Second Cancers in Survivors of Hodgkin Lymphoma: Risks and Recommendations

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Survivors of Hodgkin lymphoma (HL) who received certain oncology treatment years ago may have a lifelong risk for second cancers. This article reviews evidence-based data about subsequent solid tumor development in HL survivors. Regarding the development of solid cancer, a significant difference existed between one study group of HL survivors and same-aged people from the general population. HL treatments using combinations of radiation and chemotherapy and those using extended-field radiation have been suggested to pose an increased risk for second cancers. Changes in treatment for HL reflect researchers’ attempts to reduce late complications of oncology treatment. Oncology nurses are in a unique position to counsel patients with HL and survivors regarding the importance of follow-up assessments, cancer-prevention practices, and screening recommendations. Ultimately, results will ensure that HL survivors have a better chance of wellness.

Hodgkin lymphoma (HL) is seen more often in white people living in the United States, Canada, Switzerland, and northern Europe compared to people living in the Far East and Asia (Connors, 2004). HL is predominantly seen in young adults. Only about 5% of HL cases occur in children younger than 15 years. Experts have studied HL etiologic factors. One theory for a cause, based on inferential evidence, focuses on genetics (Connors, 2004). First-degree relatives of patients with HL have a higher risk of developing the lymphoma compared to families without a history of HL. Another theory focuses on the Epstein-Barr virus (EBV) (Connors, 2004). Some parts of the world, where crowding exists, have a higher incidence of HL in children. Perhaps such children have enhanced exposure to viruses such as EBV. Research shows that 90% of people acquire EBV infection before age 20 (Connors, 2004).

HL usually presents as painless enlargement of supradiaphragmatic lymph node(s) (see Figure 1). Only 25% of patients with HL present with classic B symptoms such as significant weight loss, persistent fever, and night sweats. The symptoms often are indicative of more advanced disease. Fairly large mediastinal HL tumors can develop without alarming symptoms. An open lymph node biopsy is required to diagnose HL histologic subtypes (Connors, 2004). The four types of HL, in order of frequency of diagnosis, are nodular sclerosing, mixed cellularity, lymphocyte predominant, and lymphocyte depleted. The nodular sclerosing subtype, which accounts for nearly two-thirds of all HL diagnoses, is characterized by sclerosing bands surrounding nodules which contain Reed-Sternberg cells in a background of inflammatory cells (Connors, 2004) (see Figure 2).

Incidence and Staging

Approximately 8,220 people living in the United States will be diagnosed with HL in 2008. This lymphoma is slightly more common in men than women (Ries et al., 2008). The incidence of HL has remained constant in the past two or three decades (Tsang, Hodgson, & Crump, 2006).

At a Glance

- Survivors of Hodgkin lymphoma (HL) may be at risk for second cancers for decades following original diagnosis and treatment.
- Present-day management of HL includes providing effective first-line treatment, which has the fewest late complications.
- Oncology nurses are in a unique position to counsel HL survivors regarding the importance of follow-up assessments, cancer-prevention practices, and screening recommendations.
Computed tomography (CT) scanning, physical examination, blood tests, chest x-ray, and bone marrow biopsy are useful in evaluating the extent of HL. Immunohistochemical studies are useful in distinguishing among subtypes (Connors, 2004). Almost 70% of patients with HL are initially diagnosed with localized (i.e., stage I or II) disease. This usually involves lymphadenopathy above the diaphragm (see Figure 1 for an illustration of the lymphatic system). Advanced-stage HL (i.e., stage III or IV) includes disease above and below the diaphragm and may involve organs outside the lymphatic system (e.g., lungs, liver) (Tsang et al., 2006).

**Survival Rate and Evolution of Treatment**

The five-year relative survival rate for HL increased from 73% from 1975–1977 to 86% from 1996–2002. This difference is statistically significant (American Cancer Society, 2007) and reflects progress in management of HL. Major improvements in treatment for HL have occurred since the early 1900s. Some of the changes are outlined in Table 1. From the 1990s to present day, the focus on altering HL treatment has been “to properly balance high effectiveness of early treatment with minimization of the late hazards of that same treatment” (Connors, 2003, p. 3389).

