Arden-Close, E., Eiser, C., & Pacey, A. (2011). Sexual functioning in male survivors of lymphoma: A systematic review (CME). Journal of Sexual Medicine, 8 (7), 1833-41. DOI: 10.1111/j.1743-6109.2011.02209.x.

# Sexual Functioning in male survivors of lymphoma: A systematic review

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**Conflict of Interest:** None

**Acknowledgement:** This research was made possible by grant C481/A8141 awarded by Cancer Research UK to C Eiser and A Pacey

Abstract

Introduction: The lymphomas [Hodgkin's Lymphoma (HL) and Non-Hodgkin's Lymphoma (NHL)] are among the most common cancers affecting men under 45 years. Survival rates are now excellent, but treatment is associated with a number of side effects including sexual dysfunction with potential implications for compromised QoL (quality of life).
Aims: To address the: (i) prevalence of sexual dysfunction among lymphoma survivors relative to the general population, survivors of other cancers, and in survivors of HL and NHL; and (ii) relationships between sexual functioning and disease and treatment, demographic, and psychological variables.

Methods: Inclusion criteria were quantitative studies that focused on adult male survivors of lymphoma, included a comparison group and presented results separately for HL and NHL. Standardized systematic searches were used. Information about design, sample size, age, time since diagnosis, type of treatment, comparison group, measures and findings were extracted from eligible studies.

Results: Ten articles met the inclusion criteria, of which nine included patients with HL only, and one included patients with HL or NHL. Sexual function was compromised relative to the general population, better than testicular cancer survivors, and worse than leukaemia survivors. Depression was consistently associated with sexual dysfunction. There was evidence that chemotherapy, relapse, reduced testosterone levels, older age at survey and worse physical QoL were associated with worse sexual function.

Conclusions: Conclusions are limited by methodological issues including lack of utilization of standardized measures of sexual function and longitudinal research. Even so, there is evidence of sexual dysfunction among lymphoma survivors. Clinicians need to be sensitive to these issues. Future longitudinal work is necessary to determine the likelihood of recovery.

Keywords: sexual function, Hodgkin's Lymphoma, Non-Hodgkin's Lymphoma, review; chemotherapy and sexual dysfunction

The lymphomas including Hodgkin's Lymphoma (HL) and Non-Hodgkin's Lymphoma (NHL), are among the most common cancers affecting men under 45 years of age [1]. Survival rates for both cancers have improved rapidly, and current five-year survival rates of 87% for HL [2] and 65% for NHL [3] have been reported. However a number of late effects have been identified [4] which may significantly compromise health-related quality of life (HRQoL).

Since lymphoma does not usually affect the sexual organs, sexual dysfunction may not be considered by clinicians. However, sexual functioning may be affected by the physical impact of treatments such as chemotherapy and radiotherapy, as well as more psychological issues such as anxiety, depression, low self-esteem and loss of control over bodily functions [5]. Five or more years after diagnosis, as many as 28% of lymphoma survivors want information about their sexual function [6-7]. Sexual dysfunction has been associated with anxiety and depression in healthy individuals [8], and may cause distress if left untreated. Taken together these findings suggest that lymphoma survivors may be vulnerable to sexual dysfunction, and the associated psychological consequences.

Sexual dysfunction might be a distressing late effect of cancer treatment. Both radiotherapy and chemotherapy can cause testicular damage, which may lead to sexual dysfunction. Although direct radiation to the sexual organs is rare, a significant amount of scatter radiation may be received during pelvic irradiation, which can lead to erectile dysfunction through scarring of blood vessels that supply the penis, and subsequent inadequate blood supply [9]. Alternatively, damage to the pituitary gland or hypothalamus following cranial radiotherapy leads to decreased levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and thus to testosterone deficiency [10]. However, sexual dysfunction following treatment for lymphoma is more likely to be caused by chemotherapy [9]. Seminal research demonstrated that many chemotherapeutic agents progressively deplete the germinal epithelium lining of the seminiferous tubule, and decrease serum testosterone levels, leading to testicular atrophy [11-14]. Although evidence has suggested that current treatments are less likely to cause sexual dysfunction [15], a recent case-control study [16] demonstrated that male cancer survivors (41% with lymphoma), had lower testosterone levels than controls, and reduced sexual function. Similarly, in a study of

