METRICS FOR AYA CANCER CARE IN CANADA

METRICS FOR EVALUATING SYSTEM LEVEL CHANGE IN ADOLESCENT AND YOUNG ADULT (AYA) CANCER CARE IN CANADA

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements for
the Degree Doctor of Philosophy

McMaster University DOCTOR OF PHILOSOPHY (2021) Hamilton, Ontario (Health Research Methods, Evidence, and Impact)

TITLE: Metrics for evaluating system level change in adolescent and young adult (AYA) cancer care in Canada

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NUMBER OF PAGES: 183

LAY ABSTRACT

A person 15 to 39 years old with cancer will face many challenges. This is a time of life with many changes such as continuing schooling, getting married, starting a career, or starting a family. To make sure that young people with cancer are getting the best care, and that they have the best chance to achieve their goals and contribute to society, we need to measure what is important to this group. These measures can be used to compare hospitals, or changes over time to help make care better. This paper looks at what we already measure in this group, and what patients, researchers and healthcare workers think also should be measured to help provide the best care for these patients. Measures discussed in this paper could be used in programs to monitor the quality of care given to young people with cancer.

ABSTRACT

Adolescents and young adults (AYAs, 15-39 years of age) with cancer face unique challenges. Efforts have been made to improve both care and outcomes for this population. Metrics to evaluate AYA cancer care efforts help to ensure that objectives and outcomes are being met. This thesis comprises 7 papers which explore system performance metrics for cancer care and control in AYAs. A scoping review introduces the topic and addresses the current state of indicator metrics for the AYA cancer population. The second paper extends this work and develops a consensus-based list of relevant indicators. The subsequent papers focus on further development of two of the identified indicators for implementation in Canada (identification of patient reported outcome measures (PROMS) for assessing distress; a referral indicator for oncofertility care).

This thesis describes 14 indicators in 5 care areas. Two identified indicators were further developed to aid in implementation ("*Proportion of AYA patients screened for distress with standardized AYA specific tools*" and "*Proportion of AYA patients who had fertility preservation discussion before treatment*"). Criteria from the National Quality Forum (NQF) were used to assess commonly used PROMs for distress. It was found that although all PROMs had acceptable psychometric properties, only the "Impact of Cancer" scale of the CDS-AYA had strong content validity for AYA with cancer. For Oncofertility, the indicator "*Proportion of cases attending a fertility consult visit ≤ 30 days from diagnosis of cancer*" was recommended for use. Finally, factors associated with attending such a fertility consult were identified. Important factors for both men and women included: age at diagnosis, risk to fertility, year of diagnosis, treatment with radiation or chemotherapy, region of care, income and residential instability. The information presented in this thesis can be applied to national system performance initiatives to identify and implement metrics to monitor and evaluate cancer care in AYA.

ACKNOWLEDGEMENTS

I would like to acknowledge my supervisor Dr. Andrew Costa for his guidance and support of this work. As well I would like to thank Dr. Hsien Seow for his advice and comments throughout this work. And I would like to especially express my deepest gratitude to Dr. Ronald Barr for his many years of mentorship and dedicated support of both my career and this thesis work.

I am also grateful to everyone whom I have worked with over the course of these projects. Especially the members of the System Performance Working Group of the Canadian Task Force for Adolescent and Young Adults with Cancer who contributed their time and expertise to the Delphi process to develop the indicator set for adolescent and young adults with cancer. As well as, the Task Force Co-ordinator, Sonja De Pauw, for her guidance, support and thoughtful advice during this work. A special thanks also to Drs. Anne Klassen and Norma D'Agostino for their thoughtful comments and contributions to the patient-reported outcome section of this thesis. Finally, I would also like to acknowledge Ahmad Rahim and Glenda Babe for their help assembling the ICES data for this thesis.

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LIST OF ALL ABBREVIATIONS AND SYMBOLS

ALR	Cancer Activity Level Reporting
AUC	Area under the curve
AYA	Adolescent and young adult
BC	British Columbia
CDS-AYA	Cancer Distress Scales – adolescent and young adults
CPAC	Canadian Partnership Against Cancer
CQSI	Cancer Quality System Index
DT	Distress thermometer
ESAS-r	Edmonton Symptom Assessment System-revised
HADS	Hospital Anxiety and Depression Scale
HiREB	Hamilton Integrated Research Ethics Board
ICC	Intra-class Correlation Coefficient
ICES	Institute of Clinical and Evaluative Sciences
IPDB	ICES Physician Database
IVF	in vitro fertilization
LHIN	Local Health Integration Network
NCCN	National Comprehensive Cancer Network
NCCN-DT	National Comprehensive Cancer Network Distress Thermometer
NGOs	Non governmental organizations
NQF	National Quality Forum
OCR	Ontario Cancer Registry
OHIP	Ontario Health Insurance Plan Claims Database
PM	Performance measure
PMCC	Princess Margaret Cancer Centre
POGO	Pediatric Oncology Group of Ontario
PRO	Patient Reported Outcome
PRO- PM	Patient Reported Outcome – Performance Measure
PROM	Patient Reported Outcome Measure
RCC	Regional Cancer Center
RPDB	Registered Persons Database
ROC	Receiver operating characteristic
SPM	System performance metrics
SPSS	Statistical Package for Social Sciences
TF	Canadian Task Force on AYA with Cancer
TRT	Test Retest

DECLARATION OF ACADEMIC ACHIEVEMENT

This document is a 'sandwich' thesis comprised of 7 publications/manuscripts including:

1) Rae, C., Shah, N., De Pauw, S., Costa, A. and Barr, R.D., 2019. System Performance Indicators for Adolescent and Young Adult Cancer Care and Control: A Scoping Review. *Journal of Adolescent and Young Adult Oncology*.
2) Rae, C.S., Pole, J.D., Gupta, S., Digout, C., Szwajcer, D., Flanders, A., Srikanthan, A., Hammond, C., Schacter, B., Barr, R.D. and Rogers, P.C., 2019. Development of System Performance Indicators for Adolescent and Young Adult Cancer Care and Control in Canada. *Value in Health*.
3) Rae, C., Klassen, A.F., Tsangaris, E., Breakey, V. and D'Agostino, N., 2019. Distress Screening in Adolescents and Young Adults with Cancer: Development of Cut-Points for the Cancer Distress Scales-Adolescent and Young Adults. *Journal of Adolescent and Young Adult Oncology*.
4) Rae, C.S., Tsangaris, E., Klassen, A.F., Breakey, V. and D'Agostino, N., 2019. Comparison of Patient-Reported Outcome Measures for Use as Performance Metrics in Adolescent and Young Adult Psychosocial Cancer Care. *Journal of Adolescent and Young Adult Oncology*.
5) Development and validation of an indicator for oncofertility care in Ontario Canada for adolescents and young adults with cancer
6) Factors associated with adolescent and young adult attending a fertility consultation within 30 days of a cancer diagnosis in Ontario, Canada.
    Part A. Males
    Part B. Females

CHAPTER 1: INTRODUCTION

It has been recognized internationally that adolescents and young adults (AYAs) with cancer represent a unique patient population due to both the biology of their diseases and circumstances in life.[1] This population has been defined as 15 to 39 years of age by the Progress Review Group convened in 2005 by the US National Cancer Institute.[2] In Canada, approximately 8000 people aged 15 to 39 are diagnosed each year with cancer.[3] Common cancers which occur in the AYA population include thyroid cancer, breast cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, testicular cancer and melanoma.[3] This distribution of cancers in AYAs is different than in either pediatric or older adult populations, and requires resources from both the pediatric and adult healthcare systems to best meet the needs of this population. In Canada, the healthcare system is dichotomous with pediatric and adult care, creating many challenges for treating AYA cancer patients.[4] These challenges include the availability of clinical trials, which should be the standard of care. An AYA over 18 years of age with a cancer typical of childhood may not be able to access a trial that best meets their needs because it is likely only offered within pediatric centers.[5] Psychosocial issues are also a major concern for the AYA cancer population. A cancer diagnosis in AYAs comes during a time of immense change. Patients are experiencing key milestones in life such as graduating from high school, entering university, developing their career, gaining independence or starting a family.[6] One of the greatest concerns and challenges in treating this population is fertility. Many cancer treatments have gonadal toxicity, therefore fertility preservation is another important aspect of the care given to AYA patients.

In order to meet the needs of AYA cancer patients and survivors there have been several initiatives in other countries with public health care systems to help improve clinical outcomes.[7] These include AYA cancer treatment centers established by Teenage Cancer Trust in the United Kingdom, and organizations developed to oversee care in this population such as CanTeen in Australia. In Canada, a Task Force was created by the Canadian Partnership Against Cancer (CPAC) in 2008 to make national recommendations for the care of AYAs with cancer. The Canadian Task Force on AYAs with Cancer held two international workshops, in 2010 and 2012, to develop a framework and a plan for action. The two workshops involved all relevant stakeholders across Canada, and international advisors. Two publications Fernandez et al[8] and Rogers et al[9] provided detailed principles of care and recommendations based on the findings of these workshops. As strategies and resources to improve AYA cancer care and control are implemented it is important to evaluate and monitor outcomes, which requires well developed metrics specific to this population. The overall objective of the work described in this thesis was to identify and evaluate system performance metrics for the monitoring and evaluation of AYA cancer care, achieved through seven papers which applied various health research methods to address the topic:

1) A scoping review of the academic and grey literature to assess the current state of indicator development and use for AYA cancer care and control.
2) Development of indicators for AYA cancer care and control using a modified-Delphi approach involving relevant stakeholders.

3) Examination of patient-reported outcome measures (PROMs) for use in a patient reported outcome - performance measure (PRO-PM) for AYA psychosocial care.
    a. Development of cut-points for the Cancer Distress Scales – AYA (CDS-AYA)
    b. Comparison of PROMs for use as a PRO-PM in AYA psychosocial care
4) Examining a potential oncofertility referral indicator for monitoring the use of fertility consultations in AYA cancer patients, using administrative data.
    a. Development and validation of an indicator of the proportion of AYA with cancer who attend a fertility consultation in Ontario
    b. Describing the current state of referral of AYA with cancer to fertility consults in Ontario, Canada for both males and females

Chapters 2 and 3 focus on the process to develop a list of indicators for AYA cancer care and control in Canada. In chapter 2 a scoping review was undertaken to address the broad objective "*to describe the quality indicators which are used currently for AYA (15 to 39 years of age) cancer care and control in a Canadian context*." A scoping review was a necessary part of the development process to facilitate the presentation of existing indicators to the stakeholder group who were working on identifying a set of indicators for use in Canada. The review also aimed to highlight any gaps in indicator availability based on the framework adapted from the Fernandez et al[8] principles and recommendations for AYA cancer care.

Chapter 3 represents the core piece of this thesis, creating a consensus-based list of indicators involving stakeholders across Canada. The first report on indicators for

AYA cancer care and control was published by CPAC in April 2017.[3] This work was based on a list of indicators which represented outcomes and aspects of care that were feasible to report on in Canada. The System Performance Working group that was charged with compiling the 2017 report recognized that a consensus-based process was necessary to develop a list of indicators which would be important for AYA cancer care and control in Canada, regardless of current feasibility. The methods to develop this list were based on the development process for childhood cancer indicators that were created by the Pediatric Oncology Group of Ontario (POGO).[10,11] There were two objectives to the process:

a) To develop a consensus-based list of system performance indicators to be used for monitoring, evaluating, and benchmarking progress for cancer care and control in AYAs in Canada.
b) To create a refined list of indicators based on feasibility and the availability of relevant data.

The final chapters of this thesis focus on specific indicators identified in chapter 3 to help further develop them for implementation in Canada. Psychosocial care and oncofertility were selected as topics for these chapters because of their specific importance to AYAs with cancer.

Chapters 4 and 5 focus on screening for distress in AYA cancer patients and survivors, an important part of psychosocial care. Distress has been recognized as the 6th vital sign in cancer care, and screening is recommended as part of the standard of care.[12]

These two papers were based on field-test data collected as part of the development process for a new distress screening tool designed specifically for the AYA cancer population, the Cancer Distress Scales – Adolescent and Young Adult (CDS-AYA).[13] The objective of chapter 4 was to develop cut-points for identification of distress for the five scales that comprise the CDS-AYA. Cut-points are important for the interpretability and utility of a patient-reported outcome measure (PROM), and were utilized in the subsequent paper that compared PROMs for use in performance measurement.

There are many PROMs available for screening of distress in cancer patients which could be used for performance measurement indicators. The Edmonton System Assessment Scale (ESAS) is currently recommended for use in Canada, and the number of cancer patients screened using this instrument is a metric reported on by CPAC.[14,15,16] However, it is important to assess PROMs for use in the target population to ensure that the PROM meets selection criteria described by the National Quality Forum (NQF).[17] This will help to ensure the appropriateness of the PROM for use in performance measurement based on the selected target population and outcome. The objective of chapter 5 was *"to compare the Cancer Distress Scales for Adolescents and Young Adults (CDS-AYA)-Emotional and Impact scales-with the Edmonton Symptom Assessment Scale-revised (ESAS-r), Hospital Anxiety and Depression Scale (HADS), and the National Comprehensive Cancer Network Distress Thermometer (NCCN-DT) for use as a patient-reported outcome-performance measure (PRO-PM) for AYA cancer care."* This paper will help to inform the selection of a PROM for use in indicators related to distress metrics within the AYA cancer population.

