The late effects of cancer and cancer treatment: a rapid review

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This paper aims to synthesize literature about the definition, prevalence, onset and treatments associated with late effects. A rapid review was conducted using Google Scholar to identify reviews related to the late effects of adult-onset cancers. Papers were included if they provided a definition of late effects and/or presented a review of late effects as a result of adult-onset cancers in patients aged 18 years or older. Reviews related to nonmelanoma skin cancer were excluded. Reviews focusing on late effects in survivors of childhood-onset cancers (younger than 18 years) were ineligible for inclusion in the review. A total of 16 reviews were identified. Between 0% and 100% of survivors experienced a range of physical, psychological and social late effects. The onset of physical late effects was defined broadly as 'months or years' after treatment, whereas psychological late effects were defined as occurring at the end of treatment or similarly to physical late effects as 'months or years' after treatment. Few reviews provided an operational definition of late effects, and the onset of late effects was not often reported. Thus, reviews may have included the acute and long-term effects of cancer treatment. Evidence regarding causes, prevalence, and onset was incomplete for many late effects. Understanding the cause and onset of late effects is important in order to provide timely interventions to reduce the risk of late effect development in cancer patients.

Improving understanding about the development of late effects after treatment is becoming an increasingly important area of investigation because of the rising number of cancer survivors worldwide.[1-2] Previously, survivors of adult cancers did not live long enough for late effects to develop because they were more likely to die from the disease or from acute treatment effects.[3] As the prospect of long-term survival for adult-onset cancers has improved greatly, there is a need to devote efforts to further understanding about late effects in this population, including addressing research on the prevalence of late effects and associated treatments.[4-5] Understanding when late effects emerge and identifying treatments for them is important to assist cancer care professionals in generating treatment summaries and survivorship care plans for patients' after hospital recovery and follow-up care.[6] Cancer survivors with late effects experience significantly poorer physical and mental health, report more unmet needs for care, and have significantly greater use of health services compared with survivors without late effects.[7] Therefore, it is important to try to identify and assess survivors who are affected by specific late effects and to provide data to facilitate the design and delivery of appropriate services that will meet the needs of survivors with late effects.

This paper provides a rapid review of relevant research to identify which late effects are experienced by survivors of adult-onset cancers, when those late effects first appear in relation to treatment completion, how many survivors are affected by late effects, and which treatments are associated with each late effect. Examples are provided of clinically relevant assessment tools for each late effect.

Methods

We adopted a rapid review approach rather than a full systematic review because we needed to transfer relevant knowledge into service planning and practice under given time constraints. The review was informed by 2 empirical studies of review methodology. First, a typology of reviews identified 14 varieties of literature review. In this typology, rapid reviews were defined as an "assessment of what is already known about a policy or practice issue, by using systematic review methods to search and critically appraise existing research" (p. 95). The completeness of searching in a rapid review is defined or delimited by time constraints and there is a time-limited formal quality assessment. Synthesis is typically narrative and tabular. Analysis addresses the quantity of studies and the overall quality and direction of the observed effect.[8] Second, a comprehensive review of the term "rapid review" suggested that

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internationally there is not yet a consensus about its meaning or how it differs from a systematic review.[9] Key features appear to be restricted research questions and truncated search strategies and an argument that the transparency of the methods used for each review is more important than the development of a formalised methodology by which to conduct rapid reviews.

An initial scoping exercise of bibliographical databases (eg, MEDLINE and CINAHL) identified more than 10,000 primary studies that were relevant to late effects as a result of treatment for adult cancers. The scope identified a number of existing reviews, including relatively recent reviews. Therefore, we decided to conduct a rapid review of reviews. We used Google Scholar to identify reviews about the different late effects that may occur after treatment for cancers, including how they were defined and measured. Google Scholar is a large search engine that contains a range of published, peer-reviewed academic papers. Abstracts and papers from large bibliographic databases such as PUBMED and MEDLINE are uploaded regularly onto Google Scholar. The search engine uses a ranking algorithm that takes into account the full text, author, citation counts, key terms, and source of publication, so that the most relevant papers tend to be ranked first.[10] We used search terms including *adult cancer*, *late effects* and *review* to identify relevant papers between 1980 and July 2012. Reviews that synthesised primary studies (about definition, causes, onset, and prevalence) on late effects (including social and psychological effects as well as physical health effects) which developed after treatment for cancers diagnosed during adulthood (18 years or older) were included in the rapid review. Mixed reviews of studies of late effects in childhood (younger than 18 years) and adult cancer survivors were included if the review provided a separate analysis and discussion section for adult survivors. In all, 10,800 papers were identified by Google Scholar, and we searched the first 20 pages (200 papers) of the results for relevant reviews. We decided to use data from the first 20 pages given the nature of Google Scholar's ranking algorithm and the absence of additional relevant reviews in later pages. From this search, we identified 12 reviews and another 5 were identified from the subsequent reference lists. The reviews were supplemented by referring to primary empirical studies when we needed clarification. Data regarding the definition, causes, onset, and prevalence of late effects were extracted from each review using a standardised pro forma. A narrative synthesis of the results is presented in Tables 1-4.

