Screening Childhood Cancer Survivors for Breast Cancer

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Key Words. Breast neoplasm/prevention and control · Second primary/epidemiology · Mass screening · Risk factors · Child · Time factors

ABSTRACT

The development of second primary solid tumors, especially breast neoplasms, is increased among patients who have survived childhood or adolescent malignancies. With the increased long-term survival of patients with pediatric cancer, questions regarding breast cancer screening in this group have been raised. At this time, there are no established guidelines for breast cancer surveillance in this high-risk population. The objective of this review is to summarize the incidence, list additional risk factors for the development of breast cancer, and discuss the benefits of early detection of second primary breast cancers in pediatric cancer survivors. We have devised an algorithm for breast cancer screening in survivors of childhood malignancy. Implications of treatment with radiation and chemotherapy and the influence on prognosis of genetic abnormalities such as p53 mutations are debated. The Oncologist 1997;2:228-234

INTRODUCTION

Breast cancer has emerged as a common secondary malignancy in survivors of many childhood cancers [1-36]. Most recently, those cured of Hodgkin’s disease have been reported to develop secondary breast cancers at an alarming rate [5]. Based on several studies, the cumulative risk for the development of these cancers ranges from 5% to 12% over a 25-year follow-up interval, and these cancer survivors develop second primary breast cancer at a younger age [2-30]. The incidence of breast cancer in the general population increases with age. The probability for developing breast cancer for American women is 1 in 26 at ages 40 to 59 years and 1 in 15 at ages 60-79 years [37].

Cancer screening implies that early detection yields a higher likelihood of disease control and reduced mortality [37]. Questions arise as to which histological pediatric cancer types and treatments predispose to a second primary breast malignancy; whether screening and early detection are efficacious in this population; and what chemical, radiation, immunologic, or genetic defects are responsible for this increased incidence. This report is an effort to summarize and update the existing literature on the incidence, etiology, natural history, and management of those patients with secondary breast cancer following the treatment of childhood malignancies.

INCIDENCE

The reports of second primary breast cancers are frequent in survivors of Hodgkin’s disease, but may also be seen after other childhood malignancies (Table 1). Those who have been treated with radiation for childhood Hodgkin’s disease have a higher risk of developing second primary breast cancer than does the normal population [5]. The estimated cumulative risk of second malignancies increased from 1.5% at 5 years to 7.7% at 15 years [4] (Table 2). Several studies, such as those of Brody [32] and Smith [35], do not even list breast cancer as a site of second cancer development. However, the total patient numbers

| Table 1. Types of pediatric malignancies with a second breast primary neoplasm |
|---------------------------------|---------------------------------|---------------------------------|
| ▲ Acute lymphoblastic leukemia | ▲ Acute non-lymphocytic leukemia | ▲ Neuroblastoma |
| ▲ Ewing’s Sarcoma               | ▲ Hodgkin’s disease              | ▲ Osteosarcomas |
| ▲ Retinoblastomas               | ▲ Rhabdomyosarcoma               | ▲ Wilms’ tumor |

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The Oncologist 1997;2:228-234
Table 2. Reported incidence for development of second primary cancers

<table>
<thead>
<tr>
<th>Study</th>
<th>Time interval (years)</th>
<th>% Breast secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhatia [5]</td>
<td>20</td>
<td>(17/36) 30%</td>
</tr>
<tr>
<td>Boivin et al. [8]</td>
<td>15</td>
<td>(39/521) 7.5%</td>
</tr>
<tr>
<td>Breslow et al. [38]</td>
<td>8.1 ± 17.3</td>
<td>(243) 4.6%</td>
</tr>
<tr>
<td>Sankila et al. [33]</td>
<td>1 - 38</td>
<td>(2,543/19,800) 13%</td>
</tr>
<tr>
<td>Van Leeuwen et al. [3]</td>
<td>17 - 22</td>
<td>(8/146) 5.6%</td>
</tr>
<tr>
<td>Breslow et al. [34]</td>
<td>1 - 38</td>
<td>(2,543/19,800) 13%</td>
</tr>
</tbody>
</table>

Table 3. Survival of women who develop secondary cancers

<table>
<thead>
<tr>
<th>Study</th>
<th>Time interval (years)</th>
<th>Survival (years to death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhatia [5]</td>
<td>20</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Boivin et al. [8]</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Breslow et al. [38]</td>
<td>8.1</td>
<td>&gt;2.8</td>
</tr>
<tr>
<td>Van Leeuwen et al. [3]</td>
<td>17 - 22</td>
<td>&gt;3.1</td>
</tr>
<tr>
<td>Hancock et al. [9]</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Smith et al. [35]</td>
<td>16.6</td>
<td>5.1</td>
</tr>
</tbody>
</table>

reported in these series are fewer than larger cohort studies which note a significant risk for developing secondary breast tumors. The time interval between the diagnosis of childhood malignancy and the development of breast cancer varies from 2 to 17 years. Those studies with low reported risks also have shorter follow-up intervals and may underestimate the true incidence for the development of breast cancer, since the latency period may be greater than 10 years [27, 29, 31, 32].