**Second Cancer Development**

Second primary cancer is a leading cause of death for patients who were diagnosed and initially treated for HL before the age of 41 years (Aleman et al., 2003). Solid tumors account for most second malignancies in HL survivors. Patients with HL who develop more common types of second cancer have risk factors (Mauch et al., 2005), some of which are listed in Figure 3. Second solid cancer sites for HL survivors are listed in Table 2.

Researchers from Europe, Canada, and the United States completed a study to evaluate the risk of HL survivors developing second solid cancers over time. They evaluated the health records of 18,862 five-year HL survivors. Data results were based on assessment that simultaneously considered attained age and age at HL diagnosis. The calendar year of patient diagnosis for this study group ranged from 1970–2001. With respect to age at HL diagnosis, the highest number of patients fell into the age group of 20–29 years. The duration of follow-up ranged from 5–32 years (Hodgson et al., 2007).

The researchers discovered that 1,490 patients with HL had developed a second solid cancer. This is approximately 850 more cases than expected. The study showed that men and women diagnosed with HL at age 20 have four and five times, respectively, the chance of developing a solid cancer by age 50, compared to same-gender 50-year-olds in the general population. The 30-year cumulative risk of second solid cancer for men and women, each diagnosed with HL at age 30 years, is 18.3% and 26.1%, respectively. This compares to same-aged men and women in the general population having a 6.9% and 8.9% risk, respectively, of developing a solid cancer (Hodgson et al., 2007). Findings show that relatively young patients with HL have an elevated risk of breast and colorectal cancer in the period 10–25 years before the age when screening for those cancers is recommended.

While assessing overall second cancer risk in HL survivors, Franklin et al.’s (2006) meta-analysis investigated trials which used the following first-line HL treatments: radiotherapy alone, chemotherapy alone, and combined chemotherapy and radiotherapy. Most patients included in the analysis were from trials conducted in the 1990s. Comparing radiotherapy alone and combined chemotherapy and radiotherapy as treatment for HL, the overall risk of second cancer was higher (p = 0.03) with radiotherapy alone. The increase was marked in stage III HL compared to early-stage disease (Franklin et al.). Comparing chemotherapy alone and combined chemotherapy and radiotherapy, the overall risk of second cancer was higher (p = 0.05) with the use of combined chemotherapy and radiotherapy (Franklin et al.).

While assessing breast cancer risk, the meta-analysis compared involved-field radiotherapy and extended-field radiotherapy as treatment for HL (Franklin et al., 2006). Involved-field radiotherapy is radiation delivered only to areas of the body involved with lymphoma. Extended-field radiotherapy refers to radiation delivered to the lymphoma site and surrounding non-malignant sites. Extended-field radiation is given to the mantle field (i.e., lymph nodes above the diaphragm such as in the neck, chest, and axillae) and/or to the inverted Y field (i.e., spleen, lymph nodes in the upper abdomen, and pelvis) (American Cancer Society, n.d.). The risk of breast cancer was significantly higher when patients with HL had received extended-field radiotherapy (Franklin et al.).

Patients younger than 21 diagnosed with HL have the greatest excess risk of death from cancer other than HL (Connors, 2003). Several large trials had only a short median observation time (i.e., four to six years) (Franklin et al., 2006), which may lead to an underestimation of the number of secondary cancers.

**Figure 1. Illustration of the Lymphatic System**

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A significant decline occurred in the use of radiation therapy as first-line treatment for HL from 1982–1996 in Ontario, Canada (Hodgson et al., 2003). This probably reflects the negative impact of extended-field radiotherapy, used as initial treatment for HL for many years prior to 1982 (Hodgson et al., 2003). Fewer second cancer diagnoses have been made in HL survivors treated after the 1980s, with improved radiation therapy delivery and dosimetry (Connors, 2003).

Chemotherapy has been used to treat HL for decades. However, the role of specific anticancer drugs in causing subsequent solid tumors is uncertain (Behringer et al., 2004). For standard HL treatments used during the 1990s, follow-up times have been too short to evaluate how effective the treatments are in lowering survivors’ risk of second cancers (Ng & Mauch, 2006).