Results

Only 3 reviews provided definitions of late effects. The other 15 reviews did not conceptualise late effects in any explicit way. Two of the definitions included physical problems (eg, pain) and psychological problems (eg, fear of recurrence).[5,11] One review focused on physical effects only.[3] Each review defined the onset of physical late effects as occurring during an undefined period, "months or years after treatment" completion.[3,5,11] Stein and colleagues[5] differentiated between the onset of psychological late effects and physical late effects (but without providing any evidence or explanation to support their approach). The onset of psychological late effects emerged from around the end of treatment onwards[5] whereas the second review defined the onset of psychological late effects as occurring "some time" after treatment similar to physical late effects.[11] The lack of precision regarding the onset of late effects may be a result of individual variation between survivors (eg, the increased risk of treatment-induced menopause in women who receive treatment after the age of 30 years) or to individual differences between the natural course followed by late effects, or to other factors. The impact of late effects was characterised as a long-term change in health status and/or health-related quality of life.[11] This conceptualisation of late effects as involving change may suggest that they were not present before the cancer experience or that they were not experienced to the extent to which they were experienced after cancer treatment. The duration of late effects tended to be couched in terms of being long-lasting, though the period of time was not defined.[11] The extent to which late effects are chronic, long-lasting, or dissipate after a period of time has not been empirically assessed, and there appears to be a lack of precision about the onset of late effects.

Physical late effects

Secondary malignancies. Secondary malignancies tend to develop years after cancer treatment and include solid tumors and hematological cancers across a number of cancer sites.[1,3,11-14] The causes of secondary malignancies have been attributed to the carcinogenic properties of chemotherapy and radiotherapy, environmental factors, genetic predisposition, lifestyle factors, or a combination of those factors. Secondary leukemia emerges within 10 years of treatment, whereas secondary solid tumors emerge 10 years or more after treatment.[11-13] A review of the epidemiology of secondary cancers showed that just under one-fifth of new-incidence cancers recorded in the SEER programme are secondary cancers.[13] Lymphoma survivors treated with radiotherapy or chemotherapy are at an increased risk of developing secondary leukemia or solid tumors, particularly an increased risk of breast cancer 10 or more years after radiotherapy.[11-13] One review highlighted a dose-response relationship for the risk of developing leukemia as a secondary cancer after receipt of alkylating or platinum-based chemotherapeutic agents to treat ovarian and testicular cancers.[13] Table 2 presents data about the prevalence, onset of late effects and any associated treatments. Secondary cancers tend to be identified during routine cancer surveillance.[13]

Cognitive and neurological. Cognitive impairment may occur as a consequence of radiotherapy and chemotherapy.[1,15] Cranial radiation for brain tumors can cause necrosis and atrophy of the brain, leading to impairment in normal cognitive, visual, and auditory functioning.[14] Chemotherapy-induced cognitive problems have also been documented in survivors of breast, ovarian, prostate, small-cell lung cancer, and lymphoma.[1,3,5,14-17] Brain atrophy and necrosis have been reported in survivors of brain tumors. However, it is difficult to disentangle the extent to which these effects may be attributed to treatment or to the tumor itself.[14] Prevalence rates for cognitive decline as high as 48% and 61% have been reported for prostate cancer and breast cancer survivors, respectively.[17] It is important that the interpretation of findings from these studies take into account the potential for other factors to confound cognitive functioning in cancer survivors such as stress and anxiety levels (eg, at follow-up appointments) and previous cognitive impairment that may be affected by cancer therapy receipt.[18] Neurological late effects include radiotherapy-induced brachial plexopathy in breast cancer survivors, and chemotherapy-induced peripheral sensory neuropathy and tinnitus in 2%-25% of testicular and up to 92% of ovarian cancer survivors.[1,11,14,15] In addition to brain imaging techniques, obtaining a patient history and conducting neuropsychological tests help to detect the presence of cancer treatment-induced cognitive impairment.[3]

Endocrine. Cancer therapies may affect the thyroid, pituitary, or adrenal glands; the hypothalamus; or the pancreas, which could result in metabolic disorders.[19] In particular, hypothyroidism may result from radiation, radiation combined with chemotherapy, or hematopoietic stem-cell transplantation to treat head and neck cancers or after total body radiation in lymphoma survivors.[1,11,13] The mechanisms by which radiotherapy causes hypothyroidism may occur directly through the vascular system or indirectly through the immune system. Hypothyroidism emerges at least 5 years or more after treatment, and incidence rates vary between 7% and 85%, depending on the diagnostic criteria and the treatment history of the survivor.[11,19] Disorders of the endocrine system can be detected by the presence of excessive or deficient levels of hormones (eg, thyroid stimulating hormone) in blood and urine tests.[3]

Cardiopulmonary. Cardiovascular effects have been experienced by head and neck cancer, breast cancer, testicular cancer, acute myeloid leukemia, and lymphoma survivors.[1,14,20] The development of cardiovascular disorders can occur between 5 and 20 years after treatment, and mortality from cardiovascular late effects can occur after 10 years.[14,20] Chemotherapy and chemotherapy-radiation combined regimens have been associated with cardiovascular disorders because of the generation of free radicals.[1,14,20] Incidence rates of radiotherapy-induced cardiovascular toxicity have been reported in 10%-30% of survivors, and the toxicities have emerged within 10 years of treatment completion.[20] Pulmonary late effects include radiation pneumonitis, pulmonary fibrosis, idiopathic pneumonia syndrome, and generally impaired pulmonary function induced by chemotherapy, radiotherapy, and stem-cell transplantation.[1,14,20] A thorough cardiac and pulmonary assessment, including imaging, will help to identify cardiopulmonary late effects.[3]