Chapters 6 and 7 address oncofertility an important area of care for AYA with cancer. Many AYA will lose their ability to have biological children due to toxicity of treatments or surgical procedures. In order to preserve the choice for AYA to have biological children in the future, it is essential that AYA are provided information regarding fertility risks and options for fertility preservation. Oncofertility was included as a key recommendation for healthcare for AYA with cancer in the area of Active Care whereby Fernandez et al[8] states "*Fertility risks and options for considering or not considering fertility preservation must be discussed with each patient.".* There is a lack of indicators in this area, and in an earlier paper in this thesis a working group recommended the indicator "Proportion of AYA patients who had fertility preservation discussion before treatment" to address this area of care. The aim of chapter 6 and 7 is to lay the framework to develop and implement an indicator that captures this concept for AYA cancer care in Ontario. Chapter 6 focused on the objective *"to develop and evaluate the validity of the proposed indicator the "proportion of cancer patients who attend a fertility consultation during treatment" for use in Ontario, Canada."* The objective of chapter 7 was to describe the pattern of referrals to fertility consults in Ontario, for AYA diagnosed with cancer between 15 and 39 years of age, and the factors associated with attending a referral. These papers are important for informing ongoing work in the AYA cancer care in the area of oncofertility.

The papers described above are presented in this "sandwich" thesis as published manuscripts. Each paper represents a piece of the indicator development and implementation process. The papers build on each other, starting from a description of the

scope of indicators used in AYA cancer care and control. This work formed the basis to develop a list of indicators for Canada. From the list, two areas were chosen to further develop the identified indicators. The papers have the common theme of system performance metrics for AYA cancer care and control. All published manuscripts were reprinted with permission of the publisher.

CHAPTER 2 – A REVIEW OF INDICATORS FOR ADOLESCENT & YOUNG ADULT CANCER CARE AND CONTROL

System Performance Indicators for Adolescent and Young Adult Cancer Care and Control: A Scoping Review.

Reprinted from *Journal of adolescent and young adult oncology*; Rae C, Shah N, De Pauw S, Costa A, Barr RD; 2020; 9(1); pages 1-11.

doi: 10.1089/jayao.2019.0069.

JOURNAL OF ADOLESCENT AND YOUNG ADULT ONCOLOGY
Volume 9, Number 1, 2020

DOI: 10.1089/jayao.2019.0069

Review Articles

System Performance Indicators for Adolescent and Young Adult Cancer Care and Control: A Scoping Review

Charlene Rae, MSc,[1] Nishwa Shah, BSc,[2] Sonja De Pauw, MESc,[3] Andrew Costa, PhD,[3] and Ronald D. Barr, MB, ChB, MD[1]

Adolescents and young adults (AYAs) with cancer represent a unique group with unmet needs. Metrics and quality indicators are important for evaluating AYA cancer care. The purpose of this study is to describe the quality indicators in a Canadian context that are used for AYA (15–39 years of age) cancer care and control. The Arksey and O'Malley methodological framework was applied to undertake a scoping review of the peer-reviewed and gray literature for indicators related to AYA cancer care and control. OVID Medline was searched from January 1995 until April 2018 for English language articles. Inquiries were made to AYA cancer organizations and a Google search conducted to identify unpublished material. Articles were included if they incorporated AYAs and contained cancer care indicators. Data were summarized at the article and indicator level. A total of 610 abstracts were reviewed. Eighty-nine full-text articles and reports were assessed for eligibility, with 19 included in analyses which identified 146 indicators or indicator concepts. Most of the indicators were specific to the AYA age group (65.8%) and dealt with the active care theme (57.5%), almost half focusing on guideline adherence and treatment (26.4%) and multidisciplinary/specialized care (20.7%). Notable deficits in indicators were in fertility, psychosocial care, and prevention. Important progress has been made internationally and within Canada on developing indicators for AYA cancer care and control. However, there is a lack of well-defined AYA-specific cancer care indicators developed through a consensus process.

Keywords: quality care, indicators, system performance, scoping review

Introduction

It has been recognized widely that adolescents and young adults (AYAs) with cancer are a unique population due to the nature of their diseases and their particular needs, which are related to their stage of life and development.[1,2] There is no international consensus on the age range for AYAs, although the lower limit is generally agreed upon as 15 years of age.[3] The upper limit varies, with 24, 29, or 39 years of age being used depending on the context and country.[3] The Progress Review Group, formed by the National Cancer Institute in the United States with the Live-Strong Foundation, has recommended a range of 15–39 years.[4]

AYAs face many hurdles throughout diagnosis, treatment, and survivorship.[1,2,5] The types of cancer prevalent in this age group differ from those common in children and older adults.[6] This presents many challenges for the care of AYA patients, including the availability of clinical trials, as well as appropriate services and expertise that may not be available in their treatment centers due to the dichotomous pediatric and adult health care systems which exist in many countries. There have been numerous approaches to improving cancer care for AYAs, including the development of age-specific units in the United Kingdom and AYA-focused organizations such as CanTeen in Australia.[7–9]

Metrics are important for evaluating AYA cancer care, and ensuring that programs and policies being implemented are addressing relevant problems while improving outcomes for this population. A quality indicator is defined as a measure that can be used to monitor or evaluate the impact of governance, management, clinical, or support processes on system or patient outcomes.[10,11] There have been many indicators developed by cancer institutions and agencies to evaluate and monitor cancer care.[12–14] Due to the aforementioned differences in AYAs with cancer it is important to examine which indicators have been developed with

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consideration for this unique population. This will help guide the development and application of indicators to monitor and evaluate their cancer care.

The Canadian Task Force on AYAs with Cancer (TF) was formed in 2008 to address issues of cancer care and control for the age group 15–29 years. As part of their work the TF developed a set of principles and recommendations,[15] and a plan for action in Canada.[16] In 2017, the System Performance Working Group of the TF reported on metrics for AYA cancer care based on these recommendations.[17] As a parallel process, the group worked on developing a list of system performance indicators needed to monitor and evaluate important metrics and outcomes in AYA cancer care in Canada. The purpose of this study is to describe the quality indicators which are used currently for AYAs (15–39 years of age) cancer care and control in a Canadian context.

Methods

An initial review of the literature was undertaken to assess the current state of indicator development for AYA cancer care and control. A search of OVID found no previous scoping review on this topic. A scoping review is a summary of the literature that addresses broad questions and can be used to identify key concepts or gaps in knowledge. The Arksey and O'Malley[18] methodological framework was applied to undertake a scoping review of the peer-reviewed and gray literature for indicators related to AYA cancer care. OVID Medline was searched from January 1995 until April 2018 for English language articles. The search strategy was adapted from one used in a review of childhood cancer care indicators[19,20] and is provided in Supplementary Appendix SA1. A search of the gray literature, which consists of materials produced outside of traditional academic publications, was conducted using the search terms adolescent, young adult, cancer, and quality indicator. Queries were sent to international groups involved in AYA cancer care and control regarding their use of quality indicators. These were CanTeen, Teenage Cancer Trust, Children's Oncology Group, and Critical Mass. Websites of Canadian cancer agencies and the Rossy Cancer Network were also reviewed for AYA indicator content. E-mails were sent to key individuals in the cancer agencies to verify findings on websites.

Articles or gray literature were included if they incorporated AYAs and if the indicator focused on an aspect of cancer care or control. Inclusion of AYAs in the study or report was confirmed if all or a portion of the 15–39-year age range was considered or the mean age reported in the study was between 18 and 50 years. Articles were considered AYA specific if the indicator discussed focused on all or part of the AYA age range, or on an AYA-relevant cancer issue such as peer support or fertility. Articles which contained the AYA age range were considered AYA included. Indicator studies were included in the review if the objective was to develop, validate, benchmark, assess, review, or report on an indicator that evaluates system performance, clinical outcomes, or care in the AYA cancer population. Primary prevention of nonprevalent cancers in AYAs (e.g., smoking cessation), and indicators related to procedures not related directly to cancer care, such as breast reconstruction, were considered out of scope for the current review.

The authors C.R. and N.S. reviewed the titles and abstracts independently to assess suitability. If both agreed, the articles were subjected to full-text review; abstracts on which no agreement was reached were referred to S.D.P. who assessed them independently then met with C.R. to discuss ratings and determine eligibility. All literature or indicators collected from organizations devoted to AYAs with cancer were selected for full-text review. C.R. and S.D.P. assessed all full texts to determine suitability for the current review based on the inclusion criteria.

Data were abstracted by C.R. for descriptive analysis of both the entire publications and individual indicators. For the publications the following data were abstracted: publication year, study objective, country, type of study, institutional level, and age range. Data abstracted for each indicator were: age range(s), gender, type of indicator, disease, theme, indicator construct, indicator name, and indicator definition. Types of indicators included outcome (metrics related to functionality and survival of patients), process (metrics related to the implementation of care such as adherence to guidelines), and structure (metrics related to adequacy of facilities or equipment, administrative structure, staff qualifications).[10] Data were summarized at both the article and indicator levels. Indicator themes were taken from the framework proposed by Fernandez et al.[15] which identifies themes and provides key recommendations and priority areas that need to be addressed within the Canadian context to improve care and outcomes for AYAs with cancer. The seven themes are: active therapy and supportive care; psychosocial needs; palliation and symptom management; survivorship; research; education, awareness, and advocacy; and prevention. A theme on economics was also included on the basis of the report by Greenberg et al.[21]

Results

A total of 697 full-text abstracts were identified from OVID, 87 duplicates were removed, and the remaining 610 abstracts were reviewed for eligibility (Fig. 1). The majority (54.1%) were excluded because the study was ''not indicator related''; for example, objectives were focused on data quality, identifying associations, predictors, or risk factors, or the development of measurement instruments. Nine documents were identified from the Google search of the gray literature and included in the full-text review. A total of 89 full-text articles and reports were assessed for eligibility, with 19 included in analyses. A majority of full-text exclusions (66.7%) were because the article did not address the AYA age group.

Articles

The review consisted of 16 articles and 3 reports, with the characteristics of full texts summarized in Table 1. The studies were conducted primarily in North America, within either the United States (26.3%) or Canada (21.0%). Results from the studies were reported mostly at the national level (47.4%), with a focus on the development of indicators (36.8%). Most articles or reports included the AYA subpopulation (15/19) rather than focusing solely on this age group (4/19).

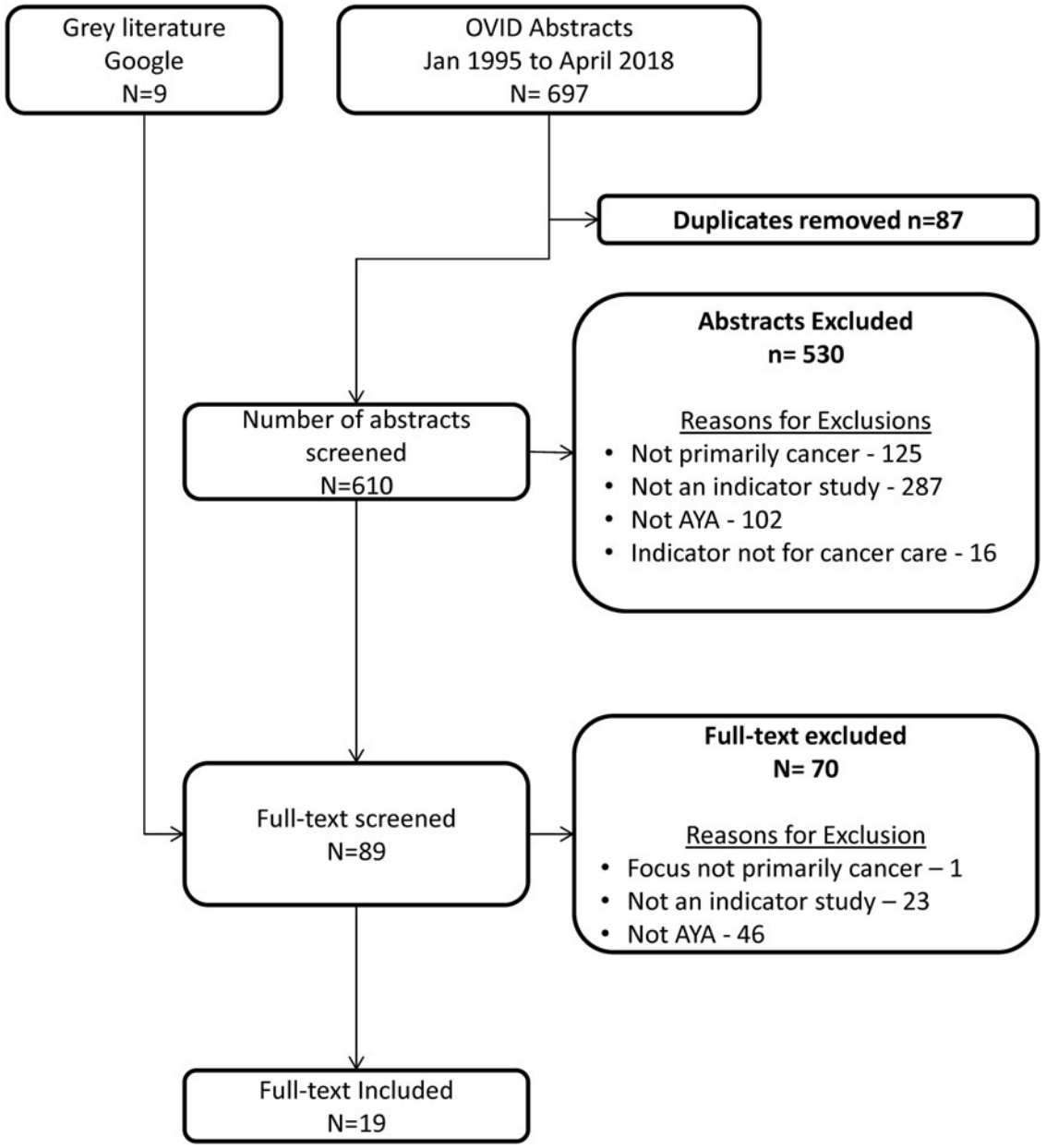

FIG. 1. Flow diagram of scoping review process.