patients with lymphoma treated from 1980-2002 [10], those receiving chemotherapy classified as gonadotoxic were most at risk of low testosterone levels, which can lead to testicular atrophy. This finding suggests that sexual dysfunction potentially remains a significant side effect of chemotherapy.

Several studies have addressed the issue of sexual functioning in survivors of HL and NHL, but the evidence has not been reviewed systematically. Such a review would facilitate understanding of long-term sexual functioning among lymphoma survivors and the extent to which this may be influenced by medical, biological, demographic and psychosocial factors. Such information could enable healthcare professionals to inform patients about the likely long-term impact of their disease on sexual functioning and how problems may be addressed. Given the differential survival rates for HL and NHL [2, 3], we decided to analyze the results both for all survivors of lymphoma and separately by diagnosis.

We therefore report a systematic review of sexual functioning in men with HL or NHL. It was decided to focus on men in order to facilitate comparisons with testicular cancer survivors (where there have been several useful reviews on sexual dysfunction: [17-18]), and because there has been only limited research on sexual functioning in female survivors of lymphoma. The specific aims were to determine: (i) the prevalence of sexual dysfunction among lymphoma survivors relative to the general population and survivors of other cancers, and between survivors of HL and NHL; and (ii) the relationships between sexual functioning and disease and treatment, demographic, and psychological variables.

**Method**

The literature search aimed to identify any research study published in a peer reviewed journal that quantitatively assessed sexual functioning in male survivors of lymphoma (HL or NHL only, or if both, had conducted separate analyses for each group) at least six months post treatment, and included a comparison group (in order to provide information on risk relative to other men of a similar age; [17]. Articles were excluded if they: (i) included childhood cancer survivors only; (ii) were case reports or reviews of previous literature; or (iii) did not conduct analyses separately by diagnosis.

Three methods were used to locate relevant studies: a keyword search, a backward search, and a manual search of relevant journals. First, the databases Medline, PsycInfo and Web of Knowledge were searched for articles published in the English language covering the period from January 1985 (when articles were more likely to be identified) to June 2010 (when the search was conducted). The search included the following terms: Hodgkin's disease, lymphoma (non-Hodgkin's), libido, sexual function, sexual dysfunction, orgasm, erectile dysfunction, and erection.

After each term had been entered into the keyword function the cancer-related terms were combined using the OR function, as were the sexual function terms. This generated 11 hits from PsycInfo, 33 hits from Medline, and 153 hits from Web of Knowledge. After initial review of the abstracts based on the inclusion and exclusion criteria, 21 articles were identified and obtained. Following the keyword search, we then carried out a backward search in which we located papers by examining the reference lists of all papers obtained from the first step. This identified five further articles. Following a manual search of the journals 'Psycho-Oncology,' 'European Journal of Cancer,' and 'Journal of Clinical Oncology' for the period January 1985 to June 2010, one further article was identified. Thus, overall 27 articles were identified, obtained, and assessed against the inclusion criteria.

Due to heterogeneity between samples regarding size and time since treatment, and measurement tools (only two studies used the same measure), data pooling and meta-analysis was deemed inappropriate. A narrative commentary was therefore used to synthesize the resulting data.

**Results**

Following detailed review of the articles against the inclusion/exclusion criteria, 10 articles that included eight data sets were retained. Articles were excluded because they did not include a comparison group (n=10), did not report analyses separately by diagnosis (n=6) or did not assess survivors at least six months post treatment (n=1). Given the clarity of eligible papers, it was not necessary to contact researchers for additional information.