TABLE 1 Definitions of late effects

Source	Definition
Aziz[3]	Late effects refer specifically to unrecognised toxicities that are absent or subclinical at the end of therapy and manifest months or years later, due to the identification of previously unseen injury, organ senescence and the failure of compensatory mechanisms.
Tichelli[11]	Late effects are long-term changes in the health status of a cancer survivor that are often absent immediately after cancer treatment and may produce physical or psychological morbidity. Late effects also have an impact on the survivor's relationships (eg, graft versus host disease).
Stein[5]	*General* Problems that are not present or identified after treatment but may develop as outgrowths of the effects on organ systems or the psychological process. These effects have a negative impact on the quality of life of a cancer survivor (eg, cardiopulmonary dysfunction). *Specific – psychological* Psychological or emotional responses that emerge at the end of treatment completion and may include positive effects (eg, anxiety).

Renal and hepatic. Liver complications such as hepatitis B and C have been documented in long-term cancer survivors who have received hematopoietic stem cell transplant or blood transfusions as part of their treatment. Chemotherapeutic agents such as cisplatin, methotrexate, and nitrosoureas have led to impaired renal function and in some cases patients have required dialysis.[1,11] Renal late effects can be detected with blood and urine tests, as well as imaging of the kidneys.[3]

Fertility and sexual dysfunction. A significant late effect – particularly for survivors of childbearing age or of hematological or reproductive organ cancer – is a loss of fertility because of gonadal failure, including treatment-induced menopause.[1,12,14-15,19,21] The prevalence of gonadal failure in survivors of Hodgkin lymphoma is reported to be between 15% and 35%.[12] Up to 63%, 47%, and 32% of ovarian, testicular, and brain cancer survivors, respectively, experience gonadal failure.[19] Prostate cancer survivors and survivors from other cancer sites also experience gonadal failure.[1,3,14] Treatment-induced infertility has been associated with chemotherapy and radiotherapy to the abdomen.[1,12]

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TABLE 2 Physical late effects: onset, prevalence, associated treatments, and clinical assessment tools

Late effect [associated treatment: onset] Cancer site (prevalence, %)	Assessment
Secondary cancers[13] (20% of new primary cancers)	
Hematologic malignancies [CTX, RTX, or both: 5-10 y] Lymphoma[a,12, 13] Ovarian[a,3, 13] Multiple[a,1, 3, 11, 13]	■ Routine cancer surveillance, eg, complete blood test
Solid tumors [CTX, RTX, or both: ≥ 10 y] Breast[a,13] Thyroid[a,13] Lymphoma[a,12-14] Testicular[a,14] Multiple[a,1, 3, 11, 13]	■ Routine cancer surveillance, eg, physical exam or blood tests for tumor markers
Neurotoxicity[3]	
Cognitive impairment – generalised [CTX or prophylactic cranial irradiation: unknown] Lymphoma[a,16] Breast (31-61)[1,3,5,17] Prostate (48)[17] Ovarian[a,15] Small-cell lung cancer[a,1] Not reported[a,3, 5, 14]	■ Cognitive assessment, eg, RBANS Brain imaging, eg, MRI ■ Patient history including interview with partner, family
Brain necrosis [RTX: unknown] Brain tumors[a,14]	■ Brain imaging
Brain atrophy [RTX: unknown] Brain tumors[a,14]	■ Brain imaging
Dementia [RTX: unknown] Brain tumors[a,1,14]	■ See under Cognitive Impairment
Visual and auditory impairment [RTX: unknown] Brain tumors[a,14]	■ Ophthalmic and auditory assessment
Nervous system[3]	
Peripheral nervous system impairment [CTX: unknown] Not reported (2-5)[14]	■ Neurological exam, including imaging, eg, CT scan
Brachial plexopathy [RTX: unknown] Breast[a,14]	■ Neurological exam, including imaging
Peripheral sensory neuropathy [CTX: unknown] Ovarian (57-92)[15] Testicular (2-25)[14]	■ Neurological exam, including imaging
Endocrine system[3]	
Hypothyroidism [cranial irradiation, CTX , or HSCT: ≥ 5 y] Head and neck (7-85)[11] Lymphoma[a,1,14,19]	■ Blood test to measure TSH levels
Hypothalamic dysfunction [cranial irradiation or surgery: unknown] Head and neck[a,19]	■ Blood and urine tests for hormones regulated by the hypothalamus, eg, cortisol
Hypopituitarism [cranial irradiation: unknown] Multiple[a,14,19]	■ Blood tests for hormones regulated by the pituitary gland
Hyperparathyroidism [RTX: unknown] Multiple[a,19]	■ Blood tests for PTH
Adrenal dysfunction [CTX: unknown] Head and neck[a,19]	■ Blood tests, urine, or salivatory tests for ACTH

ACTH, adrenocorticotrophic hormone; BPI, Brief Pain Inventory; CT, computed tomography; CTX, chemotherapy; DXA, dual energy X-ray absorptiometry; ECG, electrocardiogram; FAI, Fatigue Assessment Instrument; HSCT, hematopoetic stem cell transplantation; MPQ, McGill's Pain Questionnaire; MRI, magnetic resonance imaging; PTH, parathyroid hormone; RBANS, Repeatable Battery for Assessment of Neuropsychological Status; RTX, radiotherapy; TSH, thyroid stimulating hormone

[a]Prevalence rates not reported.