Indicators

A total of 146 indicators or indicator concepts were identified in the 19 articles and reports reviewed (Table 2). The majority of indicators referred to the national level were either outcome or process based (Fig. 2). Outcome indicators tended to be reported at the national level with process indicators prevalent at all three levels of reporting (Fig. 2). Very few structural indicators were identified ($n = 11/146$). Most of the indicators were specific to AYAs (65.8%), focusing solely on the 15–39-year age group. Of the 96 AYA-specific indicators, 48 came from the three reports[17,22,23] while the remaining 48 were from two published articles.[19,21] One of the articles that provided 47 indicators reported results from an initial brainstorming session of concepts and represented a very early stage of indicator development. Of the three reports two included defined indicators[17,22] and one provided high-level concepts for development.[23] Indicators tended to be neither gender (80.1%) nor disease specific (69.2%) (Table 3). The most prominent disease-specific indicators were for testicular (8.2%) and breast (6.8%) cancers (Table 3).

A summary of themes and constructs addressed by the indicators is shown in Table 4. More than half of the indicators dealt with the active care theme (57.5%). Within this theme, 2 of 10 identified constructs, guideline adherence and treatment (27.4%), and multidisciplinary/specialized care (21.4%), accounted together for almost half the identified indicators (Table 4). Only 1/84 indicators in active care addressed fertility as ''Number of referrals to fertility preservation services for adolescents and young adults with a cancer diagnosis.''[22] A single indicator (4.2%) addressed

Table 1. Summary of Article Characteristics

	N	%
Reporting level		
Local	5	26.3
National	9	47.4
Provincial/State	5	26.3
Study type		
Application/descriptive	4	21.1
Benchmarking	1	5.3
Development	7	36.8
Reporting	4	21.1
Stratification/benchmarking	1	5.3
Validating	2	10.5
Country		
Australia	3	15.8
Belgium	1	5.3
Brazil	1	5.3
Canada	4	21.1
China	2	10.5
Germany	1	5.3
Italy	1	5.3
Sweden	1	5.3
United States	5	26.3

fertility in survivorship focusing on the availability of *in vitro* fertilization (IVF) clinics. The psychosocial needs theme was only addressed by 2.7% (4/146) of the indicators examining screening, service use, caregiver psychosocial health, and general outcomes (Table 4). The prevention theme was only represented by a single indicator identified during the review process (0.7%). Clinical trials, another important aspect of AYA cancer care, were covered by 11 indicators, 7 under the active care theme which addressed enrollment and 4 under research theme that addressed availability (Table 4).

Discussion

This scoping review examined the current state of indicators for AYA cancer care and control. Some work has been done on the development and reporting of indicators specifically for the AYA cancer population. However, the majority of articles and reports only included AYAs and were not specific to this population. The few AYA-specific indicators included in this review covered many important aspects of cancer care and control, but most were at the earliest stage of development.[17,22] Despite the large number of indicators identified in this review, gaps still exist in key areas important to AYA cancer patients and survivors, particularly in the areas of psychosocial care and oncofertility.

Future fertility is an especially important issue for AYAs with cancer due to the risks associated with treatment. Ronn and Holzer[24] highlighted the need for AYAs with cancer to be informed of the fertility risk associated with treatment. In a four-part series these authors explored a wide range of issues relating to oncofertility in Canada.[24–27] The current scoping review found only two indicators that addressed fertility, one focused on the number of referrals to fertility services whereas the other examined IVF service availability to survivors. Neither of these indicators addressed directly the important recommendation that all patients be informed about potential compromise to fertility associated with treatment.[15] An indicator focusing on the number of patients who received information on fertility risks would be important for improving care for AYA patients. However, collection of this type of data for reporting on an indicator regarding the receipt of information may be challenging. Further work needs to be done in the development of indicators for oncofertility to help evaluate how well the system is informing patients of their risk, and its ability to provide appropriate services to AYAs who request consultation on fertility preservation procedures.

Another important area that was lacking is indicators of psychosocial care. AYA cancer patients and survivors have special needs in this area, given their stage of development and the many changes which are occurring in their lives.[5,28–30] Only a single indicator found in this review was fully developed, ''time from diagnosis to referral to AYA psychosocial team.''[22] Many of the indicators suggested for psychosocial care were still in the brainstorming stage of development, with no clear definition of the metric.[21,23] In particular, screening for psychosocial issues is an important aspect which was not well represented in the indicators relating to this area. Distress has been identified as the sixth vital sign in cancer and screening for distress is recommended for all cancer patients.[31–34] There is a lack of AYA-specific measurement instruments that address psychosocial issues,[35,36] which represents a challenge for the development of both appropriate screening and psychosocial outcome indicators. A lack of appropriate and valid instruments to measure psychosocial outcomes in this population could be a major contributor to the observed gaps in indicator development.

The prevention theme had the fewest identified indicators of all themes described in this article. Prevention is an important area for AYA oncology. However, very little work has been done on the etiology of cancers in AYAs. This lack of knowledge in the area may have contributed to the lack of prevention indicators identified in this review. The review also did not include prevention indicators related to smoking cessation which, for the purposes of this report, were considered to be indicators more broadly relevant to population health and prevention of cancers in older adults, such as lung cancer. Prevention of cancers in AYAs is an important area for further research.

In Canada some work has been done to develop a set of performance indicators for AYA cancer care and control. A list of indicators with definitions and technical specifications was developed for the report from the Canadian Partnership Against Cancer (CPAC).[17] However, a formal approach to selecting the indicators was not taken. The CPAC report[17] covered key areas of AYA cancer care and control based on the recommendations and priorities described by Fernandez et al.[15] The indicators were selected by considering the feasibility of obtaining data, which excluded many potential indicators in important areas that lack data. An important issue that is highlighted by the CPAC document[17] is the inability to report nationally by stratifications such as disease, risk group, or province. An example of this issue in the CPAC report is the ''place of death'' indicator that could only be reported provincially for Ontario and Quebec.[17] Cell size issues are especially challenging for many disease-specific indicators related to diseases that have a low incidence, leading to concerns on privacy.

Table 2. Summary of Identified Indicators

Author, year published	Age (years) Min	Max	AYA subgroup reported	Gender	Disease	Indicator
Wall, 1998[38]	16	78	16–35	Female	Breast	DDI
Clinical Oncological Society of Australia, 2008[23]	15	25	15–25	Both	All cancers	Increased number of available trials Increased enrollment of AYA cancer patients Assessment at MDT meetings (treatment and psychosocial) Referrals from primary care Patients entered into late-effects follow-up program Recurrence Survival Psychosocial outcomes Education and career outcomes Financial outcomes patient's family/partner outcomes financial, psychosocial etc. Research activity nonclinical trial Research (nonclinical trial) outcomes for example, psychosocial, fertility, biology/translational shared care networks—compliance with agreed standards Availability, participation in and efficacy of training program Patients who are at private facility who have their care discussed at tumor-specific MDT How many patients have a treatment plan How many patients have late-effects plans or end-of-treatment guidelines Use of national minimum dataset
Olaya, 2010[39]	19	105	<40	Both	Breast	Proportion of patients receiving SLND alone or with ALD who had clinical stage I/IIA/IIB breast cancer
de Camargo, 2010[40]	0	19	15–19	Both	All cancers	Recurrence
Adolescent and Young Adult Working Party of the Statewide Cancer Clinical Network, 2010[22]	15	25		Both	All cancers	Measurable change in cancer awareness and behavior in 15–25-year age group Number of appropriate referrals to AYA Cancer Care Coordinators Number of patients treated in evidence recommended setting Percentage of total number of patients presented at MDT meeting Percentage of AYA with documented treatment plans following MDT assessment Time from diagnosis to MDT assessment; identification of meetings when goals of care change. Number of AYA assessed for eligibility for clinical trials Number of clinical trials available to AYA and number of enrollments into clinical trials Time from diagnosis to referral to AYA psychosocial team AYA patients' place of death Number of families confirming appropriate supports and referrals to facilitate optimal end-of-life care Number of AYA families with established bereavement plans Patients report feeling informed and know where to seek help on completion of treatment Number of documented AYA end-of-treatment plans Number of referrals to fertility preservation services for adolescents and young adults with a cancer diagnosis.

(*continued*)

TABLE 2. (CONTINUED)

Author, year published	Age (years) Min	Max	AYA subgroup reported	Gender	Disease	Indicator
Greenberg, 2011[21]			AYA—no age range specified	Both	All cancers	Incidence Rates of HPV vaccination Cervical cancer incidence Time of first symptom Time of first health care contact Time of first oncology visit Time of diagnosis Time of initiation of treatment Specialty of first health care contact Number of providers available Site of care (pediatric vs. adult; teaching vs. community; AYA focus) Patient satisfaction with age and developmental appropriateness of care Number of disease-appropriate and age-appropriate clinical trials open in cooperative groups Number of AYA-appropriate clinical trials open per center Proportion of incident cases enrolled in clinical trial Use of protocol-guided therapy 5-Year overall survival 5-Year overall event-free survival Cause of death (malignancy, complication of therapy, or other) Early mortality Psychosocial screening assessment of self-efficacy, locus of control, anxiety, and mood at: diagnosis, mid-treatment, end of treatment, survivorship Evaluation of patient's family/spouse/supporters' psychosocial health Use of mental health and support services Impact of cancer on HRQL Involvement/timing of palliative care/hospice Locus of end-of-life care Pain control Caregiver costs; work time and income lost HRQL (Palliative care) Medication and care-provision costs Family satisfaction QALYs Healthy years equivalents Willingness to pay Incidence of late effects and chronic disease Creation and use of a survivor care plan Stage of late-effects illness or recurrence at diagnosis (including rates of preclinical diagnosis) Attendance at follow-up care (post-transition from primary oncologic care Patient knowledge of health history and risk Patient satisfaction with care Patient self-empowerment Compliance with recommended monitoring guidelines (cardiac postanthracycline, breast cancer after chest radiation) Cost of surveillance for and treatment of late effects Volume and type of health care services used (scheduled vs. emergency) Cause-specific mortality HRQL (Impact of model of care) Measures of educational, social, and vocational achievement

(*continued*)

Table 2. (Continued)

Author, year published	Age (years) Min	Max	AYA subgroup reported	Gender	Disease	Indicator
Marnitz, 2012[41]	16	86	No AYA subgroup — mean age 39 years	Female	Cervix	Availability, participation in, and efficacy of training program
Vlayen, 2012[42]	0	95	No AYA subgroup— mean age 34.5 years	Male	Testis	Patients who are at private facility who have their care discussed at tumor-specific MDT How many patients have a treatment plan How many patients have late-effects plans or end-of-treatment guidelines Use of national minimum dataset Proportion of patients with testicular cancer undergoing CE-CT or MRI for primary staging Proportion of patients with testicular cancer discussed at the MDT meeting Number of annual surgically treated patients with testicular cancer per center Radiation dose and field in patients with testicular cancer treated with radiotherapy by stage Proportion of patients with stage I nonseminoma treated with active surveillance Proportion of patients receiving CE-CT or MRI for residual disease assessment at the end of systemic treatment Degree and duration of active surveillance in patients with stage I nonseminoma or seminoma Proportion of patients with relapsing testicular cancer after curative treatment that are included in a clinical trial
Bristow, 2013[43]	18	70+	<45	Female	Uterus/ovary	Survival
Bradley, 2013[19]	0	18	15–18	Both	All cancers	Psychosocial outcomes Education and career outcomes Financial outcomes patient's family/partner outcomes financial, psychosocial etc Research activity nonclinical trial Research (nonclinical trial) outcomes for example, psychosocial, fertility, biology/translational shared care networks—compliance with agreed standards
Decker, 2015[44]	20	69	20–29, 30–39	Female	Cervix	Assessment at MDT meetings (treatment and psychosocial) Referrals from primary care Patients entered into late-effects follow-up program
Dasenbrock, 2015[45]	18	70+	18–45	Both	CNS/brain	Increased enrollment of AYA cancer patients
CPAC, 2017[17]	15	39	15–29, 30–39	Both	All cancers	Number of new cases of cancer (malignant neoplasms) newly diagnosed among AYAs per year, per 100,000 people, age-standardized
			15–29, 30–39	Both	All cancers	RSR as the ratio of observed survival for a group of patients with cancer (malignant neoplasms) to expected survival for members of the general population with the same main characteristics (sex, age, place of residence)
			15–29, 30–39	Both	All cancers	Point prevalence, which is the number (rate) of individuals alive at a specified point in time who have had a previous diagnosis of cancer (malignant neoplasm).
			15–29, 30–39	Both	All cancers	Treatment wait time, defined as the time between definitive diagnosis (date of pathology) and start of treatment (any treatment modality, including surgery) for women diagnosed with breast cancer
			15–29, 30–39	Female	Breast	Proportion of patients with breast cancer receiving surgery at a specialized center
			15–39	Both	Colorectal	Proportion of patients with colorectal cancer receiving surgery at a specialized center
			15–19, 20–29, 30–39	Both	All cancers	The percentage of AYA (15–39 years of age) cancer patients who die in hospital versus nonhospital locations
			20–24, 25–29, 30–34, 35–39	Both	All cancers	Percentage of AYAs (20–39 years of age) reporting ever having had cancer who achieved postsecondary education
			20–24, 25–29, 30–34, 35–39	Both	All cancers	Percentage of AYAs (20–39 years of age) reporting ever having had cancer who did not work at a job in the last 12 months
			20–24, 25–29, 30–34, 35–39	Both	All cancers	Percentage of AYAs (20–39 years of age) reporting ever having had cancer with a current personal income of less than $40,000
			18–29	Both	All cancers	Percentage of negative responses reported by AYA (18–29 years of age) cancer patients for dimensions of care (access to care, coordination and continuity of care; emotional support; information, communication, and education; physical comfort; and respect for patient preferences) in the AOPSS

