tied to depression. Further, younger women perceive cancer as more threatening (Vinokur et al. 1990) and report greater fear of cancer recurrence (Lebel et al. 2013) than older women.

In terms of physical symptoms, younger women report higher levels of bodily pain, vasomotor symptoms, fatigue, and sleep disturbance (Avis et al. 2012, 2013; Bower et al. 2000; Ganz et al. 2003; Palesh et al. 2010). These symptoms likely contribute to the increased depression and distress observed in younger women, and also have independent (negative) effects on quality of life. Indeed, fatigue is now recognized as one of the most common and distressing side effects of cancer treatment, as discussed in Chap. 6. Fatigue, depression, pain, and sleep problems not only erode quality of life but may also influence adherence to treatment, and possibly survival (Groenvold et al. 2007).

Many women are able to find some benefit from their experience with cancer, including positive changes in relationships with others, an enhanced feeling of self-worth and mastery, and a deepened appreciation for life. Younger women are particularly likely to report these positive changes (Koutrouli et al. 2012), perhaps because breast cancer may be one of the first highly stressful events they have experienced. Among younger women, finding benefit is facilitated by approach-oriented coping strategies and a sense of optimism about the future (Boyle et al. 2015). Thus, although the experience of breast cancer can be particularly devastating for younger women, they may experience more positive life changes in the aftermath of the experience, which prompts an increased appreciation of the preciousness (and fleetingness) of life.

## Social Consequences

The experience of breast cancer challenges young women's interpersonal spheres, deepening some relationships and diminishing others. As an "off-time" non-normative event, being diagnosed with breast cancer under age 50 can carry several social consequences (Adams et al. 2011). Specifically, the young woman who has no one among her similarly aged peers who has had breast cancer can feel isolated and have few models for adaptive coping. Moreover, friends and co-workers may not know how to provide effective support, having never encountered another young woman with breast cancer. The threat of mortality might become real for the first time in some social network members, leading even well-intentioned friends to avoid the young woman. Greater social support is associated with better psychological adjustment in young women with breast cancer (see Howard-Anderson et al. 2012 review). Even when among other breast cancer survivors, however, young women can feel alone; younger breast cancer survivors report feeling more isolated and less satisfied with cancer support groups due to their age (Thewes et al. 2004).

When diagnosed in young adult women, breast cancer also prompts developmental interpersonal challenges, as documented in clinical and qualitative reports (Corney et al. 2014; Schnipper 2003). Just as they are attaining adult independence, very young women with breast cancer can find themselves relying on their parents, other family members, and friends for care. At the same time, young breast cancer survivors who are mothers can feel that they are slighting their children's care. Women who have not forged relationships with intimate partners can experience anxiety about doing so and feel that treatments delay precious time for establishing adult relationships. Questions are common about when to raise the issue in a dating relationship, whether potential partners will be rejecting, and how to consider having children.

Existing intimate partner relationships also are affected by the breast cancer experience for young survivors (Baucom et al. 2005; Lewis et al. 2012). The threat of mortality often is paramount, with each partner afraid of the potential losses that can accompany cancer, as the assumption of a long life together is called into question.

Plans for having children can change, as can caretaking for children or elderly parents. Sexual intimacy also is affected. Young, partnered breast cancer survivors are less sexually active and have more body image and sexual problems than are similarly aged healthy women, although it is important to note that approximately a third of young survivors do not report problems in those realms (Fobair et al. 2006). Relationship, sexual, and body image problems all are related to lower quality of life in young survivors, likely with reciprocal causality (Avis et al. 2005). The potential for strengthening the relationship also can occur as the couple faces the cancer experience together.

## Research Challenges and Opportunities

In much of the world, breast cancer is primarily a disease of younger women, whereas in North America and Europe, younger women are in the minority because of the high incidence of postmenopausal breast cancer. Understanding the biological and psychosocial context of breast cancer in younger women is one of our central challenges. To the extent that risk factors for poor outcomes after a breast cancer diagnosis can be modulated by interventions directed at biological or behavioral factors, then research needs to focus on identifying those risk factors and developing specific post-treatment cancer control interventions. They may be as simple as providing information regarding normative psychosocial experiences of younger women with breast cancer or more complex, such as reducing tobacco and alcohol use, promoting adherence to endocrine therapy, or providing evidence-based therapy to women or couples to reduce anxiety and depression and enhance well-being. The double-edged sword of the benefits of amenorrhea for reduction in risk of breast cancer recurrence, and its negative consequences for women who want to have children, may interfere with effective treatment strategies.