**Screening Recommendations**

Participation in early-detection programs is important for high-risk HL survivors. Unfortunately, many HL survivors are lost to follow-up (Mauch et al., 2005). High-risk patients with HL include those who have received bleomycin and/or chest radiation (National Comprehensive Cancer Network [NCCN], 2008). For Hodgson et al.’s (2007) study group of HL survivors, the most common solid tumor sites were lung, breast, colorectal, and prostate. Other second hematologic cancers that caused a significant number of deaths in a study group of patients with HL were leukemia and non-Hodgkin lymphoma (Aleman et al., 2003). See Figure 4 for ways to monitor late effects of HL treatment.

**Lung Cancer**

Lung cancer was one of the most common types of second cancer in a study group of HL survivors (Hodgson et al., 2007).

<table>
<thead>
<tr>
<th>TIME PERIOD</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1902</td>
<td>Radiation therapy was introduced as the first nonsurgical anticancer treatment.</td>
</tr>
<tr>
<td>1930s</td>
<td>Extended-field radiation therapy was part of an individualized treatment plan.</td>
</tr>
<tr>
<td>1946</td>
<td>Mechlorethamine (derived from mustard gas) was the first chemotherapy drug to show promise. The next few decades saw the discovery and use of other anticancer drugs such as vincristine, vinblastine, procarbazine, bleomycin, doxorubicin, and dacarbazine.</td>
</tr>
<tr>
<td>1960s</td>
<td>A staging laparotomy was introduced to evaluate the extent of disease. It was discontinued in the 1980s. Accurately measured mega-voltage radiation therapy was introduced. Extended-field radiation (e.g., mantle, inverted Y) therapy was first used for stage I and II disease. The chemotherapy regimen of mechlorethamine, vincristine, prednisone, and procarbazine (MOPP) became common practice for advanced disease.</td>
</tr>
<tr>
<td>1970</td>
<td>Researchers reported that 80% of patients who received MOPP for advanced-stage disease went into complete remission. A great number (i.e., 20%–30%) of those patients eventually relapsed.</td>
</tr>
<tr>
<td>1980s</td>
<td>Chemotherapeutic regimen of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) was introduced in 1982 and was used initially for MOPP-resistant patients. During the 1980s, cycles of MOPP alternating with ABVD was the preferred chemotherapy regimen. Stem cell transplantation became available after the mid-1980s.</td>
</tr>
<tr>
<td>1990s</td>
<td>Greater focus was put on reducing harmful long-term effects of chemotherapy and radiation therapy. ABVD was the standard chemotherapy regimen. The use of radiation therapy, particularly for early-stage disease, declined 10% from 1990–1994 compared to the previous five-year period.</td>
</tr>
<tr>
<td>2005</td>
<td>For early-stage disease, standard treatment included four cycles of ABVD followed by involved-field radiation therapy, for which a dosage of &gt; 30 Gy was necessary only when patients had less than acceptable response to chemotherapy.</td>
</tr>
<tr>
<td>2006</td>
<td>For advanced disease, standard treatment focused on more intensive chemotherapeutic agents.</td>
</tr>
</tbody>
</table>

*Note. Based on information from Connors, 2003; De Vos, 2006; Kennedy et al., 1998; Mauch et al., 2005; Ng & Mauch, 2006; Tsang et al., 2006.*
It may result from patients having received extended-field radiotherapy or alkylating chemotherapy as treatment for HL (Das, Ng, Earle, Mauch, & Kuntz, 2006). Das et al.'s analysis used a specially designed model to determine whether annual lung cancer CT screening was beneficial in HL survivors. The researchers believed that the prognosis of lung cancer in HL survivors is poor, possibly because of comorbid conditions and poor candidacy for further chest irradiation. Study results show that, of the total number of CT-screened lung cancer diagnoses, 82.8% had localized disease. In contrast, of the total unscreened lung cancer diagnoses, only 21.1% were diagnosed with localized disease. The probability of smokers developing lung cancer more than five years after diagnosis of HL is at least four times that of nonsmokers. The study showed that CT screening in HL survivors who are smokers may extend survival by more than seven months.

Breast Cancer

Female HL survivors may have an increased risk of developing breast cancer years before the age when screening for this malignancy in the general population is recommended (Hodgson et al., 2007). A report describing research highlights from the 2002 annual meeting of the American Society of Clinical Oncology (Lobert, 2002) summarized results of a prospective study of almost 400 women younger than 19 who were treated for early-stage HL. The average follow-up time was 14.5 years. Findings show that women with HL had a breast cancer risk equal to 45 times that of same-aged women from the National Cancer Institute Surveillance Epidemiology and End Results database. The study recommended possibly using a lower dose of radiotherapy for treating early-stage HL. It also suggested that prophylactic second breast mastectomy, if the first breast contained a malignancy, might help to reduce the risk of bilateral breast cancer, which also was increased in the study group of women with HL.