(*continued*)

Table 2. (Continued)

Author, year published	Age (years) Min	Max	AYA subgroup reported	Gender	Disease	Indicator
			15–39	Both	All cancers	Proportion of cancer research grants from major funding organizations between 2005 and 2013 that involve AYAs
			15–17	Both	All cancers	Clinical trial accrual: the ratio of the total number of patients 15–17 years of age newly enrolled in cancer-related clinical trials to the number of new incident cancer cases in patients 15–17 years of age
			15–39	Both	All cancers	The number and proportion of clinical trials addressing the most prevalent cancers in AYAs (15–39 years of age)
			15–39	Female	All cancers	Ratio of incident cases (2015) of cancer in adolescent and young adult women (15–39 years of age) to number of in vitro fertility centers, by province, all cancers
Forsberg, 2017[46]	18	None	18–30, 30–40	Both	Colorectal	Prevalence of PCCRC for colonoscopies performed during 2001–2010
Dasenbrock, 2017[47]	18	None	18–45	Both	CNS/brain	30-Day readmission
Roos, 2017[48]	18+	None	18–79, median 39	Both	Lymphoma	Baseline staging investigations Discussion in MDM Type of chemotherapy No. of cycles of chemotherapy Radiotherapy planning technique Use of DVHs for organs at risk Radiotherapy dose Radiotherapy timing
Su, 2017[49]	18	69	<40	Female	Breast	Preoperative core biopsy HER-2 testing Sentinel lymph node biopsy Breast conserving surgery Receiving at least four cycles of adjuvant chemotherapy Adjuvant radiotherapy after mastectomy Hormonal treatment
Pucciarelli, 2017[50]	18	None	18–49	Both	Colorectal	LOS of the index hospitalization In-hospital mortality 30-Day readmission
He, 2017[51]	0	None	5 Year groups	Both	All cancers	Age-specific incidence rate

AYA, adolescent and young adult; DDI, diagnostic delay index; MDT, multidisciplinary team; SLND, sentinel lymph node dissection; ALD, axillary node dissection; HPV, human papilloma virus; HRQL, health-related quality of life; QALY, quality adjusted life years; MRI, magnetic resonance imaging; CE-CT, contrast-enhanced computed tomography; CNS, central nervous system; RSR, relative survival ratio; AOPSS, Ambulatory Oncology Patients Satisfaction Survey; PCCRC, postcolonoscopy colorectal cancer; MDM, multidisciplinary meeting; DVH, dose/volume histogram; LOS, length of stay; CPAC, Canadian Partnership Against Cancer.

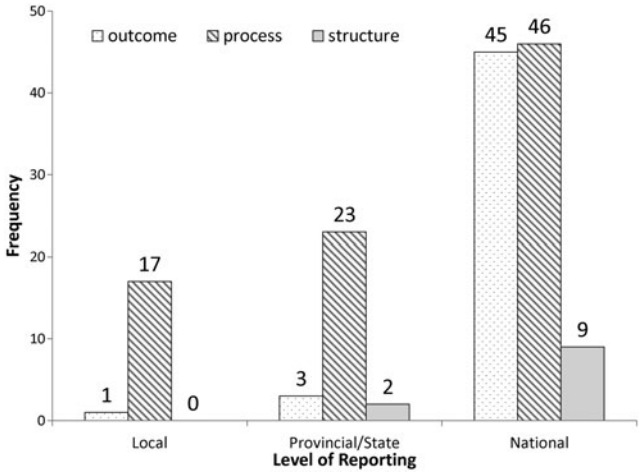

FIG. 2. Frequency of indicator type by level of reporting ▨ Outcome ▨ Process ▨ Structure.

Australia has contributed also to the development of AYA-specific indicators for cancer care.[22,23] The Australian indicators cover important concepts such as clinical trial enrollment, multidisciplinary care, referrals for psychosocial care, and fertility preservation.[5,22,24,37] Interestingly these concepts are also described in the recommendations and principles of care for AYA cancer care in Canada.[15] Given the similarity of issues among countries with respect to AYA cancer care and control, and the small sample sizes within some disease groups, international cooperation would be beneficial. Cooperation could include the development of key indicators, minimum datasets, and joint reporting. The ability to generate international comparisons would greatly facilitate many aspects of AYA cancer care and control, including program evaluation and benchmarking.

A limitation of this scoping review is that the exercise focused only on a single database, OVID. However, this was thought to be appropriate as the review focused mainly on the gray literature. It was believed that most indicators in use currently would not be published in the scientific literature because most are reported by government agencies and may not have academic papers associated with their development.

Table 3. Summary Statistics of Indicator Characteristics ($N = 146$)

	n	%
AYA focus		
AYA included	50	34.2
AYA specific	96	65.8
Gender		
Not gender specific	117	80.1
Female	17	11.6
Male	12	8.2
Disease		
All cancers	101	69.2
Breast	10	6.8
Cervix	4	2.7
CNS	3	2.1
Colorectal	5	3.4
Lymphoma	8	5.5
Testis	12	8.2
Uterus/ovary	3	2.1

Table 4. Summary of Indicators by Construct and Theme

Theme—construct	N	%
Active care	**84**	**57.5**
Care plans	2	2.4
Clinical trials enrollment	7	8.3
Diagnostic	5	6.0
Fertility	1	1.2
Guideline adherence/treatment	23	27.4
Length of stay/readmission	4	3.6
Multidisciplinary/specialized care	18	21.4
PROs (QoL, satisfaction of care, patient/family finances)	3	3.6
Survival/mortality—treatment	11	13.1
Wait times	10	11.9
Economic	**4**	**2.7**
Economic/system cost	2	50.0
PROs (QoL, satisfaction of care, patient/family finances)	2	50.0
Education and awareness	**2**	**1.4**
Education	1	50.0
PROs (QoL, satisfaction of care, patient/family finances)	1	50.0
Palliation	**11**	**7.5**
Economic/system cost	1	9.1
Multidisciplinary/specialized care	4	36.4
PROs (QoL, satisfaction of care, patient/family finances)	3	27.3
Supportive care	3	27.3
Prevention	**1**	**0.7**
Vaccination rate	1	100.0
Psychosocial	**4**	**2.7**
Multidisciplinary/specialized care	1	25.0
PROs (QoL, satisfaction of care, patient/family finances)	1	25.0
Psychosocial general	2	50.0
Research	**16**	**8.9**
Clinical trial availability	4	25.0
Incidence/prevalence	8	50.0
Research (nonclinical trial activity, implementation)	4	25.0
Survivorship	**24**	**16.4**
Aftercare	4	16.7
Care plans	4	16.7
Economic/system cost	2	8.3
Employment and education	5	20.8
Fertility	1	4.2
Guideline adherence/treatment type	1	4.2
Late effects	1	4.2
PROs (QoL, satisfaction of care, patient/family finances)	5	20.8
Survival/mortality—in survivorship	1	4.2
Grand total	**146**	**100.0**

PRO, patient-reported outcomes; QoL, quality of life.

Although the development of indicators specifically for the AYA cancer population is relatively recent, important progress has been made internationally and within Canada. This review has found that there is a lack of well-defined AYA-

specific indicators for cancer care and control, developed through a consensus process. The CPAC report[17] represented the first identification and application of indicators for AYA cancer care and control at the national level in Canada. Although comprehensive, the indicators were chosen based on data accessibility and availability, and may not represent the most important indicators to capture for AYA cancer care.[17] It will be important to create a consensus-based list of indicators related particularly to AYA cancer care and control in a Canadian context, regardless of their current feasibility, to provide a basis for the development of minimal datasets. The TF has laid a strong groundwork for the development of system performance indicators in Canada, particularly through the work of Fernandez et al.[15] and Greenberg et al.[21] Fernandez et al.[15] provided a framework that was developed with representation from all provinces and stakeholder groups, including patients and families. The work of Greenberg et al.[21] provides an initial list of metrics and a starting point for developing a consensus-based list of AYA cancer care indicators for Canada. As programs are developed in Canada with the goal of improving outcomes in AYAs with cancer it will be important to have indicators to help monitor progress and ensure that programs implemented are helping achieve intended outcomes. However, along with the development of metrics there is an urgent need to focus on developing AYA-specific data and integrating the AYA age group into existing databases to ensure the feasibility of reporting relevant indicators for this population, not only in Canada but internationally.

Acknowledgments

The authors acknowledge valuable contributions from Pandora Patterson (CanTeen), David Freyer (Children's Oncology Group), and Heidi Adams (Critical Mass), the Pediatric Oncology Group of Ontario (POGO), the Atlantic Provinces Pediatric Hematology Oncology Network, and the Canadian Partnership Against Cancer.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

No funding was received for this article.

Supplementary Material

Supplementary Appendix SA1

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CHAPTER 3 – DEVELOPMENT OF INDICATORS FOR ADOLESCENT AND YOUNG ADULT CANCER CARE AND CONTROL

Development of System Performance Indicators for Adolescent and Young Adult Cancer Care and Control in Canada.

Reprinted from *Value in Health*; Rae CS, Pole JD, Gupta S, Digout C, Szwajcer D, Flanders A, Srikanthan A, Hammond C, Schacter B, Barr RD, Rogers PC; 2020 Jan 1;23(1):74-88.
doi: 10.1016/j.jval.2019.08.004.

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Health Policy Analysis

Development of System Performance Indicators for Adolescent and Young Adult Cancer Care and Control in Canada

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ABSTRACT

Objectives: To develop an expert-group, consensus-based list of system performance indicators to be used for monitoring, evaluating, and benchmarking progress for cancer care and control in adolescents and young adults (AYAs) in Canada.

Methods: A national multidisciplinary panel of AYA oncology experts was convened; they prepared a literature review and undertook a brainstorming exercise to create a comprehensive list of indicators based on a previously defined framework for AYA cancer care and control in Canada. A modified Delphi process was then undertaken to cull the list based on 3 quick screen criteria. Three rounds of ranking were required. The fourth stage employed a face-to-face meeting, and the final stage utilized a survey to rank the indicators on the basis of importance and feasibility.

Results: Nineteen participants contributed to the 5-stage process. From an initial list of 114 indicators, 14 were ultimately endorsed, representing 5 themes: active care, survivorship, psychosocial issues, palliative care, and research. The 5 highest ranked indicators were assessed as very to moderately feasible, with only a single indicator (clinical trial enrollment) in the top 5 assigned a least feasible ranking.

Conclusion: The 14 indicators provide a starting point for the development of a standard set of metrics for AYA cancer care and control in Canada and have potential for international utility.

Keywords: AYA, cancer, indicators, performance, system.

VALUE HEALTH. 2020; 23(1):74–88

Introduction

There have been considerable efforts in several high-income countries to improve the care of adolescents and young adults (AYAs) with cancer,[1] a group defined as those 15 to 39 years of age at the time of diagnosis.[2] AYAs with cancer have many unmet needs, which are distinct from those of pediatric and older adult cancer patients.[3] The biology of their disease and their stage in development make them a unique cancer population who require tailored interventions to address their specific needs[4] and specific measurements of the performance of these interventions on AYA cancer care and control. Canada is a nation with both population-based cancer control programs and an effective public health system[5]; however, it still faces many challenges to providing optimal cancer care and control for AYAs. Although the funding for healthcare is in part federal, the health system is administered by each of the individual provinces and territories, making the implementation of national programs and standardized data collection politically and administratively challenging. To improve outcomes in AYAs with cancer and overcome these challenges, a national initiative is required.[3,6] Key to such an investment are metrics for monitoring and evaluating AYA cancer care and control.