Among the things we must do for all breast cancer patients, but particularly for younger women, is to tailor cancer treatments so that we do not over treat with very toxic therapies that have no benefit. For example, patients with small tumors and favorable, low risk tumors are unlikely to receive benefit from multi-agent chemotherapy. Yet, that is often the normative treatment for a younger premenopausal woman. Both she and the physician want to do “everything.” This may also include prophylactic mastectomy and oophorectomy in women who are not at hereditary risk for breast and ovarian cancer. Finding better ways to clarify actual risk and to communicate it will be critical (Institute of Medicine 2013). In contrast, there are some younger women who will avoid receiving recommended therapies either due to their belief systems or because they are unable to cope with the diagnosis in an effective way (see below for psychological challenges). Patients’ active engagement in medical decision-making and care is critical for support of clinical decisions that best fit the needs, values and preferences of the patient. For this patient population, having concomitant expert mental health support as part of the treatment team is crucial in light of the evidence of their heightened psychosocial morbidities (Adler and Page 2007).

## **Identification of Psychological Risk Groups in Need of Intervention**

In light of the evidence that younger breast cancer survivors as a group are more likely than older women to experience cancer as psychologically disruptive, all younger women stand to benefit from education regarding what to expect after diagnosis of and treatment for breast cancer, including strategies for managing the attendant life changes. Patient age does not appear to influence the efficacy of psychosocial interventions for distress and quality of life in adult cancer survivors generally (Faller et al. 2013). However, it is possible that interventions for younger women with breast cancer, specifically directed toward and tailored to address their predominant concerns, might produce more robust effects than current evidence-based approaches for the general population of adults with cancer. Development of effective strategies for promoting healthy behaviors, including physical exercise, healthy eating patterns, and adherence to endocrine therapies, also are warranted for young survivors.

Intervention development for young breast cancer survivors who are at particular risk for untoward psychological outcomes also is needed. Within the group of young breast cancer survivors, a number of psychosocial factors are associated with poorer psychological outcomes, including low social support, more cancer-related intrusive thoughts and feelings regarding cancer, and abruptly experienced menopausal symptoms, among others. Unfortunately, most research regarding risk and protective factors for positive quality of life in young survivors is cross-sectional in design, which precludes causal inference. Targeting survivors who might be in most need of intervention, such as socially isolated or depressed young women, is an important future direction for intervention.

## **Development of More Specialized Approaches to the Younger Patient in Practice Settings**

Just as the geriatric or pediatric cancer patient may need specialized services, so are there a number of critical services that need to be offered to younger women. First, honest and careful discussion of the reproductive health implications of the planned cancer treatment is essential. Just as we consider breast reconstruction as a covered benefit of rehabilitation from cancer treatment, fertility preservation should be organized, available, and potentially financed at an affordable rate. While there are likely only small numbers of patients who will need this service, its availability reinforces to the woman that she is expected to survive and that she may be able to have a family or more children in the future. Fortunately, increasing numbers of younger survivors now are able to have children either naturally or through preservation mechanisms.

We need to provide survivorship care for young women that focuses on their long time horizon after breast cancer, addressing lifestyle, health behaviors, and emotional well-being. Such care can maximize their chance of a healthy life including prevention of cancer recurrence if possible, and early detection of second cancers should they occur. Many younger women avoid mammograms because the first one did not detect their initial cancer. Effective and trusting long-term relationships with oncology professionals and knowledgeable primary care providers are necessary to address the health promotion and disease prevention that is a necessary part of follow-up for younger women. Finally, we should re-assess family history and re-evaluate the need and opportunity for genetic counseling and testing in younger women, as these options may have been overlooked initially in the rush to treat. As survivors, women will benefit from new knowledge about hereditary predisposition syndromes that may affect their future health and that of their family members.

In closing, younger women have been the beneficiaries of the major advances in the treatment of breast cancer, including adjuvant chemo- and hormonal therapies, hereditary predisposition testing, breast reconstruction, and breast conservation treatments. However, they are most at risk for psychological difficulties as a result of a breast cancer diagnosis and can benefit from information and psychosocial resources to help them adapt and cope with the untimely diagnosis. Because of their extended potential life span, they are especially vulnerable to the long term and late consequences of cancer treatment. As a result, cancer survivorship care planning should be an important component of young women's post-treatment care (see Chap. 17), to help mitigate preventable conditions that may result from or be exacerbated by cancer treatments.

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