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TABLE 2 *continued from p. 140*

Late effect [associated treatment: onset] **Cancer site (prevalence, %)**	**Assessment**
Cardiopulmonary system[3]	
Cardiomyopathy, congestive heart failure, arrhythmias, endothelial dysfunction [CTX: 5-20 years]	
Breast[a,14] Testicular[a,14] Lymphoma[a,1,14] Multiple[a,20]	■ Cardiac assessment, eg, ECG
Coronary artery disease; pericardial disease; cardiomyopathy; valvular disease [thoracic radiation:10 or more years]	
Multiple (10-30)[3,20]	■ Cardiac assessment
Radiation pneumonitis, pulmonary fibrosis, idiopathic pneumonia syndrome, bronchiolitis obliterans [CTX, RTX or HSCT: unknown]	
Multiple[a,20]	■ Pulmonary function assessment
Lymphoma[a,1,20]	■ Chest X-ray
Liver and kidney damage[3]	
Hepatitis B or C [HSCT or blood transfusions: unknown]	
Not reported[a,11]	■ Hepatitis virus screening
Impaired renal function [CTX: unknown]	
Not reported [a,1]	■ Blood tests, eg, creatinine ■ Urine tests, eg, urinanalysis ■ Imaging, eg, ultrasound of the kidney
Fertility and sexual dysfunction	
Gonadal failure[3] [CTX, abdominal/pelvic radiation: unknown]	
Prostate[a,14] Unknown[a,1,3] Ovarian (63)[19] Testicular (10-47)[19] Brain (10-32)[19] Lymphoma (15-35)[12]	■ Endocrine system functioning (see Endocrine System) ■ Clinical interview incl. medical history ■ Blood tests ■ Semen analysis ■ Physical exam, eg, laparoscopy
Treatment-induced menopause [CTX: unknown]	
Breast[a,3,5] Hodgkin's disease[a,12] Multiple cancer sites (21-100)[1,3,12,14-15,19]	■ Endocrine system functioning (see Endocrine System) ■ Clinical interview to assess menstrual cycle history ■ Blood tests
Sexual dysfunction incl. loss of libido, erectile dysfunction and pain [surgery, CTX, and RTX]	
Testicular[a,5,15,23] Gynecologic (31-71)[5,15-16,21] Functioning Inventory[23] Prostate (5-85)[5,14-16,21] Colorectal (24- 77)[15,21] Breast (28-57)[3,12,21] Lymphoma (15-50)[12] Leukemia[a, 23] Brain (47)[5] Bladder[a,15] Multiple cancer sites (20-61)[5,19,22]	■ Clinical interview about sexual activity[3] ■ Patient-reported outcome measure, eg, Brief Sexual
Urinary and bowel disorders	
Urinary leakage and blockage [RTX, surgery: unknown]	
Bladder (0-70)[14] Prostate (6-50)[5,14-15] Ovarian[a,15] Colorectal (6-8)[14] Cervical (6-8)[14]	■ Clinical interview ■ Renal functioning tests (see under Liver and Kidney)
Bowel disorders [RTX: unknown]	
Colorectal (10-20)[14,24] Prostate (10-20) [5,14] Cervical (10)[14]	■ Clinical interview

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TABLE 2 *continued from p. 141*

Late effect [associated treatment: onset] Cancer site (prevalence, %)	Assessment
Musculoskeletal disorders[3]	
Osteoporosis/necrosis [RTX, steroids: unknown] Multiple cancer sites[a,14]	▪ Measure of bone density, eg, DXA scan ▪ Blood tests ▪ Clinical interview, eg, fracture and break history
Pain [RTX: unknown] Breast (19-70)[5,15,17,25] Colorectal (11-27)[17,24] Prostate (50-70)[17] Breast (50-70) [5,17] Testicular[a,5] Multiple cancer sites[a, 3,5]	▪ Patient-Reported Outcome Measures, eg, BPI[26] or MPQ[27] ▪ Clinical interview, assessment and history of pain
Muscle atrophy [RTX: unknown] Multiple cancer sites[5]	▪ Clinical interview ▪ Imaging, eg, X-rays ▪ Blood tests
Other late effects[3]	
Fatigue [treatments unknown: unknown] Breast (16-56)[14-15,17] Lymphoma (20-33)[5,14-15] Gynecologic (17-33)[15,17] Multiple cancer sites[5,14] Lung[a, 12] Prostate (60)[17]	▪ Thyroid gland functioning (see under Endocrine System) ▪ Patient-reported outcome measure, eg, FAI[30] ▪ Clinical interview
Lymphedema [surgery: unknown] Breast[a,15] Gynecologic[a,15]	▪ Functional assessment, eg, limb mobility ▪ Measure diameter of affected limb ▪ Imaging of lymphatic system, eg, ultrasound