Approximately 8000 AYAs receive a diagnosis of cancer each year in Canada and more than 80% survive their disease.[7] In 2008 a National Task Force was formed to address AYA cancer care and

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https://doi.org/10.1016/j.jval.2019.08.004

control with funding from the Canadian Partnership Against Cancer (CPAC). The Task Force's mission was "to ensure that AYA Canadians with cancer and AYA survivors of cancer have prompt, equitable access to the best care, and to establish and support research to identify how their health outcomes and health-related quality of life can be optimised."[8] The Task Force held an international workshop in 2010 to develop a framework for AYA cancer care and control in Canada[9] and another in 2012 to develop a plan for action.[10,11] Stakeholders at these workshops came from all provinces with representatives from health professionals, administrators, researchers, nongovernmental organizations (NGOs), and survivors. The framework identified themes with key recommendations and priority areas, which needed to be addressed within the Canadian context to improve care and outcomes for AYAs with cancer.[11] To help facilitate and monitor expected improvements based on this framework, it became important to determine appropriate system performance indicators. Relevant metrics can identify opportunities to improve quality of care and benchmarks to achieve short-term, medium-term, and long-term outcome-improvement goals. AYA-specific metrics would help to inform decisions regarding policy and resource allocation within the healthcare system.

Previous work on indicator development for cancer care and control in Canada has focused predominantly on the separate pediatric and adult age groups.[12-18] Recently a comprehensive set of pediatric cancer indicators was developed by the Pediatric Oncology Group of Ontario (POGO), which included a few specific indicators for adolescents between 15 and 18 years of age.[13] At a national level, CPAC has developed indicators for cancer control that are included in its system performance reports, but these are not focused specifically on cancer in AYAs.[18] In April 2017, based on the accomplishments of the indicator working group of the AYA Task Force, CPAC released a system performance report on indicators for AYA cancer care in Canada.[7] These indicators were selected on the basis of current feasibility to accrue the appropriate data from an initial list produced by the Task Force. Greenberg et al also summarized metrics for AYA cancer care, which were identified through brainstorming with stakeholders.[19] No further effort was made to develop and finalize the list since that publication. Internationally, some work has been done in Australia to develop indicators for AYA cancer care,[20] but much more remains to be undertaken in this important area. It is crucial to build on this work with a rigorous approach to ensure that indicators address key priorities and recommendations for AYA cancer care and control in Canada and to allow for stakeholder involvement to help improve the uptake and use of the indicators.

The overall objective of this study was to develop an expert-group, consensus-based list of system performance indicators to be used for monitoring, evaluating, and benchmarking progress for cancer care and control in AYAs in Canada. Our secondary objective was to create a refined list of indicators based on feasibility and the availability of relevant data.

Figure 1. Overview of modified Delphi process.

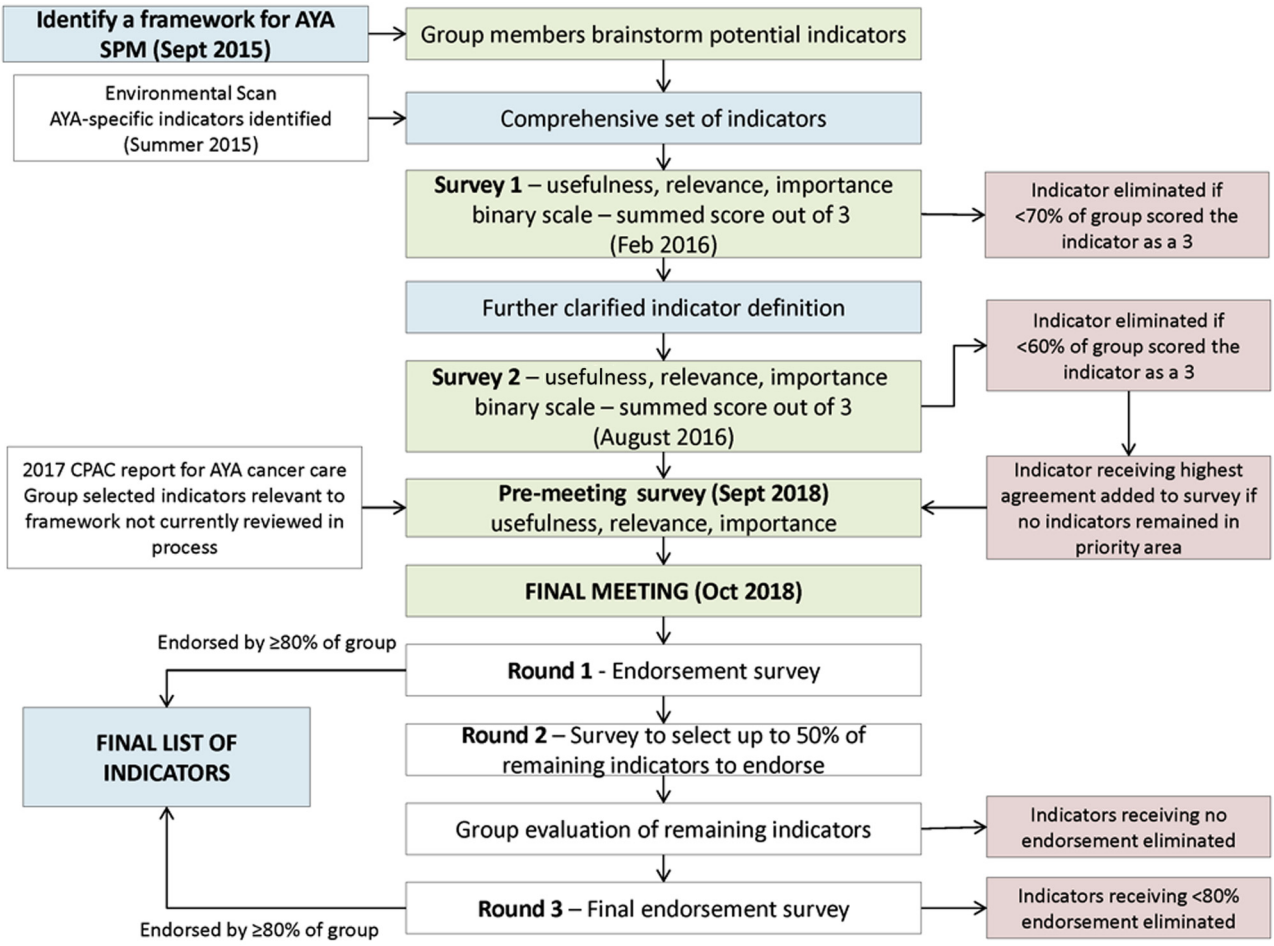
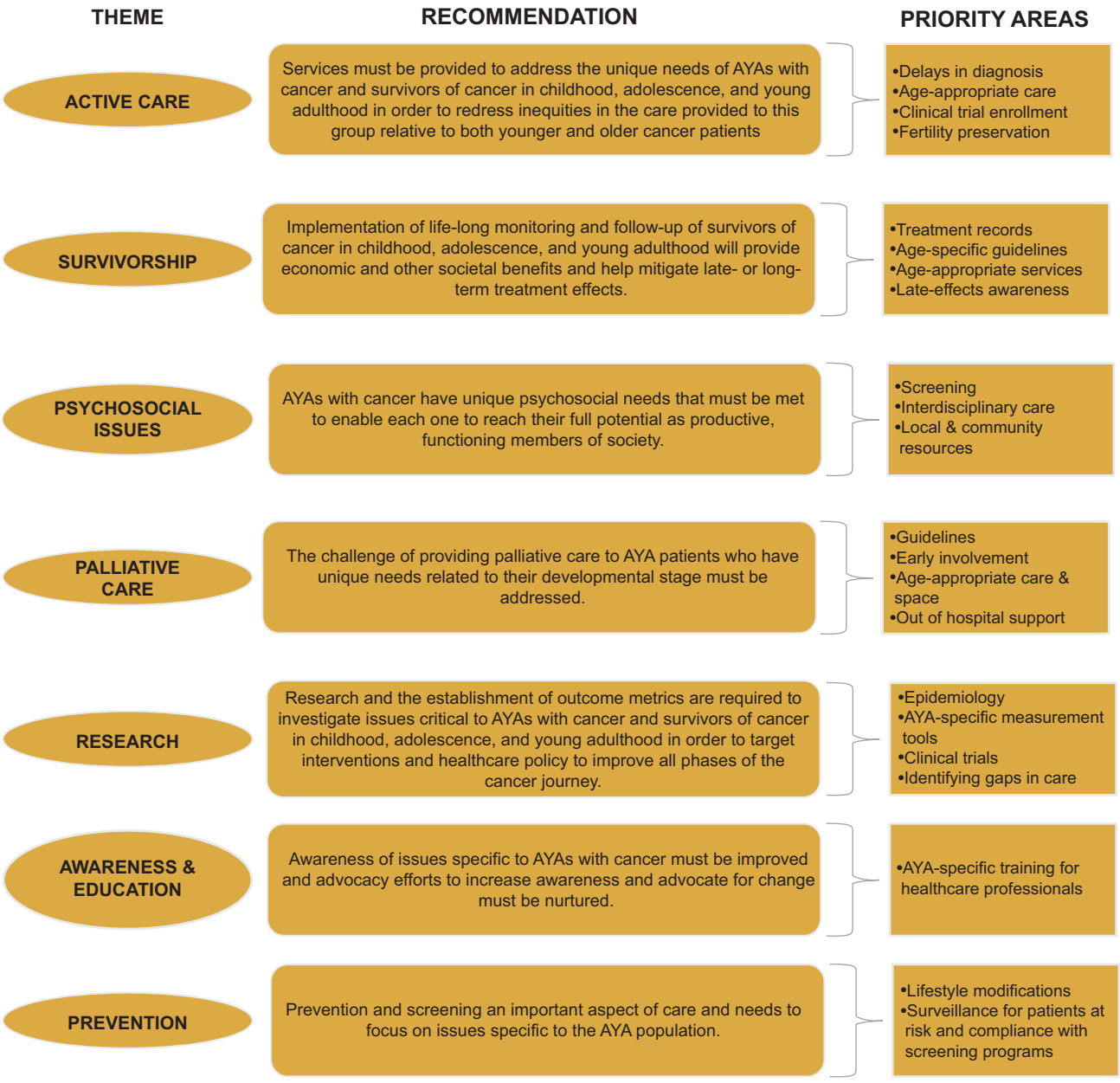


Figure 2. Indicator development framework.



Adapted from Fernandez et al.[11]

Methods

Methods for indicator development were based largely on those used by POGO in their compilation of a list of indicators for childhood cancer.[12,13] Briefly, the methods entail the formation of an expert group who develop a comprehensive list, followed by a modified Delphi[21] process to arrive at a culled list. A final assessment of importance and feasibility was undertaken by survey. Figure 1 provides an overview of the process used in this study.

Participants

An invitation was sent to participants who had contributed to the Canadian Task Force on AYAs with Cancer or who had attended at least one of its workshops. Responding participants were selected to ensure representation from all stakeholder groups and to engage as many provinces as possible. The group was referred to as the system performance metrics (SPM) group.

Framework

The SPM group reviewed the principles and recommendations for AYA cancer care and control that were created from the 2010 multistakeholder workshop and revised at the 2012 workshop.[11] These workshops involved input from 100 individuals representing healthcare professionals, administrators, survivors, advocates, and international content experts.[7] The resulting comprehensive framework addressed 7 themes: active therapy and supportive care; psychosocial needs; palliation and symptom management; survivorship; research and metrics; education, awareness, and advocacy; and prevention (Figure 2).[10,11]

Development of a Comprehensive List of Potential AYA Cancer Care Indicators

A literature review was undertaken of both the scientific and gray literature to provide the foundation for the work of the SPM group. The Ovid database was utilized to search the scientific literature based on a modified search strategy, adapted from the systematic review conducted by Bradley et al (see Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.08.004).[13] Search strategy constructs included: cancer, quality indicators, healthcare, adolescents, and young adults. Titles and abstracts were reviewed in EndNote, version X7.7.1, for relevance to AYA cancer and quality of care. Only work focused on cancer specifically in the AYA age range (15-39 years) was included. The following data were extracted: age range(s), indicator, and indicator definition. Selected indicators were categorized by framework theme. Queries were sent to international AYA cancer groups regarding their use of indicators, including CanTeen (Australia), Teenage Cancer Trust (UK), Children's Oncology Group (USA), and Critical Mass (USA). The websites of provincial cancer agencies and the Rossy Cancer Network were viewed to collect information regarding cancer indicator work at the provincial level within Canada. For the gray literature search, Google was searched using the constructs described earlier. Search results were reviewed for items focused specifically on indicators for cancer care in AYAs. In addition, SPM group members completed a brainstorming exercise wherein they provided indicators or measurement constructs they thought would be important to capture based on the framework. A worksheet (see Appendix 2 in Supplemental Materials) was emailed to participants along with the framework document. Results were aggregated and duplicate indicators and concepts were removed. Indicators were grouped according to the 7 framework themes.[11]

Item Reduction

To reduce the list of indicators compiled from the literature review and brainstorming exercise, two rounds of item reduction were conducted using surveys. Item reduction deviated somewhat from the POGO methods.[12,13] During this stage, POGO utilized 4 expert reviewers to assess 4 quick screen criteria: importance, relevance, applicability to the mission statement, and alignment with strategic objectives. We aimed to maximize stakeholder involvement and so decided to include all stakeholders rather than limit it to expert review. Maximizing stakeholder involvement was thought to be important because of the nature of AYA cancer care across pediatric and adult institutions and the current lack of formal entities addressing AYA cancer care in Canada. To gain "buy-in" from all stakeholder groups, we believe it was important to include them throughout the entire process. From the POGO experience,[12] overall importance and relevance were selected because it was thought that alignment with mission statements and objectives was covered by the use of the AYA framework. Importance addressed whether the indicator captured a critical aspect of care for AYA cancer patients. Relevance captured the use of the indicator for measuring quality care specific to AYA, rather than to general cancer care. The last criterion represented a simplification of POGO's primary selection criteria[12] to capture the "usefulness" of the indicator in quality improvement. Usefulness captured the face validity of the indicator, which, if implemented, would make sense with the potential for change. The 7 POGO primary selection criteria were simplified to reduce the survey burden without hindering the judgments of respondents.