Survival

There is speculation that secondary malignancies are more aggressive tumors with an increased mortality rate (Table 3) [1, 3-5, 9, 14, 17-20, 22-29, 31-34]. Salloum et al. [34] found a high frequency of median quadrant tumors and bilateral breast cancers. Mortality due to secondary primary was 75% for all second cancers and 50% for breast cancer [34]. Breslow et al. [38] listed three patients with secondary breast cancer; two were alive at three years and the other died at 2.6 years. Formal studies looking at survival from second primary breast cancers need to be conducted.

Role of Radiation and Chemotherapy

Most second malignancies are thought to be treatment-related. The risk after the treatment of childhood Hodgkin’s disease was greater after six or more cycles of MOPP-based chemotherapy and after radiation doses exceeding 60 GY [1]. This demonstrates the importance of current efforts to limit the use of intensive chemotherapy and radiation therapy in this population, which are now applied only to patients with the most aggressive disease.

Radiation doses used to treat Hodgkin’s disease are higher than the doses shown to cause breast cancer in other settings [9]. In the study by Smith [35], half of the patients developing breast cancer as a second primary cancer received radiation at doses greater than 60 GY or chemotherapy with alkylating agents. The reported trends of increasing risk of breast cancer with time implies that the breast is more susceptible to oncogenesis during the physiological changes of puberty. Therefore, those receiving aggressive chemotherapy or radiation during puberty are at higher risk of genetic damage [19, 25, 27, 28, 34, 39].

Role of Splenectomy

Splenectomy and splenic irradiation are standard therapies for the treatment of Hodgkin’s disease and other lymphomas. Deitrich et al. [2] studied 892 disease-free patients with Hodgkin’s disease and found that splenectomy increased the risk for treatment-related second cancers. After more than 15 years of follow-up, women treated with mantle-field irradiation to the spleen prior to age 20 had a forty-fold increased risk of breast cancer [2]. The mechanism by which asplenism may aid in the induction of second primary cancers is unknown. The role of the spleen in immunity to infection with encapsulated organisms is well established. A competent immunologic system is necessary to control and suppress cancers. The spleen may therefore have a role in tumor immunosurveillance [40].

Three well-conducted epidemiologic studies have been reported on cancer occurrence following traumatic splenectomy [2, 39, 41, 42]. Patients undergoing splenectomy for external trauma or nonmalignant conditions had a slightly higher but not statistically significant risk of developing cancer compared to the general population. However, Linet’s [42] study of 985 patients splenectomized in conjunction with surgery for nonmalignant conditions of adjacent organs had a 40% elevated risk for developing cancer with significant increases of lung and ovarian cancers. The excess lung and ovarian cancers may be due to chance since other risk factors such as tobacco use were not controlled [42]. The relative risk of developing breast cancer following splenectomy from external trauma is reported as 3.3 and the relative risk following splenectomy for nonmalignant conditions is 1.8 [42].
Those patients who have had splenectomy for Hodgkin’s disease should be screened more closely than the normal population for the development of a second breast primary [16].

**Metastases Versus Second Primary**

The breast is an unusual site of cancer metastasis. However, in patients with known extramammary malignancies, metastatic disease should be considered in the differential diagnosis of a breast mass [43, 44]. In children, rhabdomyosarcoma is the tumor most commonly associated with breast metastases [44]. Isolated breast metastases from sarcomas and lymphomas have also been described in adults and children. Metastatic disease to the breast has a very poor prognosis [44, 45]. A full metastatic work-up must be included in the management of patients with a history of childhood malignancy who present with a breast mass. Conservative treatment with palliative surgery options should be offered.

**Genetic Links**

Cytologic examination of malignant secondary breast tumors shows recurring alterations on chromosomes 1, 6, 7, and 11 [46-50]. Suppressor genes for Wilms’ tumor and breast cancer have been found on chromosome 11. In an attempt to support the theory that breast and pediatric tumors are related genetically, Frederick [21] presented two sisters, each with a history of Hodgkin’s disease who both developed breast cancer, one four years and the other 12 years after treatment. A study by Russo [48] found inactivation of the p53 gene in three patients with breast cancer following treatment for osteosarcoma.