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Premature-onset menopause in women who survive cancer is associated particularly with alkylating chemotherapeutic drug receipt.[12] Between 21% and 100% of survivors (including gynecologic cancer survivors who have been treated with surgery) experience treatment-induced menopause.[1,3,5,12,14-15,19] The risk of treatment-induced menopause or amenorrhea increases if women are treated for cancer when they are older than 30 years. Many female cancer survivors who experience early-onset menopause lose the protective effects of estrogen against heart disease and osteoporosis that can be counteracted with the use of hormone therapies.[1] However, there may be an increased risk of cancer recurrence with the use of hormone therapies.[12]

Sexual dysfunction in the form of loss of libido, pain with sexual activity, or erectile dysfunction can be experienced by many cancer survivors (Table 2). Between 5% and 85% of cancer survivors of the reproductive organs including gynecologic, prostate and testicular survivors experience sexual dysfunction.[5,14-15,17,21,22] Sexual dysfunction is experienced by survivors of breast (57%), colorectal (77%), lymphoma (50%), brain (47%) and other (61%) cancers.[3,5,12,15,17,19,21] Sexual late effects can occur as a result of damage to the physiological systems involved in sexual functioning as a consequence of surgery, radiotherapy and chemotherapy treatment, but may also be attributed to intra-individual psychological changes.[5,21] See Table 2 for clinically relevant tools and tests that assess fertility-related problems and sexual late effects.[3,23]

Urinary and bowel. Treatment for bladder cancer may result in up to 70% of cancer survivors experiencing urinary leakage.[14] Urinary problems such as blockage or incontinence have been experienced by men who have been treated for prostate cancer.[5,15] After radical prostatectomy, up to 50% of prostate cancer survivors may experience urinary leakage.[14] Urinary problems have also been reported in survivors of ovarian cancer.[15] Between 6% and 8% of cervical and colorectal cancer survivors experience urinary late effects.[14] Urinary dysfunction is assessed using a clinical interview and renal assessment. Bowel disorders have also been documented in prostate and ovarian cancer survivors.[5,14-15] Between 10% and 20% of colorectal, prostate, and cervical cancer survivors experience bowel-related late effects after treatment.[14,24]

Musculoskeletal disorders. One review reported that musculoskeletal late effects are the most common physical late

effects experienced by cancer survivors, including pain and impairments in physical functioning.[5] Pain has been reported in lymphoma and testicular survivors, up to 27% of colorectal, up to 70% of prostate, and up to 70% of breast cancer survivors after treatment.[5,15,17,22, 24--25] Significant predictors of pain include radiotherapy and younger age at treatment.[15] Pain may be assessed using patient-reported outcome measures such as the Brief Pain Inventory and the McGill's Pain Questionnaire.[26,27] Radiotherapy has been attributed directly to muscle atrophy, osteonecrosis, and increased risk of fractures. The development of osteoporosis after treatment has been associated with receipt of radiotherapy and steroids, whereas the development of osteonecrosis is associated with chemotherapy, radiotherapy, and steroid receipt.[11,14] Chronic pain, which is experienced by a high number of cancer survivors, may be attributed to scarring of the tissue surrounding joints or peripheral nerves.[1]

Other physical late effects. Impaired immune functioning such as an increase in infectious diseases may result from removal of the spleen. This has been documented in Hodgkin lymphoma survivors.[1,14] Immune system impairment may be experienced as a direct result of the disease in this survivor group.[1] Fatigue can be a debilitating, long-lasting effect for cancer survivors after treatment. Up to 56% of breast, 33% of gynecologic, 50% of colorectal, 60% of prostate, and 33% of lymphoma survivors may experience fatigue after treatment.[12,14-15,17,24] The exact etiology of fatigue after treatment is unknown.[14] However, fatigue is often experienced before or during treatment. As a result, this may be a long-lasting effect rather than an effect with a delay before presentation after treatment (ie, a late effect).[15] Fatigue may be assessed by patient-reported outcome measures, clinical interview and an assessment of thyroid gland functioning.[3,30] Damage to lymph nodes following curative surgery has led to edema.[5] Lymphedema is particularly prevalent in the upper limbs of breast cancer survivors and the lower limbs of gynecologic cancer survivors.[15,25,28-29]

Psychological late effects

Table 3 presents data on the prevalence, onset of late effects, and the associated treatments. Examples of patient-reported outcome measures that may be used in clinical settings to identify psychological late effects in cancer survivors are provided in the Table 3.

Psychological distress (generalised and specific). Psychological distress incorporating cancer-related worries, anxiety, and depression has been experienced by survivors of cancers from various sites.[5,22,31-32] For example, high levels of distress were reported by up to 31% of head and neck cancer survivors who had been treated with radiotherapy, in 17%-19% of breast cancer survivors, 36%-44% of prostate cancer survivors, 26%-41% of cancer survivors from a number of sites, and an unspecified number of lymphoma survivors.[22,31-32] The psychological distress experienced by cancer survivors may be more specific, such as distress related to attendance for follow-up tests. Fear of recurrence is a common and persistent effect experienced by many survivors.[1,5,24,31] Research aimed at measuring or understanding fear of recurrence is limited.[4] Other anxiety-related effects include fear of disease progression, sleep disturbances, psychosexual problems, fertility concerns, and body image concerns.[1,5,12,15-17,22,24] Distress can be measured using patient-reported outcome measures and screening tools.[33-41]