Each SPM group member assessed each indicator based on the responses to the 3 screening criteria of importance, relevance, and usefulness. Survey responses were dichotomous (yes/no) to have respondents commit to whether the indicator met the criteria. An overall score for each indicator from each participant was calculated by summing the total number of "yes" responses. Therefore the highest possible score for each indicator was 3. The proportion of all respondents providing a total score of 3 was calculated for each indicator. During the POGO reduction rounds, the agreement of 4 experts was the criterion for inclusion of indicators.[13] Because we modified the process to maintain stakeholder participation, we instituted a cut-point of 70% for the first two surveys. This cut-point was 10% less than the higher agreement threshold of 80% used in the consensus meeting because we wanted to be more conservative, given the potential variability of survey responses from a wide range of respondents. For the first round, indicators were retained if 70% or more of the respondents had a total score of 3 for the specific indicator. Indicators meeting this criterion were included in the second round survey after further wording clarification was undertaken by the group. The second round survey followed the same format and analysis plan as the first round survey. The chosen cut-point was altered for the second reduction round with a more conservative cut-point of 60% implemented because of a smaller number of survey respondents. The group required that one indicator be retained under each theme until the final meeting, regardless of score and cut-point. When no indicator was selected, the indicator that was closest to the cut-point was retained. In the event of a tie, both indicators were kept. After completion of the second round survey, the CPAC technical report, based on a selection of feasible indicators from the brainstorming round of this work, was released.[7] A review of this list was conducted by the group in a teleconference to determine whether any of the previously discarded indicators should be rescued and considered at the final meeting.

Final Meeting

The third and final round of consensus-building was established via a face-to-face meeting. In advance of the meeting, group members were invited to complete a survey scoring the remaining indicators based on the 3 criteria used in the previous 2 survey rounds: importance, relevance, and usefulness. The assessment scale was a 6-point scale ranging from 0 (not at all) to 5 (highest); a large scale was used to provide more information regarding each criterion for ranking purposes. Results from this survey were summarized and distributed to the group 1 week before the meeting. Analyses were conducted in SPSS 25.0 (IBM SPSS Statistics, version 25, IBM Corp) and included summary statistics (mean, standard deviation, median, minimum, and maximum), agreement statistics, and overall within group ranking. Ranking was based on percent agreement ordered by importance, relevance, and usefulness. Participants were asked to review the results before the meeting and complete a further survey selecting indicators, which they would endorse based on these results. Cutoff values were chosen to correspond with those described in the stakeholder agreement stage of the POGO indicator selection process.[13] If an indicator received an endorsement of 80% or greater on the survey, the indicator was considered endorsed and excluded from further discussion. The final meeting was held in Toronto in October 2018. Members were invited to attend in person or via teleconference. The first part of the meeting provided a review of the process to date and a more in-depth review of the results of the surveys completed before the meeting. After discussion, a second survey was circulated to the group, and they were asked to review and endorse (yes/no) up to 50% of the remaining indicators based on the criteria presented.[13]

Table 1. Demographics.

	Brainstorming N = 11		Survey 1 N = 13	
	n	%	n	%
Province				
British Columbia	1	9.1%	2	15.4%
Alberta	1	9.1%	1	7.7%
Manitoba	2	18.2%	2	15.4%
Ontario	3	27.3%	4	30.8%
Quebec	0	0.0%	1	7.7%
Nova Scotia	2	18.2%	2	15.4%
Newfoundland	1	9.1%	1	7.7%
USA	1	9.1%	0	0.0%
Sex				
Male	7	63.6%	9	69.2%
Female	4	36.4%	4	30.8%
Stakeholder Group				
Pediatric Oncologist	2	18.2%	5	38.5%
Adult Oncologist	1	9.1%	3	23.1%
Nurse	2	18.2%	0	0.0%
Researcher	2	18.2%	2	15.4%
Administrator	1	9.1%	2	15.4%
NGO/Charity	2	18.2%	1	7.7%
Patient Representative	1	9.1%	0	0.0%

NGO indicates nongovernmental organization.

Indicators not receiving any endorsement after this round were considered not endorsed and removed from the process. The final part of the meeting involved an in-depth discussion of each of the remaining indicators. A third round survey was circulated after the discussion, and participants were asked to select the remaining indicators they would endorse. Any indicator receiving an endorsement of 80% or greater on this final survey was considered endorsed, with all other indicators considered not endorsed.

Ranking

A survey was sent to participants after the final meeting to rank the endorsed indicators for both current feasibility and importance and to elicit potential data sources for each indicator. For the feasibility criterion, participants were asked, "Given current data availability, how feasible would it be to implement this indicator nationally?" The importance criterion was worded as in previous surveys. Both criteria were rated on a scale of 0 (not at all) to 10 (highest). The mean was calculated for the criteria and indicators were rank-ordered based on the mean from highest to lowest for both feasibility and importance. Ties in rankings were broken by totaling the number of 9 and 10 ratings received by the indicators; the higher ranking was assigned to the indicator with more 9+10 ratings. Final indicator selections were mapped onto the quality dimensions from the Cancer Quality System Index (CQSI)[22] to support the applicability of the indicators for improving the quality of the cancer system for AYAs.

Results

Participants

Nineteen participants were involved throughout the various stages in the process, but not all participants contributed to each phase. Variation in participation stemmed from multiple factors, including changes in employment, length of time to complete process, and competing priorities. Participants included representatives from 7 Canadian provinces and the United States. Stakeholders consisted of pediatric oncologists, adult oncologists, nurses, researchers, administrators, nongovernmental organizations or charity representatives, and a patient representative. Sustained engagement was maintained for 8 representatives, who participated in the majority of stages throughout the indicator selection process. Because of the time span of the work, maintaining engagement for all members was challenging.

Comprehensive Indicator List

A total of 5287 articles were identified from the literature review; after review, 93 were deemed relevant to cancer care indicators. Upon further review, only two articles were judged to be relevant to indicators for AYA cancer care and control: the article by Greenberg et al[19] on AYA outcomes and metrics and the POGO childhood cancer indicator study that included adolescent-specific indicators.[12,13,19] The gray literature search provided a report on optimizing outcomes for all South Australian AYAs with a cancer diagnosis.[20] This listed 15 indicators, focused on the 15- to 25-year-old age group, on the themes of active care, survivorship, palliative care, and cancer awareness. The brainstorming exercise was completed by 11 of 19 respondents. Results from the brainstorming were combined with the literature review, resulting in 131 indicators. Seventeen were considered duplicates, leaving 114 indicators for further consideration.

Indicator List Reduction

Forty-three indicators remained after the first survey, which was completed by 13 of 18 respondents (Table 1). The group clarified the indicator text afterward from survey feedback and group discussion. The survey was updated based on the revised indicator list and redistributed to the group. The second survey

Table 1. Continued

Survey 2 N = 8		Pre-meeting survey N = 11		Final meeting and ranking N = 10	
n	%	n	%	n	%
3	37.5%	2	18.2%	1	10.0%
1	12.5%	0	0.0%	0	0.0%
1	12.5%	2	18.2%	2	20.0%
1	12.5%	5	45.5%	5	50.0%
0	0.0%	0	0.0%	0	0.0%
2	25.0%	2	18.2%	2	20.0%
0	0.0%	0	0.0%	0	0.0%
0	0.0%	0	0.0%	0	0.0%
4	50.0%	7	63.6%	7	70.0%
4	50.0%	4	36.4%	3	30.0%
3	37.5%	4	36.4%	4	40.0%
1	12.5%	3	27.3%	2	20.0%
1	12.5%	1	9.1%	1	10.0%
1	12.5%	1	9.1%	1	10.0%
1	12.5%	1	9.1%	1	10.0%
0	0.0%	1	9.1%	1	10.0%
0	0.0%	0	0.0%	0	0.0%

was completed by 8 of 18 respondents. Participation in the second survey dropped because of competing priorities with the publication of the CPAC AYA system performance report.[8] The 60% endorsement criterion was met by 29 indicators, with one indicator ("proportion of oncology professionals with AYA certification/expertise") being retained to ensure that an indicator was included under the education theme. The group agreed to rescue the "research funding" indicator from the CPAC report list, as it had been discarded at an early stage in the process. Thirty-one indicators were selected to continue for review; these are listed in Table 2.

Final Meeting

All 11 participants invited to the final meeting completed the survey. Results of the premeeting survey are provided in Table 2. Nine participants were able to attend the final meeting, 4 in person and 5 via teleconference. Table 3 summarizes the results of the 3 endorsement rounds at which a total of 15 indicators were endorsed from 5 of the 7 framework themes. There were no indicators endorsed for the prevention or education and awareness themes. Owing to the similarities between the 2 survival indicators endorsed by the group, it was agreed to create 1 survival indicator with 2 metrics for a final total of 14 indicators.

Ranking

The ranking survey was completed by 10 of the 11 invited respondents. Final rankings of endorsed indicators, together with potential data sources, are displayed in Table 4, mapped onto both the framework and CSQI quality dimensions. Four of the 5 most important indicators were considered to be moderately to very feasible. Clinical trial enrollment was the only top 5 indicator for importance considered to be the least feasible to obtain.

Discussion

This modified Delphi process produced 14 indicators, which covered all of the themes identified at the 2010 AYA cancer care workshop [9,11] to monitor, evaluate, and benchmark cancer care and control for AYAs in Canada. No indicators were identified in the 2 additional themes, education and prevention, which were added to the framework after the 2012 international workshop.[10] Many of the endorsed indicators work in concert, such that improvements in one indicator would lead to long-term improvement in indicators in other areas. For example, it has been suggested that multidisciplinary care is necessary to improve fertility preservation uptake in AYA cancer patients.[23] It is likely, therefore, that increases in the number of patients presented at multidisciplinary meetings would lead to improved rates of referrals to psychosocial oncology professionals and to an increase in the number of patients who have referrals for fertility preservation because these items would be part of discussions at the meeting regarding comprehensive patient care.

A major challenge to metrics for AYA cancer care and control is the collection of reliable age-specific data, in areas important and relevant to AYAs, which are comparable across provinces. AYAs represent a small subpopulation in cancer care and control; without provincial co-operation on data collection initiatives, barriers will remain to reporting metrics at both the provincial and national levels. Enrollment in clinical trials was identified as an important metric in this process. Nevertheless, obtaining information regarding this metric remains challenging. In Canada, there is no comprehensive national data source for clinical trial enrollment that contains age as a variable, with much of the data retained by individual sponsors of the trials.[24] Oncofertility is another area in which access to high-quality national data remains a challenge. Ronn et al[25] highlighted the need for a national database to capture important variables for oncofertility in their plan for action on this challenge in Canada. Because many fertility

Table 2. Summary statistics for pre-meeting survey.

	Importance Is this indicator important and appropriate from a systems perspective for managing the care of AYA cancer patients?				Relevance Does this indicator capture an issue relevant to improving quality of care for AYAs with cancer?				Usefulness If initiatives were taken in the healthcare system, would we expect to see change in this indicator?				Rank	
Indicator	Med	Min	Max	%	Med	Min	Max	%	Med	Min	Max	%	Overall	Within Group
Active														
Proportion of AYA patients who had fertility preservation discussion before treatment	5	3	5	90.90%	5	1	5	90.90%	5	3	5	81.80%	3	1
Proportion of AYA patients treated according to a clinical trial protocol	4	2	5	81.80%	5	2	5	81.80%	4	3	5	63.60%	10	2
Time from first healthcare visit with symptom to diagnosis	5	2	5	72.70%	5	2	5	90.90%	4	0	5	72.70%	14	3
Proportion of AYA diagnosed with cancer who have met with or are referred to a social worker	4	2	5	72.70%	4	2	5	54.50%	4	1	5	54.50%	20	4
Proportion of AYA diagnosed with cancer reporting positive ratings for satisfaction of active care	4	2	5	63.60%	4	2	5	54.50%	4	1	5	63.60%	22	5
Proportion of patients presented at multidisciplinary team meeting	4	2	5	63.60%	4	2	5	54.50%	3	2	5	45.50%	23	6
Proportion of AYA diagnosed with cancer who report having knowledge about diagnosis and treatment options	4	3	5	60.00%	3	2	5	45.50%	4	1	5	54.50%	24	7
Proportion of AYA patients referred for fertility treatment	4	1	5	54.50%	4	2	5	72.70%	5	2	5	63.60%	26	8
Survivorship														
Proportion of patients who are provided with a treatment summary at end of treatment (record of cancer treatment received)	5	3	5	90.90%	5	3	5	81.80%	5	3	5	81.80%	5	1
Proportion of AYA patients who have access to age-appropriate resources for educational, vocational, and psychosocial support	4	2	5	81.80%	5	3	5	81.80%	4	2	5	72.70%	8	2
Proportion of AYA patients with cancer who received reproductive counseling in follow-up care	5	2	5	81.80%	5	2	5	81.80%	5	3	5	72.70%	9	3
Proportion of female cancer survivors who received chest radiation and have been screened for breast cancer according to follow-up guidelines	5	2	5	81.80%	5	2	5	72.70%	5	2	5	72.70%	12	4