Specialists advise careful monitoring of hormone-replacement therapy in postmenopausal HL survivors. Yearly clinical breast examination and monthly breast self-examination are advised (Mauch et al., 2005) because a high percentage of breast cancers can be detected initially by patients themselves (Wolden et al., 2000).

Colorectal Cancer

For the general U.S. population, screening for colorectal cancer is recommended to start at age 50 (Pignone, Rich, Teutsch, Berg, & Lohr, 2002). This may include one or more of the following tests: fecal occult blood test, fecal immunochemical test, sigmoidoscopy, barium enema, colonoscopy (American Cancer Society, 2007). For HL survivors, colorectal cancer screening should commence sooner than age 50 because relatively young patients with HL have an increased risk of developing colorectal cancer; but specific timing and frequency of tests, in relation to HL treatment, are yet to be determined (Hodgson et al., 2007).

Prostate Cancer

Prostate cancer represented nearly 7% of all solid cancers diagnosed in a study group of five-year survivors of HL (Hodgson et al., 2007). It is the most commonly diagnosed cancer in the general population of U.S. men. The American Cancer Society recommended that, beginning at age 50, men in the general population should have an annual digital rectal examination and a serum prostate-specific antigen test (NCCN, 2007).

Primary Prevention Practices

For cancer survivors, self-care behaviors such as healthy nutrition and cardiovascular exercise reduce the risk of subsequent cancer (U.S. Department of Health and Human Services, 2000). Self-examination for tumors may lead to cancer diagnosis at earlier stages (U.S. Department of Health and Human Services). Oncology nurses must offer empathetic listening. Once a relationship is established, cancer survivors are more open to nurses’ counsel. Regarding breast health, cancer survivors can learn through individual or classroom presentations (e.g., videos), communication with other survivors, question-and-answer

<p>| Table 2. Second Solid Cancer Sites for Survivors of Hodgkin Lymphoma, With Respective Number of Cases |
|---------------------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>ORDER OF FREQUENCY</th>
<th>FIVE-YEAR SURVIVORS (N = 1,490)</th>
<th>10-YEAR SURVIVORS (N = 1,001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lung: 306</td>
<td>Breast: 226</td>
</tr>
<tr>
<td>2</td>
<td>Breast: 277</td>
<td>Lung: 173</td>
</tr>
<tr>
<td>3</td>
<td>Colon: 110</td>
<td>Colon: 74</td>
</tr>
<tr>
<td>4</td>
<td>Prostate: 104</td>
<td>Prostate: 54</td>
</tr>
<tr>
<td>5</td>
<td>Female genital: 70</td>
<td>Stomach: 50</td>
</tr>
<tr>
<td>6</td>
<td>Buccal: 69</td>
<td>Female genital: 48</td>
</tr>
<tr>
<td>7</td>
<td>Stomach: 64</td>
<td>Buccal: 46</td>
</tr>
</tbody>
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*Note. Based on information from Hodgson et al., 2007.*
sessions, and hands-on breast self-examination practice. Survivors who partake in health-promotion activities are sometimes motivated by fear of second cancer. Research shows that childhood cancer survivors are not well informed about treatment-related health risks (Crom, Hinds, Gattuso, Tyc, & Hudson, 2005). A newly developed model of health behavior regarding childhood cancer focuses on “family and peer responses to survivors’ disease and treatment and to their health related behaviors” (Cox, 2003, p. E93). This may have a large impact on whether young cancer survivors follow recommended health practices that could reduce future disease. The model’s previous objective was to change young cancer survivors’ beliefs about risks associated with oncology treatment (Cox). HL survivors’ future health will greatly benefit from positive family and peer support networks.

Follow-up assessments for HL survivors are important. New symptoms such as a breast lump, persistent cough, or change in bowel habits may require more aggressive investigation when occurring in HL survivors compared to the same symptoms in the general population. Recognizing early warning signs of a possible second malignancy will ultimately ensure that patients with HL have a better chance of wellness and survival.

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