Depression and anxiety. Studies have documented that up to 58% and 48% of survivors from a number of cancer sites have nonclinical depressive and anxiety symptoms, respectively.[5,17,22,25] Variation in reporting of depressed mood and anxiety may be due to variation relating to cancer site, measurement, and other factors. Similar to the general population, female cancer survivors were more likely to experience depressive symptoms than were their male counterparts.[31] Clinical depression occurs less frequently in the cancer survivor population than does depressive mood, while up to 31% of gynecologic, lung, colorectal, and prostate cancer survivors, are assessed as being clinically depressed.[17,31] None of the reviews reported the prevalence of clinical anxiety disorders in cancer survivors. However, individual studies have reported a prevalence rate of 12% for clinical anxiety and of 31% for subclinical anxiety by survivors of various cancer sites, including gynecologic, testicular, and lymphoma.[42] Depression and anxiety (including many anxiety-related effects) may be measured by patient-reported outcome measures and a clinical interview based on the Diagnostic Criteria Manual (DSM) for Mental Disorders criteria.[43]

Posttraumatic stress disorder. The diagnosis of a life-threatening illness such as cancer has been added to the DSM since its fourth revision in 2000.[44] Between 0% and 32% of breast, head, and neck, and other cancer survivors have experienced PTSD.[5,31] Recent research has suggested that head and neck and hematological cancer survivors are more vulnerable to PTSD, although explanatory mechanisms for this vulnerability are not known.[5] PTSD may be identified by using a specific scale (eg, Post-Traumatic Diagnostic Scale) or through clinical interview using the DSM criteria.[45]

Posttraumatic growth. Receiving a cancer diagnosis and subsequent treatment can be a traumatic event for many patients and lead to negative psychological effects in survivors and their families, positive effects such as posttraumatic growth (PTG) have also been reported. PTG involves an intra-individual spiritual change and is characterised by improvements in relationships, a positive change

TABLE 3 Psychological late effects: onset, prevalence, associated treatments, and clinical assessment tools[a]

Late effect [onset] Cancer site (prevalence, %)	Assessment[b]
Psychological distress [unknown] Multiple primary (26-41)[32] Breast (17-19)[32] Prostate (36-44)[32] Head and neck (31)[31] Lymphoma[c,22]	▪ Screening tool, eg, distress thermometer[33] ▪ Symptom-specific scale, eg, HADS[33] ▪ Cancer-specific scale, eg, PDQ-BC[34]
Depression – symptoms of[43] [unknown] Breast[c,25] Multiple cancer sites (0-58)[5] Multiple cancer sites (21-48)[17] Lymphoma[c,22]	▪ Specific symptom scale, eg, CES-D
Depression – clinical[43] [unknown] Gynecologic, prostate, lung (14-31)[31] Gynecologic (5.5-19)[17] Prostate (14-17)[17] Colorectal (14)[17]	▪ Specific symptom scale (with clinical cut-off), eg, BDI ▪ Clinical interview based on DSM criteria
Anxiety – subclinical [unknown] Multiple cancer sites (6-48)[5,17]	▪ Symptom-specific scale, eg, HADS[33]
Fear of recurrence/cancer progression[35] [unknown] Not reported[c,5] Gynecologic and other[c,31] Colorectal[c,24]	▪ Specific scale, eg, FRS
Body image concerns [36,37] [unknown] Breast[c,12] Colorectal[c,24]	▪ Cancer-specific scale, eg, BIBCQ ▪ Symptom-specific scale, eg, MBSRQ ▪ Clinical interview
Sleep disturbances [unknown] Lymphoma[c,16] Breast, prostate (14-59)[15,17] Colorectal [c,17] Not reported[c,5,15,17]	▪ Specific scale, eg, MOS Sleep Scale[38] ▪ Cancer-specific QOL scale with sleep subscale, eg, EORTC-QLQ-C30[39]
Psychosexual problems [40] [unknown] Not reported[c,5] Multiple cancer sites[c,31] Multiple cancer sites (24-71)[17] Lymphoma (20-54)[22]	▪ Cancer-specific scales with sexual functioning component, eg, FLIC-VAS ▪ Sexual functioning-specific measures, eg, Brief Sexual Functioning Inventory ▪ Clinical interview
Fertility concerns [41] [unknown] Lymphoma[c,16]	▪ Cancer-specific scales, eg, QOL-CS
PTSD stress disorder (unknown) Multiple cancer sites (0-32)[5] Head and neck (14%)[31] Multiple cancer sites (32)[31] Breast (15-18)[31]	▪ Specific scale, eg, PDS[45] ▪ Clinical interview based on DSM criteria[44]
PTSD growth [46] [unknown] Not reported[c,12] Not reported[c,5,12] Breast[c,31]	▪ Specific scale, eg, PTGI

BDI, Beck Depression Inventory; BIBCQ, Body Image after Breast Cancer Questionnaire; CES-D, Center for Epidemiologic Studies – Depression Scale; DSM, Diagnostic and Statistical Manual of Mental Disorders; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FLIC- VAS, Functional Living Index Cancer Visual Analogue Scale; FRS, Fear of Recurrence Subscale; HADS, Hospital Anxiety and Depression Scale; MBSRQ, Multi-dimensional Body Self Relations Questionnaire; MOS, Medical Outcomes Study; PDQ-BC, Psychosocial Distress Questionnaire – Breast Cancer; PDS, Posttraumatic Stress Diagnostic Scale; PTGI, Posttraumatic Growth Inventory; PTSD, posttraumatic stress disorder; QOL-CS, Quality of Life-Cancer Survivor Scale.