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Table 2. Continued

Indicator	Importance Is this indicator important and appropriate from a systems perspective for managing the care of AYA cancer patients?				Relevance Does this indicator capture an issue relevant to improving quality of care for AYAs with cancer?				Usefulness If initiatives were taken in the healthcare system, would we expect to see change in this indicator?				Rank	
	Med	Min	Max	%	Med	Min	Max	%	Med	Min	Max	%	Overall	Within Group
Mean HRQL score of cancer survivors aged 15-39 years post treatment	4	1	5	72.70%	4	2	5	81.80%	4	2	5	54.50%	16	5
Proportion of treatment centers with AYA-specific survivorship programs	4	2	5	63.60%	3	1	5	36.40%	4	2	5	72.70%	25	6
Psychosocial														
Proportion of programs that have psychology or psychiatry support available for AYA patients	5	3	5	90.90%	5	2	5	63.60%	4	2	5	72.70%	7	1
Proportion of AYA patients screened for distress	5	1	5	72.70%	5	1	5	81.80%	5	2	5	81.80%	15	2
Proportion of AYA patients identified to have distress through screening	4	1	5	54.50%	4	1	5	63.60%	4	2	5	54.50%	27	3
Palliation														
Proportions of centers offering AYA-specific palliative care services	5	2	5	90.90%	4	3	5	90.90%	4	2	5	81.80%	4	1
Proportion of facilities offering palliative home care programs for AYA patients	4	2	5	81.80%	4	3	5	63.60%	4	2	5	54.50%	13	2
Proportion of AYA patients who die in hospital	3	1	5	45.50%	4	0	5	54.50%	3	0	5	27.30%	31	3
Research														
AYA progression or event-free survival	5	4	5	100.00%	5	5	5	100.00%	5	2	5	72.70%	1	1
AYA overall survival	5	2	5	90.90%	5	2	5	90.90%	5	3	5	90.90%	2	2
Cause of death (short and long): proportion of AYA diagnosed with cancer who die of their disease at 5, 10, and 20 years post diagnosis	5	2	5	90.90%	5	2	5	81.80%	4	2	5	63.60%	6	3
Proportion of AYA enrolled into clinical trials	5	3	5	81.80%	5	2	5	81.80%	4	2	5	63.60%	11	4
Proportion of AYA diagnosed with cancer who are also diagnosed with at least one chronic condition other than original cancer	4	2	5	72.70%	5	2	5	72.70%	4	2	5	54.50%	17	5
Proportion of AYA patients accrued to treatment clinical trials	4	1	5	72.70%	5	2	5	63.60%	4	1	5	54.50%	18	6
Proportion of funded grants for AYA cancer research	4	1	5	54.50%	4	2	5	54.50%	3	1	5	27.30%	28	7
Proportion of GPs reporting that they feel comfortable recognizing common presenting symptoms of AYA cancers	3	1	5	45.50%	4	2	5	54.50%	3	1	5	36.40%	30	8

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Table 2. Continued

Indicator	Importance Is this indicator important and appropriate from a systems perspective for managing the care of AYA cancer patients?				Relevance Does this indicator capture an issue relevant to improving quality of care for AYAs with cancer?				Usefulness If initiatives were taken in the healthcare system, would we expect to see change in this indicator?				Rank	
	Med	Min	Max	%	Med	Min	Max	%	Med	Min	Max	%	Overall	Within Group
Education														
Proportion of oncology professionals with AYA certification/expertise	3	1	4	45.50%	4	2	5	54.50%	4	1	5	72.70%	29	1
Prevention														
HPV vaccination rate (primary prevention)	5	1	5	72.70%	4	1	5	63.60%	5	0	5	54.50%	19	1
HPV vaccination rate in AYA who are survivors of cancer	4	1	5	63.60%	4	1	5	63.60%	4	0	5	54.50%	21	2

AYA indicates adolescent and young adult; GP, general practitioner; HPV, human papilloma virus.

clinics are private facilities in Canada, data on visits to these clinics are not generally available in any administrative databases but are retained within individual clinics. Initiatives such as the Canadian Oncofertility Database[26] will greatly aid efforts to monitor and evaluate metrics in oncofertility. Small changes to current data collection could also enhance the feasibility of collecting data for AYA indicators. For example, if the AYA age group was identified and denoted when collecting administrative information on research grants, the AYA cancer research investment indicator identified in this process would be more readily available and likely have greater accuracy. Currently, identifying AYA-related studies is resource intensive and judgment-based, requiring a systematic approach based on abstracts in a national funding database.[7]

A focus of discussion at the final meeting was on whether an indicator was important for cancer in general or was specific to AYA. Some indicators, such as "place of death," are already collected nationally for cancer, and although some represent important metrics to capture for general use and review, these were not considered to be specific to AYA. It was noted that, for national indicators that are considered important to AYAs but not specific to the unique needs of this population, there should be concerted efforts to ensure reporting on the AYA age subgroup. Indicators specified in this article are meant to be a distinct set for the AYA cancer population and not a set to supplement the existing national indicators. We believe that reporting indicators for AYA cancer care and control in a regular report, such as the CPAC AYA cancer system performance report,[7] would be beneficial in monitoring and evaluating care and control in this population and increasing awareness regarding cancer in AYAs.

The education theme added to the framework after the 2012 workshop discusses the need for the development of AYA cancer care and control expertise in all fields to form multidisciplinary teams through training and education programs.[10] The process reported here did not endorse any indicators for this theme, despite the group's recognition of its importance to the quality of AYA cancer care. The group agreed that the proposed indicator in its current state would not be useful. Professional programs for developing AYA cancer management expertise in Canada are in their early stages, including a newly developed program from the Royal College of Physicians and Surgeons of Canada.[10] In the future, as programs to develop AYA expertise within healthcare professions are devised and implemented, this education indicator should be revisited. Prevention was another theme for which indicators were not endorsed. Although prevention was acknowledged by the group as important for AYA cancer control, there was agreement that a lack of research specific to AYA cancer prevention makes it difficult to identify any indicators specific to this group.

To ensure the successful implementation of indicators for AYA cancer care and control, the process should start with a few feasible and impactful indicators. This would help to develop a pattern of practice and build capacity and buy-in for the implementation of additional indicators. The survival indicator was determined to be the most important and feasible to implement. This indicator has been well defined for use in AYA cancer by the April 2017 CPAC report.[7] Other indicators for initial implementation include availability of AYA-specific services and AYA cancer research investment. Other indicators, although easily obtainable from administrative databases, have limitations such as consistency of coding (eg, "cause of death")[27-30] or do not include variables that would allow for the identification of AYA age subgroups.[7,24] Indicators that are ranked highly should be considered for targeted investment to improve feasibility and availability from organizations such as provincial and national cancer agencies. The new Adolescent and Young Adult National Network at CPAC will play an important role in implementation and reporting of indicators in this area because it is one in which CPAC has developed considerable expertise.

A limitation of this study is a lack of representation from all provinces. Ideally, there would have been representation of all provinces and stakeholders at every stage, but because of the limited availability of members and their changing roles throughout the study, participation varied during the process. Nevertheless, regardless of representation, many, if not all, of the endorsed indicators are likely to be important for all provinces. Overall the process had strong representation from members with substantial experience in the care of AYA patients and from those familiar with AYA cancer data and research, despite the variability in the number of participants during the project. Another weakness in the selection process was the lack of continued engagement of patient representatives throughout all the stages.

Table 3. Summary of endorsement results from final meeting.

Round	Endorsed Indicator (% agreement)	Not endorsed Indicator (% agreement)
Round 1 n = 10	Active care • Survival indicators: ◦ AYA patient progression or event-free survival (90%) ◦ AYA patient overall survival (100%) • Proportion of AYA patients who had fertility preservation discussion before treatment (90%) Survivorship • Proportion of patients who are provided with a treatment summary at end of treatment (90%) • Proportion of AYA patients who have access to age-appropriate resources for educational, vocational, and psychosocial support (90%) • Proportion of female cancer survivors who received chest radiation who have been screened for breast cancer according to follow-up guidelines (80%) • Proportion of AYA patients with cancer who received reproductive counseling in follow-up care (80%) Psychosocial • Proportion of programs that have psychology or psychiatry support available for AYA patients (80%) Palliation • Proportions of centers offering AYA-specific palliative care services (80%) Research • Cause of death (short and long): proportion of AYA survivors who die of their disease post diagnosis (80%) • Proportion of AYA enrolled into clinical trials (80%)	
Round 2 n = 9		Prevention • HPV vaccination rates in AYA patients who are survivors of cancer (0%)
Round 3 n = 9	Active care • Proportion of patients presented at multidisciplinary team meeting (89%) Psychosocial • Proportion of AYA diagnosed with cancer who have met with a psychosocial oncology professional (100%) • Proportion of AYA patients screened for distress with standardized AYA-specific tools (CDS-AYA or other) (89%) Research • Proportion of funded grants for AYA cancer research (based on both number and value) (89%)	Survivorship • Mean standardized HRQL score of cancer survivors aged 15-39 years post treatment (78%) • Proportion of treatment centers with AYA-specific survivorship programs (44%) • Proportion of AYA diagnosed with cancer who are also diagnosed with at least one chronic condition other than original cancer (22%) Active care • Time from first healthcare visit with symptom to diagnosis (33%) • Proportion of AYA patients referred for fertility treatment (22%) • Proportion of AYA patients treated according to a clinical trial protocol (11%) • Proportion of AYA diagnosed with cancer who report having knowledge about diagnosis and treatment options (11%) • Proportion of AYA diagnosed with cancer reporting positive ratings for satisfaction of active care (0%) • Proportion of AYA patients accrued to treatment clinical trials (0%) Palliation • Proportion of AYA patients who die in hospital (33%) • Proportion of facilities offering palliative homecare programs for AYA patients (0%) Psychosocial care • Proportion of AYA patients identified to have distress through screening (0%) Research • Proportion of GPs reporting that they feel comfortable recognizing common presenting symptoms of AYA cancers (0%) Prevention • HPV vaccination rate (0%) Education • Proportion of oncology professionals with AYA certification/expertise (11%)

AYA indicates adolescent and young adult; GP, general practitioner; HPV, human papilloma virus.

Table 4. Ranking of final indicators for importance.

Indicator	Framework theme	Framework recommendation or priority addressed by indicator*From Fernandez et al[11]	Importance	Potential data source	Cancer System Quality Index quality dimension[22]
Survival: a) AYA patient overall survival; b) AYA patient progression or event-free survival	Active care and survivorship	*1. Services must be provided to address the unique needs of AYAs with cancer and survivors of cancer in childhood, adolescence, and young adulthood to redress inequities in the care provided to this group relative to both younger and older cancer patients.* *4. Implementation of life-long monitoring and follow-up of survivors of cancer in childhood, adolescence, and young adulthood will provide economic and other societal benefits and help mitigate late- or long-term treatment effects.*	1	Overall survival can be obtained from provincial cancer registries; however, event-free survival requires chart abstraction and is less feasible.	Effective
Proportion of AYA patients who have access to age-appropriate resources for educational, vocational, and psychosocial support	Survivorship	4.4 Rehabilitation services should be available to provide quality evidence-based services meeting the range of AYA cancer survivors' rehabilitation needs (including physical, psychosocial, occupational, and educational).	2	Survey of services offered by institutions[†]	Responsive/ integrated[†]
Cause of death among cancer survivors (short and long): proportion of AYA diagnosed with cancer who die of their disease at 5, 10, and 20 years post diagnosis	Survivorship	*4. Implementation of life-long monitoring and follow-up of survivors of cancer in childhood, adolescence, and young adulthood will provide economic and other societal benefits and help mitigate late- or long-term treatment effects.*	3	Information is available in administrative databases but there are potential limitations because of a lack of consistency when coding the cause of death[27-30]	Integrated