Included studies were conducted in the US (n=7), the Netherlands (n=2), and Norway (n=1). Nine studies included only patients with HL, and one compared patients with HL and NHL.

Findings were tabulated for ease of presentation. This included information about aims, lymphoma sample size, age at survey, time since diagnosis, type of treatment, comparison group, and measures (Table 1).

*Aim 1: Prevalence of sexual dysfunction among lymphoma survivors relative to the general population and survivors of other cancers, and in survivors of HL and NHL*

The percentage of patients experiencing problems with sexual functioning was reported in seven studies. As shown in Table 1, between 20% and 54% of patients experienced problems with one or more aspects of sexual function. Sexual functioning was compared with general population samples in five studies. Three studies found no differences between HL survivors and the general population [19-21]. However, HL survivors scored lower than controls on the sexuality scale of the Maudsley Marital Questionnaire [22], and were more likely to have sex less frequently, were dissatisfied with the frequency of their sexual contact, and reported decreased sexual satisfaction and loss of interest in sex [23]. Lymphoma survivors (both HL and NHL) scored lower than controls on the erection, ejaculation and overall sexual function scales of the Brief Sexual Function Inventory [24], and had a higher prevalence of reduced erectile function [25].

In five studies, HL survivors were compared with survivors of other cancers. There were no differences compared to NHL [25], or testicular cancer survivors [26]. HL survivors experienced worse sexual functioning and lower satisfaction, and were more likely to report reduced sexual activity than leukaemia survivors [27]. Other work showed that testicular cancer survivors were more likely to report decreased sexual enjoyment [28], and had higher levels of ejaculatory dysfunction than HL survivors [29].

*Aim 2: The relationships between sexual functioning and disease and treatment, demographic, and psychological variables*

The relationships between sexual functioning and medical variables and treatment were assessed in three studies. The chemotherapy regimens Mechlorethamine, vincristine, procarbazine and prednisone (MOPP), Doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD), or Procarbazine, Alkeran, and vinblastine (PAVe) were associated with reduced sexual enjoyment at long-term follow up relative to radiation therapy only in survivors of HL [28]. However, a comparison between the chemotherapy regimens MOPP only, ABVD only, and MOPP alternating with ABVD [30] demonstrated no differences in terms of effects on sexual functioning for survivors of HL. HL survivors who relapsed reported more sexual problems than those who remained in remission after treatment [30]. Finally, reduced testosterone levels were associated with worse sexual function in both HL and NHL survivors in one study, relative to having normal gonadal hormones [25]. A close correlation between gonadotoxicity of treatment and elevated LH and /or low testosterone levels was reported in a previous publication on the same patient sample [10]. Also, in the multivariate analyses reported in this manuscript [25] increasing age, low testosterone/elevated LH, increasing emotional distress and reduced physical health were all significantly associated with impaired sexual function in male lymphoma survivors.

Relationships between sexual functioning and demographic and psychological variables were assessed in five studies. In two studies, (one which included HL survivors only [21] and one which included both HL and NHL survivors [25]), younger age was associated with better sexual function, particularly sexual satisfaction. No other demographic correlates of sexual functioning were identified. Increased levels of depression were associated with psychosexual problems, particularly decreased sexual activity, in HL survivors only [20] and both HL and NHL survivors [25]. HL and NHL survivors who reported better sexual function also reported better physical QoL. HL survivors who were infertile or believed they were infertile reported more distress than those who were fertile or believed they were fertile [30].

**Discussion**

Our review suggests that between 20% and 54% of patients experienced problems with one or more aspects of sexual function. It was not possible to calculate

an exact estimate as differences between studies precluded the use of meta-analysis Neither were we able to determine differences between HL and NHL, since nine of the ten studies concentrated solely on patients with HL. Where both cancers were compared, no differences in sexual function were found [25].