The Li-Fraumeni syndrome is a rare familial cancer syndrome characterized by increased incidences of breast cancer, childhood sarcomas, and other malignant neoplasms. This syndrome is transmitted through mutations in the p53 gene [37]. Patients with the Li-Fraumeni syndrome have a 50% probability of developing cancer by age 30 [45-49]. Malkin [47] has identified a subgroup of young patients with cancer who carry germline mutations in the p53 suppressor gene but who do not have the characteristics of the Li-Fraumeni syndrome. Prophylactic mastectomy has been offered to women at risk of hereditary breast cancer with gene mutation in other chromosomes (BRCA1 and BRCA2, as cited below). Those with previous tumors associated with mutations on chromosome 11 may fit in this category.

**Breast Cancer Screening**

Systematic screening for breast cancer is potentially valuable in the health care of those with a history of childhood malignancy. Currently, there are no established guidelines specifically targeted to this population. The current American Cancer Society guidelines for breast cancer screening in the normal population are as follows: A) breast self-exam every month starting after age 20; B) clinical breast exam every three years until the age of 39, then yearly for those 40 and older; C) mammographic screening at two-year intervals from the age of 40 through 49, and D) a yearly mammogram for those age 50 and older [37, 51, 52]. Recently, the American Cancer Society has recommended that women between 40 and 50 undergo yearly mammography.

Recently, two tumor susceptibility genes for breast cancer have been identified, BRCA1 and BRCA2. Some mutations in the BRCA1 and BRCA2 genes carry with them an 80% lifetime risk of development of breast cancer [37, 50, 53]. Since those with the BRCA1 and BRCA2 mutations are at greater risk than the general population for developing breast cancer, they may be offered prophylactic mastectomy. Likewise, surveillance in these high-risk patients is more intensive and consists of physical examination every six months and mammography every six months to one year beginning at ages 25-40 [49].

The mortality rate for breast cancer has decreased as a result of increased awareness of and compliance with early-detection guidelines [37]. Inherited breast cancers have clinical characteristics similar to those of second primary malignancies of childhood cancer survivors in that the age of onset is younger and bilaterality is more common [37]. The average time interval for the development of breast cancer from the completion of treatment for the primary malignancy is 10 years [1-36]. It may be reasonable to start mammographic screening earlier (age 25) and at more frequent intervals in childhood cancer survivors.

**History and Physical**

Family history of breast cancer, early menarche, and a low number of pregnancies still remain risk factors for the development of breast cancer, with the greatest risk being associated with a family history. Chemotherapy with alkylating agents and radiation therapy near the chest, past history of Hodgkin’s disease or osteosarcoma as the primary malignancy, and splenectomy should be added to this list (Table 4).

<table>
<thead>
<tr>
<th>Risk factors for developing breast cancer</th>
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</thead>
<tbody>
<tr>
<td><strong>General population</strong></td>
</tr>
<tr>
<td>Family history</td>
</tr>
<tr>
<td>Hormonal therapy</td>
</tr>
<tr>
<td>• (birth control pills)</td>
</tr>
<tr>
<td>Low-dose radiation</td>
</tr>
<tr>
<td>Early menarche</td>
</tr>
<tr>
<td>• late menopause</td>
</tr>
<tr>
<td>• few pregnancies</td>
</tr>
<tr>
<td>History of contralateral breast cancer</td>
</tr>
<tr>
<td><strong>Childhood cancer survivors</strong></td>
</tr>
<tr>
<td>Family history</td>
</tr>
<tr>
<td>Chemotherapy with alkylating agents</td>
</tr>
<tr>
<td>Radiation therapy near chest</td>
</tr>
<tr>
<td>Type of primary malignancy</td>
</tr>
<tr>
<td>• Hodgkin’s disease</td>
</tr>
<tr>
<td>• Osteosarcoma</td>
</tr>
<tr>
<td>Splenectomy</td>
</tr>
</tbody>
</table>

Table 4. Risk factors for developing breast cancer
The value of frequent self- and physician examinations in younger (age <40) women with dense breast tissue may be limited. However, Hancock et al. [9] found that 56% of the second primary breast cancers were identified by follow-up physician exam and 16% by self-exam. It makes sense to practice a more intensive screening program for women who are childhood cancer survivors.

**Mammography and Ultrasound**

Mammography as a screening tool for younger patients is controversial. Those with second breast primaries because of their younger age at diagnosis may still have dense breast tissue that limits the effectiveness of mammography [54]. However, studies at The New York Hospital have found that for cancers diagnosed primarily by mammogram, 95% of patient self-exams and 56% of physician exams were negative [55]. In Yahalom’s study [19] of breast cancer patients with a childhood history of Hodgkin’s disease, 81% of those who had a mammogram had positive findings on the study.