[a]Many reviews did not include how late effects were assessed. This information has therefore been supplemented by other studies. [b]Treatments associated with development of late effects were not identified. [c]Prevalence data unknown.

TABLE 4 Social late effects: onset, prevalence, associated treatments, and clinically relevant assessment tools[a]

Late Effect [onset] Cancer site (prevalence, %)	Assessment[b]
Relationship changes	
Family, intimate partners, social contacts [unknown] Not reported[a,12] Not reported[a,1] Ovarian (23)[31]	▪ Cancer survivor-specific scale, eg, IOC ▪ Self-report
Employment-related changes	
No return to work [unknown] Multiple cancer sites[a,15]	▪ Cancer survivor-specific scale, eg, IOC ▪ Self-report
Difficulty re-adjusting to work [unknown] Head and neck[31]	
Fear of losing benefits [unknown] Not reported[a,1,12]	
Workplace discrimination and stigma [unknown] Not reported[a,1,12]	
Job-lock[d] [unknown] Not reported[a,1,12]	
Finance-related difficulties	
Difficulty in obtaining medical or life insurance [unknown] Not reported[a,1,12,31]	▪ Cancer survivor-specific scale, eg, IOC ▪ Self-report
Concerns over paying bills, eg, child care [unknown] Not reported[a,12,31]	

IOC, Impact of Cancer Scale

[a]Many reviews did not include how late effects were assessed. This information has therefore been supplemented by other studies. [b]Treatments associated with development of late effects were not identified. [c]Prevalence data unknown. [d]Job lock refers to an employee's inability to voluntarily leave his or her job because of the risk of losing health care benefits.

in a survivor's outlook toward life and empathy toward others.[46-47] This positive late effect of the cancer experience was reported by 3 reviews.[5,12,46] Factors that may play a role in the development of positive PTG-like effects (as opposed to negative effects) from cancer include social support, information seeking behaviors and complementary and alternative therapy use.[48] These factors may act as potential modifiable factors that may be useful for the development of interventions targeted at cancer survivors. PTG may be measured using the Post-Traumatic Growth Inventory (PTGI).[46]

Social late effects

Cancer survivors may experience social effects relating to their cancer experience such as changes in relationships, and/or employment- and finance-related changes. Relationships in families, between intimate partners and social contacts may change in positive and negative ways.[1,12,31] Previous literature has found that cancer survivors are more likely than the general population to be unemployed.[16] Further employment-related effects experienced by cancer survivors include difficulty reintegrating into work life, job lock, discrimination, fear of losing benefits, and disease-associated stigma.[1,12,15,31] Cancer and cancer treatment may also lead to finance-related issues such as difficulty obtaining medical or travel insurance and securing credit, including mortgages and paying bills such as child care.[1,12,31] There do not seem to be any clinically relevant assessment tools to identify social problems after cancer diagnosis and treatment, but the Impact of Cancer Scale may be a useful tool for clinicians.[49]

Discussion

We included 17 reviews in our rapid review. We found wide variation in the reporting of late effects, which might have been the result of differences in definitions and assessment methods. For example, depression measured as a mood or a clinical disorder provided different prevalence rates.[17] The findings of this review suggest that as many as 100% of cancer survivors experience late effects. Up to 100% of ovarian cancer survivors (younger than 40 years) who had been treated with combination cytotoxic drugs experienced treatment-induced menopause.[19] The most prevalent late effects aside from treatment-induced menopause include peripheral sensory neuropathy (up to 92%), hypothyroidism (up to 85%), sexual dysfunction (up to 77%), urinary

disorders (up to 70%), and pain (up to 70%). Although some of these late effects (eg, peripheral sensory neuropathy and hypothyroidism) are limited to a few cancer sites, psychological and social late effects or physical late effects such as sexual dysfunction, pain or fatigue are experienced by survivors from many different cancer sites.

Physical late effects affecting each major organ system were found. Physical late effects as a result of cancer treatments have been studied more extensively than have other types of late effects. However, there are gaps that need to be addressed. None of the reviews reported the onset of neurotoxic, neurological, endocrine (with the exception of hypothyroidism), pulmonary, hepatic, urinary, reproductive, musculoskeletal, gastrointestinal, or other late effects (eg, fatigue and lymphedema). Many treatments associated with the onset of physical late effects have been identified. However, the particular cancer treatments and etiological pathway involved in the development of fatigue remains unknown. Furthermore, the numbers of cancer survivors who develop neurotoxic late effects, brachial plexopathy, endocrine effects (with the exception of hypothyroidism), chemotherapy-induced cardiac effects, pulmonary effects, liver and kidney effects, osteoporosis, and lymphedema were not identified by the rapid review. Limited information regarding prevalence of late effects may be explained by the broad scope of many of the included reviews giving an overview of many late effects across a number of cancer sites. Aside from traditional clinical assessments to identify many physical late effects, patient-reported outcome measures are also available for physical effects such as sexual dysfunction, pain and fatigue, which may be useful in a clinical setting. In addition, there is a need to give empirical research attention to the onset, prevalence and causes of psychological late effects, particularly anxiety-related effects such as body image concerns, fertility concerns, and fear of recurrence. Although it is likely that psychological late effects are caused by the experience of being diagnosed with, treated for, and recovering from cancer rather than occurring as a direct result of treatments, they may also occur as a result of physical late effects (eg, depression as a result of treatment-induced pain). There are symptom- or disease-specific measures available for psychological late effects.