Compared with the general population [19-21], three studies with small samples found no differences regarding sexual function, and the others suggest that sexual problems reported by lymphoma survivors, while a significant issue, may not always be directly related to their disease and treatment. Despite the large sample (N=246) utilized by Kiserud and colleagues [25], effect sizes for impairments in sexual function in lymphoma survivors relative to the general population were small. Such impairments are therefore unlikely to be clinically significant, possibly because lymphoma survivors consider compromised sexual function a minor cost of survival [29]. Certainly, they do not differ relative to the general population on satisfaction with nonsexual intimacy [23]. However, of the three studies that found no differences, one had a small sample [19] and two used non-standardized measures [20-21], suggesting that further studies are required to determine whether sexual functioning in lymphoma survivors really is compromised relative to the general population.

When compared to survivors of other cancers, lymphoma survivors had worse sexual function than leukaemia survivors [27], but better sexual function than testicular cancer survivors [28-29]. Testicular cancer survivors may experience more problems because their treatment (orchidectomy) visibly affects a sexual organ. Relative to lymphoma patients, they tend to report more dissatisfaction with information and support concerning sexual function [7].

The evidence suggested that chemotherapy, relapse and reduced testosterone levels were associated with more sexual problems. Previous chemotherapy may be associated with reduced sexual interest/ enjoyment relative to radiotherapy in lymphoma survivors [28]. Also, reduced testosterone levels were associated with reduced sexual function [25], which suggests that sexual dysfunction following treatment for lymphoma has an organic cause in at least some patients. Identification of these issues is necessary so that men can be treated appropriately i.e., with testosterone replacement therapy. Recent research [10, 16] has demonstrated reduced

testosterone levels following chemotherapy, and greater incidence of sexual dysfunction in patients who have been treated by chemotherapy, suggesting this issue is still highly relevant.

With regard to demographic and psychological variables, increasing mental distress was associated with reduced frequency of sexual activity [20, 25], in line with research on the general population [31]. Routine assessment of depression is warranted, in order to facilitate appropriate referrals (see also [32]). This is particularly important as psychological late effects of treatment are often not documented in medical notes and may not be addressed by clinicians [33]. Also, younger age was associated with better sexual function [21, 25]. This was expected, as the prevalence of sexual dysfunction increases with age [34] in studies from the general population. Better physical QoL was also associated with better sexual function, possibly because more energy and fewer health problems means patients are able to put more effort into attaining a pleasurable sex life.

Limitations are considered in relation to study design, reporting of demographics and results, and searches. A number of limitations with study design were identified. First, only three studies [19, 23, 25] used a standardized questionnaire. Standardized instruments are required in order to determine areas in which deficits may be prevalent, and make direct comparisons between studies. Furthermore, they are widely available - 25 measures of sexual function have been identified [35]. Second, there were no longitudinal studies, meaning no information is available regarding changes during the course of treatment, or processes of recovery. This particularly limited our ability to answer the question of how sexual functioning and medical treatment are related - as patients were assessed at different times post treatment it was not possible to determine the trajectory (ies) of sexual function following treatment. Third, three studies [19, 26, 29] had very small samples, with possible insufficient power to compare groups. Fourth, only one study [25] examined the correlation of sexual function with testosterone levels. This is required in order to understand the relative contribution of biological and psychosocial factors to sexual problems. Fifth, more work should address the relation between quality of life and sexual function. Finally, although this review included only studies with a control group, good control samples from the general population regarding sexual function

are difficult to obtain for several reasons. First, it is necessary to select a sample with the same percentage of the general population who are currently sexually active. This is important as cancer survivors are less likely to be in a relationship than the general population (i.e., [36]). Second, sexual function is a sensitive subject, about which many people refuse to complete questionnaires even when they are anonymized.

Several limitations were also found with regard to reporting of demographics and results. First, two studies failed to mention relationship status, which is important for the reason discussed above. Second, only three of the ten studies [23, 25, 30] reported standard deviations. These enable comparison between studies, and are necessary for calculating effect sizes in meta-analysis.