Ultrasound has been shown to be useful in avoiding unnecessary biopsies of cysts and may be a reasonable supplement to the abnormal mammogram or a clinical exam that finds a palpable mass. Serial sonography by an experienced examiner may be helpful in evaluating breast lesions and detecting breast cancers. However, sonography cannot differentiate benign from malignant solid masses and has never been recommended as a screening tool [56].

Recently, digital mammography and magnetic resonance imaging (MRI) have been introduced for breast cancer screening [57]. These are an improvement on simple mammography, which can miss approximately 10% of clinically obvious breast cancers [56]. Studies evaluating the comparative accuracy of MRI, ultrasound, and mammography show that MRI is the most accurate in assessing the size and number of malignant lesions in the breast [56]. These new modalities in breast imaging may minimize the problems associated with screening younger women with dense breasts.

**Male Breast Cancer**

Breast cancer occurring in the mammary tissue of males is uncommon and is less than 1% of the incidence in females. Although male survivors of childhood cancers are at risk for developing second primary cancers, they do not appear to have the same risk for developing breast cancer as females in the same or normal population. Sankila et al. [33] of Finland reviewed a population of 470,000 registered cancer patients for secondary malignancies; in all of their follow-up intervals, the overall incidence was lower among males than females. They did not report second primary breast cancers arising in male patients. Olsen and colleagues, in their study of 30,880 childhood cancer survivors of Nordic countries, listed no males with second primary breast cancers. The major increase in breast cancer after treatment of childhood malignancies is limited to women treated with radiation therapy or alkylating agents before the age of 30 where the follow-up period is greater than 10 years.

**Strategies for Follow-up**

Table 4 shows the possible risk factors for developing breast cancer in childhood cancer survivors. Yahalom [19] found a high incidence (22%) of bilateral breast cancer, multicentric tumors involving more than one quadrant, and a wide spectrum of histologic types represented in his study [19]. Janjan et al. [27] supports the high incidence of bilateral disease and a propensity for tumors to develop in the inner quadrants. Long-term surveillance of childhood survivors of cancer with risk factors listed in Table 4 should include the regular mammography and the examination by a health care provider skilled in performing a breast exam.

**Suggested Guidelines**

In the late effects study group of Meadows et al. [16], survivors of childhood malignancy developed breast cancer by age 40, with a median age of diagnosis of 31.5 years. One may argue that surveillance examinations should be more frequent 10 years following radiation or treatment of the childhood malignancy. Van Leeuwen [3] suggests this and makes a strong recommendation for breast palpation and yearly mammography beginning 10 years after initial treatment of the primary cancer.

Recommendations have been made for patients in other high-risk groups, such as patients with a family history of breast cancer. These patients receive their baseline clinical exams earlier (between 30 and 35 years of age) and begin yearly mammography at age 40. Suggested recommendations for patients with mutations at BRCA1, BRCA2, and other high-risk groups include: A) intensive surveillance with yearly mammogram beginning at age 30; B) possible use of tamoxifen provided there is also a yearly pelvic exam and PAP smear along with a vaginal ultrasound at three and five years after starting the therapy to evaluate the endometrial strip, and C) possible prophylactic mastectomy [37]. Patients who have survived a childhood malignancy should be treated similarly to those who have a family history of breast cancer with a more intensive program of mammography and physical exam (Fig. 1). Screening may begin at 21 years of age, with baseline mammograms along with routine Cleopatra views which screen the inner quadrants. MRI examinations may be helpful in these women with extremely dense breasts. These screening modalities are especially important for those younger women with dense breast tissue and for those patients who received mantle field irradiation for...
the treatment of their childhood malignancy. Final justification can only be made by proof of mortality reduction in those with a history of childhood cancers.

Mastectomy may be the treatment of choice for breast cancer patients whose chests have previously been irradiated for childhood cancer, since the skin of the breast may not tolerate more radiation therapy with breast conservation. Breast conservation should still be offered to those with smaller tumors and larger breasts, depending on whether the chest wall can receive more radiation.

**Conclusions**

Subsequent neoplasms among cancer patients do not pose a major public health problem. However, both retrospective studies and prospective studies are needed. It is likely that a combination of factors such as cytotoxic drug therapy, radiation therapy, splenectomy, generalized immune dysfunction, and permuted genetic defects may predispose childhood cancer survivors to develop second malignancies. This population of patients is at increased risk over time for developing breast cancer, perhaps due to the predisposition of breast epithelial cells to genetic change after exposure to cytotoxic or radiation therapy. All female childhood cancer survivors should be screened for breast cancer. Special guidelines beginning earlier than those recommended by the American Cancer Society for the normal population should be implemented. This would include a breast physical exam every six months and yearly mammography beginning 10 years after the diagnosis of the childhood cancer.

**References**