Social effects may occur as a result of the general cancer experience or after the impact of specific physical or psychological late effects (eg, the experience of lymphedema or depression), which may impact on capacity to work and thus the financial situation of cancer survivors. None of the included reviews provided findings regarding the number of survivors who experience cancer-related social effects and there is a need for further investigation.

There is extensive knowledge regarding late effects after childhood cancers. Identifying and understanding late effects in survivors of adult-onset cancers is more complex because of aging processes and comorbidities.[5,14] Generally, factors associated with the development of late effects in adult-onset survivors include a patient's lifestyle, age at treatment receipt and, as identified by the rapid review some late effects, are associated with particular treatments.[5] Moreover, there is an increased risk of late effect development when more than one treatment has been received and survivors are at risk of late effects associated with each treatment.[5,7]

In addition to the specific tools identified in the rapid review, there are a few clinically relevant generic tools that may help health care professionals to identify late effects in their patients. The Common Terminology Criteria for Adverse Events (CTCAE) is a clinician-administered scale and measures the presence and severity of long-term and late effects. However, it is lengthy and time intensive to complete.[50] The Late Effects of Normal Tissue-Subjective Objective Management Analytic (LENT-SOMA) scales originally developed by the European Organisation for Research and Treatment of Cancer (EORTC) and the Radiation Treatment Oncology Group (RTOG) is less time intensive and lengthy as the CTCAE and clinical and patient versions are available for specific cancer sites.[51] Both tools assess physical effects only. The UK National Cancer Survivorship Initiative has developed a Concerns Checklist that may be used as a screening tool for psychological and social late effects.[52]

It is important to note that this review was not conducted using a systematic search strategy though a structured and focused approach was used to identify relevant existing reviews. Also, the results of the rapid review were supplemented by results from the individual primary papers included in the reviews. There is a possibility that the rapid review of reviews may not have identified some late effects or treatments associated with the development of late effects. For example, specific social late effects such as bankruptcy and poverty were not identified.[53] There was limited coverage of studies of the development of effects in breast and prostate cancer survivors relating to the strong association between hormone replacement therapy and endocrine therapy. Many cancer survivors receive hormone therapy as adjuvant treatment to reduce their risk of cancer progression and they may receive this treatment for many years. Side-effects may occur during the course of receiving the therapy, whereas late effects emerge a period of time after treatment has been completed.[54-55] Many of the primary studies in the reviews were cross-sectional in nature; longitudinal cohort studies would be a more appropriate study design to collect onset data about late effects.[5,17] Nevertheless, the rapid review successfully collated and narrated information about late effects in a pragmatic way as well as identifying research gaps.

The rapid review is an easily accessible and quick guide for clinicians and others about specific sites and specific treatments associated with late effects. It also provides examples of clinically relevant tools to identify effects in

cancer patients. It was impossible within the scope of this review to identify every clinically relevant tool for assessing each late effect within each cancer site. Uncovering which treatment or intervention was the most effective for each late effect would require separate systematic reviews akin to Cochrane Collaboration reviews. Moreover, there are many different types of treatments or interventions that may ameliorate cancer late effects. For example, a number of Cochrane Collaboration reviews that address the effectiveness of exercise interventions,[56] psychosocial interventions,[57] pharmacological therapies,[58] and education interventions[59] to manage cancer-related fatigue have been identified. Web-based resources such as the US-based National Cancer Institute provide practical support for patients and clinicians regarding many late effects identified in this rapid review.[60]

Many of the papers included in the rapid review neglected to provide a definition of late effects. Late effects were defined in terms of their onset and were thus differentiated from other types of effects such as acute, short-term effects, and long-lasting effects that present during or prior to treatment. This review provides clarity regarding how late effects are defined and it identified commonalities regarding the onset of physical late effects as occurring "months or years" after treatment as well as pointing out that there was less agreement regarding the onset of psychological late effects. Many of the reviews did not report the onset of late effects and more research is needed to understand when psychological, social, and many physical late effects first present after cancer treatment. It is important that clinicians are aware when effects first emerge so that timely identification and intervention can be provided. For example, hypothyroidism has been identified as emerging 5 years after cranial radiation for cancers of the head and neck. Screening patients with this cancer and treatment history will help clinicians provide appropriate care and treatment at the right time.

Research is constantly contributing to the development of better, more efficacious treatment that will contribute to the achievement of optimum survival rates, by taking into account the impact of cancer treatment on the long-term morbidity and quality of life of survivors. Future research should address the gaps identified by this review and use the existing knowledge to develop interventions and strategies that reduce the risk, or prevent the development, of late effects in cancer patients and survivors.

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