There were also several limitations with regard to the searches. The review was restricted by the fact that the grey literature was not searched, and only papers published in the English language were included. This means there was a possibility of publication bias.

In conclusion, we have reported a systematic review of the evidence currently available regarding sexual functioning in male survivors of lymphoma. We conclude that sexual dysfunction is an adverse late effect for a significant minority of patients, albeit one of low clinical significance and not necessarily a direct consequence of treatment. However, given the association between low testosterone levels and impaired sexual function, patients should routinely be assessed and treated for low testosterone levels. Furthermore, the relation between depression and impaired sexual function highlights the importance of assessing psychological well-being in patients. Further well-designed studies are required to expand the evidence base regarding sexual dysfunction in lymphoma survivors, in order to facilitate doctor-patient communication regarding likelihood of sexual dysfunction and ways in which it can be ameliorated.

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**Table 1: Levels of sexual function, comparison between treatments, correlates and details of measures**

| Study | Aims | Lymphoma sample size (response rate) | Age (Mean unless stated otherwise) | Time since diagnosis (Mean unless stated otherwise) | Type of treatment | Comparison Group | Measures | Findings |
|---|---|---|---|---|---|---|---|---|
| 1. Bloom et al. (1993) [28] | 1. Compare physical, social and psychological well-being of HL and testicular cancer survivors | HL 85 (88%) | 32.2 (88.2% under 40) | 45.7 months | XRT alone: 37.6%<br>With MOPP: 24.7%<br>PAVe: 24.7%<br>ABVD: 14%<br>VBM: 3 | Testicular cancer | Structured Interview | 1. 26%: Erectional problems following treatment<br>2. 22.8%: decrease in quality of orgasm<br>3. Chemotherapy: decreased sexual enjoyment relative to radiotherapy<br>4. HL less likely to report decreased sexual enjoyment than testicular cancer |
| 2. Cella & Tross (1986) [19] | 1. Compare levels of psychological distress in HL survivors and healthy acquaintances | HL 60 (86.9%) | Mean 31.1 | Range 6 – 140 months | Early (30): 6 cycles (MOPP) + XRT<br>Advanced: 10-12 cycles (MOPP + ABVD) + XRT | General population, on and off treatment | Derogatis Sexual Functioning Inventory [37] | 1. Almost 1/5: difficulty in sexual readjustment |
| 3. Hannah et al. (1992) [26] | 1. Examine impact of cancer on couple marital and sexual function | HL 24 (married men + spouses) | 35.2 (SD 6.8) | 34.9 months | XRT alone: 10<br>PCT: 11<br>Both: 1<br>Relapse: 2 | Testicular cancer | Structured interview (non-standardized) | 1. Decrease in frequency: 62.5%, sexual satisfaction; 37.5%; erectile dysfunction: 13% (0 pre-diagnosis)<br>2. No differences between testicular cancer and HL |

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|---|---|---|---|---|---|---|---|---|
| 4. Jonker-Pool et al. (1998) [29] | 1. Compare sexual consequences of testicular cancer and HL | HL 58 (72.2%) | 43.3 (SD 11.5) | 8.7 years (SD 6.2) | XRT or PCT (details not reported) | Testicular cancer | Non-standardized questionnaire | 1. Decrease in libido: 19%; arousal: 16%; erection: 17%; orgasm: 23%; sexual activity: 24%; satisfaction:14% ejaculation: 9% (30% : decrease in 1+ sexual function), value of sexuality: 18% |
| 5. Kiserud et al. (2009) [25] | 1. Examine self-reported sexual function and identify factors a/w reduced sexual function in male lymphoma survivors<br>2. Compare sexual function in lymphoma survivors with normative group of same-aged controls | HL: 138<br>NHL: 108 (84.5%) | HL: 45.7 (10.4)<br>NHL: 49.6 (9.6) | HL: 15.2 (SD 6.7)<br>NHL: 14.3 (SD 5.0) | Chemotherapy<br>Low intensity HL: 51%, NHL: 8%<br>Medium; HL: 25%, NHL: 54%<br>High; HL: 23%, NHL: 38% | General population | Brief Sexual Function Inventory [24] | 1. NHL lower scores than HL<br>2. Low testosterone and/or elevated LH a/w worse sexual function<br>3. Younger age, less emotional distress and better physical health a/w better sexual function<br>4. After adjusting for relationship status, lymphoma survivors poorer erection, ejaculation, overall sexual satisfaction, higher prevalence of reduced erectile function and poorer sexual satisfaction than controls |
| 6. Kornblith et al. (1990)* [20] | 1. Understand nature and extent of psychosocial problems<br>2. Identify illness, socio-demographic factors a/w adaptation | HL 273 (74%) (60% men) | 37 (20-66) | 6.3 years (Range 1-20) | PCT: 80%<br>XRT + PCT: 16%<br>XRT alone: 4% | General population | 8 items, plus Global Sexual Satisfaction Index (from Derogatis Sexual Function Inventory) | 1. Sexual satisfaction similar to controls<br>2. 37% : 1 + sexual problems (decreased satisfaction: 31%; interest: 21%; activity:18%; erectional problems: 13%; )<br>3. Psychosexual problems attributed to cancer a/w increased distress (BSI; IES intrusion, avoidance; POMS; PAIS-R) |

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|---|---|---|---|---|---|---|---|---|
| 7. Kornblith et al. (1992)*[30] | 1. Compare MOPP, ABVD, and MOPP/ABVD chemotherapy in terms of physical, psychosocial and psychosexual effects on HL survivors | Subset of 6 93 (76%) (60% men) | Median 35 (20-59) | 2.2 years (Range 1-5) | MOPP: 31<br>ABVD: 33<br>MOPP/ABVD: 29 | Treatment types | As for [20] | 1. If believed infertile – more distress (PAIS; POMS)<br>2.Relapse a/w more sexual problems attributed to cancer |
| 8. Kornblith et al. (1998)* [27] | 1. Compare long-term adaptation of HL and leukaemia survivors | As 6 | 37 (20-66) | 5.9 (Range 1-20) | As 6 | Leukaemia | As for [20] | 1. HL worse sexual function than leukaemia, lower satisfaction<br>2. HL survivors more likely to report reduced sexual activity as result of cancer |
| 9. Recklitis et al. (in press) [21] | 1. Determine nature and extent of sexual dysfunction after HL | 465 (49.7% men) (60.6%) | Median 44 (20-70+) | 18.32 (SD 7.31) | XRT: 93%<br>PCT: 37% | General population (patients' siblings) | As for [20] | 1. 54.2%: decreased sexual activity; 41.4% decreased interest<br>2. No differences relative to controls<br>3. Satisfaction lower in older survivors |
| 10. Van Tulder et al. (1994) [23] | 1. Determine QoL of long-term HL survivors | HL: 81 (92%) (51.8% men) | Men: (44.3, SD 11.1) | 14 years (SD 2) | XRT: all<br>+ vinblastin: 5<br>+ MOPP: 14 | General population | Maudsley Marital Questionnaire (sexuality scale) [22] | 1. Patients lower scores on sexuality scale than controls<br>2. ¼ - no interest in sex (controls: 10%)<br>3. ½ - sex at least once a week (controls: 73%)<br>4. 29% dissatisfied with frequency of sexual contact (controls: 16%)<br>5. 12% dissatisfied with quality of sexual contact (controls: 5%) |

* These studies were drawn from the same population

** Gender was controlled for in all analyses

Glossary: XRT – radiotherapy; MOPP – Mechlorethamine, vincristine, procarbazine, prednisone; PAVe - procarbazine, Alkeran, vinblastine; ABVD – Doxorubicin, bleomycin, vinblastine, dacarbazine; VBM – vincristine, bleomycin, methotrexate; PCT – polychemotherapy; a/w – associated with