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Table 4. Continued

Indicator	Framework theme	Framework recommendation or priority addressed by indicator*From Fernandez et al[11]	Importance	Potential data source	Cancer System Quality Index quality dimension[22]
Proportion of female cancer survivors who received chest radiation and have been screened for breast cancer according to follow-up guidelines	Survivorship	4.3 Healthcare services and survivorship follow-up guidelines should be available to provide quality, evidence-based, long-term follow-up care for AYA cancer survivors; these healthcare services should be risk-stratified, considerate of patient needs and preferences, and easily integrated into the local healthcare delivery system.	4	Administrative databases contain this information but difficulty may arise when trying to combine treatment data	Effective/integrated
Proportion of AYA patients enrolled in clinical trials	Active care and research	1.5 Opportunities for AYAs with cancer to participate in appropriate clinical research trials must be increased and such patients should be offered entry into any appropriate clinical research trial for which they are eligible. 5.5 Assessment of determinants of AYA patients' access to clinical trials, the study of tumor biology, and translational research.	5	Chart abstraction‡	Effective/integrated‡
Proportion of AYA patients who had fertility preservation discussion before treatment	Active care	1.7 Fertility risks and options for considering or not considering fertility preservation must be discussed with each patient.	6	Chart abstraction.‡ This information was the goal of the Canadian Oncofertility Database.[27]	Responsive/ accessible‡
Proportion of patients who are provided with a treatment summary at end of treatment (record of cancer treatment received)	Survivorship	4.2 Every AYA cancer survivor should be provided with a record to facilitate transition.	7	Chart abstraction‡	Effective/responsive‡

continued on next page

Table 4. Continued

Indicator	Framework theme	Framework recommendation or priority addressed by indicator*From Fernandez et al[11]	Importance	Potential data source	Cancer System Quality Index quality dimension[22]
Proportion of AYA diagnosed with cancer who have met with a psychosocial oncology professional	Active care and psychosocial	1.2 Age-appropriate care should be delivered and/or supported by interdisciplinary teams populated with age- and disease-specific medical and psychosocial experts able to effectively communicate and provide evidence-based care, including age-appropriate and developmentally appropriate supportive and psychosocial care. 2.2 The interdisciplinary team should have access to experts in AYA psychosocial care and their services should be offered to all patients and their families.	8	Chart abstraction‡	Responsive/safe‡
Proportion of centers offering AYA-specific palliative care services	Palliation	3.4 AYA-specific interdisciplinary palliative care teams should be established throughout Canada; these teams should be flexible and able to work in both pediatric and adult facilities, as well as in a virtual environment to support patients being cared for in smaller communities or at home.	9	Survey of services offered by institutions†	Accessible/ responsive†
Proportion of programs that have psychology or psychiatry support available for AYA patients	Psychosocial	2.2 The interdisciplinary team should have access to experts in AYA psychosocial care and their services should be offered to all patients and their families.	10	Survey of services offered by institutions†	Accessible/ responsive†

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Table 4. Continued

Indicator	Framework theme	Framework recommendation or priority addressed by indicator*From Fernandez et al[11]	Importance	Potential data source	Cancer System Quality Index quality dimension[22]
Proportion of patients presented at multidisciplinary team meeting	Active care	1.3 AYA cancer patients must be recognized as a special population at a critical developmental stage between childhood dependency and adult independence. Systems should be in place to ensure interdisciplinary collaboration, coordination, and transition between pediatric and adult healthcare providers, and to develop and promote linkages with relevant community-based resources.	11	Chart abstraction‡	Integrated/efficient‡
Proportion of AYA with cancer who received reproductive counseling in follow-up care	Survivorship	4.1 Discussion and education about the survivorship phase should begin during active treatment to prepare the patient and family for the transition to survivorship; this must include discussion of potential long-term and late effects of treatment.	12	Chart abstraction‡	Responsive/ integrated‡
Proportion of AYA patients screened for distress with standardized AYA-specific tools (CDS-AYA or other)	Psychosocial	2.1 Implementation of routine psychosocial screening of AYAs at diagnosis and intervals throughout the illness trajectory to provide opportunities for early or prophylactic intervention.	13	Some administrative databases capture distress screening; however, currently no AYA-specific screening tools are available for use.*	Effective/responsive*
Proportion of funded grants for AYA cancer research	Research	*Research and the establishment of outcome metrics are required to investigate issues critical to AYAs with cancer and survivors of cancer in childhood, adolescence, and young adulthood to target interventions and healthcare policy to improve all phases of the cancer journey.*	14	In Canada, data available from Canadian Cancer Research Alliance database. Nevertheless, extracting AYA research requires a systemic review because coding for age is dichotomous in this database, pediatric or adult.	Equitable

Note. Data source coded by level of feasibility: * indicates very feasible, † means moderately feasible, and ‡ is least feasible.
AYA indicates adolescent and young adult

Nevertheless, there was substantial patient representation during the process to develop the framework that formed the basis of indicator selection. The selected indicators are derived from a framework, which was built on substantial robust representation from provinces and stakeholder groups, with more than 100 participants, including patient and family representatives, providing input into the development of the framework.[11] Another limitation of this study is that the indicators selected were not evaluated against quality indicator criteria and benchmarks were not described. Further work needs to be done to validate the chosen indicators and develop appropriate benchmarks.

Future research and policy development should focus on new indicators in important areas not addressed by the framework of Fernandez et al.[11] One of these areas should be health economics. Greenberg et al[19] included health economics as a section in their summary of potential AYA cancer metrics, proposing measures such as quality-adjusted life-years. Health economics was deemed important to help monitor and evaluate the use of resources to ensure efficiency, effectiveness, and sustainability of AYA cancer programs.

Conclusion

Improvements in care and outcomes for AYAs with cancer will require co-operation and co-ordination at multiple levels of the Canadian healthcare system. Developing important metrics relevant to the needs of this population, which can be compared provincially, nationally, and internationally, is required. This is necessary to facilitate the expected improvement of cancer care and control and clinical outcomes. Objective measurements are required to evaluate whether the changes to AYA cancer care and control result in the expected improvements. The indicators presented in this article provide a starting point for the development of a standard set of metrics for AYA cancer care and control in Canada and may prove to be of international utility.

Acknowledgments

The authors acknowledge valuable contributions from the Pediatric Oncology Group of Ontario (POGO), the Atlantic Provinces Pediatric Hematology Oncology Network, the Canadian Partnership Against Cancer, Dr. Mark Greenberg at the Pediatric Oncology Group of Ontario. Dr. Paul Grundy at the Canadian Partnership Against Cancer (CPAC), Rebecca Block from Critical Mass (US), and Annie Lok. Other members of the System Performance Group include Dr. Kristin Marr, Tim Buckland, and Sonja De Pauw.

Source of financial support: This study was supported in part by the Canadian Partnership Against Cancer.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2019.08.004.

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Appendix 1 – Search strategy for environmental scan

SEARCH	QUERY
1	exp neoplasms/
2	(neoplasm? or cancer? or oncology or carcinoma).tw.
3	or/1-2
4	*Benchmarking/st, td, ut [Standards, Trends, Utilization]
5	Quality Indicators, Health Care/
6	((process or performance or quality) adj3 (indicator? or measure* or benchmark? or assessment? or metric?)).tw.
7	(assess adj2 quality).tw.
8	*Quality Assurance, Health Care/
9	or/4-8
10	3 and 9
11	limit 10 to english language
12	limit 11 to yr="1995-Current"
13	12 not (addresses or comment or congresses or editorial or interview or letter).pt.
14	13 not quality of life.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
15	(teen or adolescen* or young adult or young p* or young m* or younger m* or young f* or younger f* or young wom* or younger wom*).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
16	14 and 15

Appendix 2

INDICATORS FOR AYA CANCER

Your task: *Based on* ***<u>your perspective</u>****, indicate what activities/outcomes are most important to monitor in order to improve the cancer journey for adolescents and young adults in Canada?*

The recommendations and priorities listed in the Task Force's Fernandez (2011) paper may help us identify areas of interest in AYA cancer. The Greenberg (2011) paper, Table 1, provides a list of outcomes and metrics which may also help inform this process (Please feel free to use items from Greenberg et al's Table 1). These materials are just meant to guide you; please feel free to include indicators that are not related to these materials.

We realize that each of you has a very distinct area(s) of expertise and may not be familiar with all aspects of the cancer journey. It is important for us to have all stakeholder views incorporated in this process and your perspective is of great value to this initiative. We do not expect you to provide a broad range of indicators. We ask you to focus on your area of expertise to provide suggestions that encompasses what is important from your own perspective and experience.

If you are unsure how to frame your idea as an indicator, please describe your concept as best you can.

#	Principle	INDICATOR	POTENTIAL DATA SOURCE (*if you know*)

PREFACE CHAPTER 4 AND 5: PATIENT-REPORTED OUTCOME MEASURES (PROMS) IN SYSTEM PERFORMANCE MEASUREMENT

The data used to complete the analyses for chapters 4 and 5 were part of the CDS-AYA field-test, the final stage in the development of a distress screening tool for the AYA cancer population.[13] Below is an overview of the methods used to collect the field-test data which is only briefly described in the methods sections of the papers. The development of the CDS-AYA has been fully described in:

> Tsangaris E, D'Agostino N, Rae C, Breakey V, Klassen AF, 2019. Development and psychometric evaluation of the cancer distress scales for adolescent and young adults. *Journal of adolescent and young adult oncology*, *8*(5), pp.566-580. doi: 10.1089/jayao.2019.0005.

Methods: CDS-AYA Field-Test

The CDS-AYA was developed using a mixed methods approach. Phase 1 of the project conducted qualitative and cognitive interviews with AYAs aged 15-39 years who were currently undergoing treatment or had completed treatment. Patient interviews were guided by the items on an Australian version of the NCCN-DT with a modified problem checklist specific to AYA cancer patients and survivors. These interviews were used to develop a set of scales and items for the CDS-AYA. Expert and patient feedback were obtained on this version, and revisions were completed to create a final version for the field-test.

Field-Test Data Collection

The field-test included participants between the ages of 15 and 39 who were diagnosed with cancer. Patients could be either currently undergoing treatment or finished their treatment. Recruitment occurred between August 2016 and November 2017 from

McMaster Children's Hospital, Alberta Children's Hospital, British Columbia Women's and Children's Hospital, Princess Margaret Cancer Centre, and Hospital for Sick Children in Toronto. Participants were approached during their regularly scheduled clinic appointments, and consent was obtained. A $5 Canadian gift card was offered as an incentive to participate.

A survey was completed on an iPad using REDcap (Research Electronic Data Capture) or a paper questionnaire package during the clinic visit. The survey contained a self-complete clinical and demographics questionnaire, CDS-AYA, and three measures used to assess distress: HADS, ESAS-r and NCCN-DT. All measures were completed using a past week recall period. Participants at McMaster Children's Hospital and Princess Margaret Cancer Centre were asked to complete the CDS-AYA and three distress measures again in seven days and/or four months. Those who agreed to participate in the re-test and follow-up assessments provided their email address. Each participant was emailed a link to complete the survey at the appropriate time, and one reminder email was sent for the seven day assessment and two email reminders were sent for the four month follow-up.

Field-Test Participants

A total of 515 individuals participated in the field-test representing a 74% response rate. Fewer participants completed the seven day assessment with only 86 of 200 invited participants completing the survey. The four month follow-up sample included 67 participants but the composition of the sample was too heterogeneous in terms of disease type and treatment stage for meaningful analyses. The field-test sample was

predominantly from Ontario (95.1%), with slightly greater male participation (56.1%). The majority of participants were from the 20-29 year age group (43.9%), with the 15-19 year age group comprising 24.7%, and 31.4% from the 30-39 year age group. Sample sizes presented in chapters 4 and 5 are smaller because of incomplete questionnaire data.

CHAPTER 4: IMPROVING THE INTERPRETABILITY OF CDS-AYA

Distress Screening in Adolescents and Young Adults with Cancer: Development of Cut-Points for the Cancer Distress Scales-Adolescent and Young Adults.

Reprinted from *Journal of adolescent and young adult oncology*; Rae C, Klassen AF, Tsangaris E, Breakey V, D'Agostino N; Oct;8(5); Pages 560-565;

doi: 10.1089/jayao.2019.0032.

JOURNAL OF ADOLESCENT AND YOUNG ADULT ONCOLOGY
Volume 00, Number 00, 2019

DOI: 10.1089/jayao.2019.0032

Distress Screening in Adolescents and Young Adults with Cancer: Development of Cut-Points for the Cancer Distress Scales-Adolescent and Young Adults

Charlene Rae, MSc,[1] Anne F Klassen, DPhil,[1] Elena Tsangaris, PhD,[2] Vicky Breakey, MD, Med, FRCPC,[1] and Norma D'Agostino, PhD, CPsych[3]

Purpose: Distress is an important issue facing adolescent and young adults (AYA) with cancer due to their stage of development. Metrics are necessary to help improve psychosocial outcomes in this population. This study determined cut-points for the newly developed Cancer Distress Scales (CDS)-AYA.
Methods: The CDS-AYA is a new patient-reported outcomes measure that comprises five independently functioning scales, including the following: Impact of Cancer (12 items), Physical (12 items), Emotional (11 items), Cognitive (8 items), and Cancer Worry (5 items). Canadian AYA with cancer 15–39 years of age completed the CDS-AYA and the Hospital Anxiety and Depression Scale (HADS), as part of the CDS-AYA field test. Only patients who had completed responses to the CDS-AYA and HADS were included in these analyses. Receiver operating characteristic (ROC) curve analysis was used to generate cut-points for five CDS-AYA scales based on distress defined by the HADS anxiety and HADS depression scale.
Results: In total 453 of 515 respondents had complete data for the CDS-AYA and HADS were included in analyses. Area under the curve (AUC) in the ROC analyses ranged from 0.75 to 0.85. The CDS-AYA Emotional scale had the greatest AUC. The cutoff value for the Emotional scale was 27 based on the HADS anxiety scores (78.3% and 78.9%).
Conclusions: The five CDS-AYA scales had fair to good accuracy when classifying the none/low and moderate/severe distress categories based on HADS anxiety and depression scales. For screening purposes, it is recommended that the Emotional scale or Impact of Cancer scale be utilized.

Keywords: CDS-AYA, distress, screening, cut-point, receiver operator curve

Introduction

The National Comprehensive Cancer Network (NCCN) has defined distress as *an unpleasant experience of psychological, social, and/or spiritual nature*.[1] The experience of distress can range from mild feelings of fear and sadness to more severe conditions such as depression and anxiety.[1] For adolescent and young adults (AYA), a diagnosis of cancer comes at a time when they are reaching developmental milestones, including developing self-identity and values, obtaining autonomy from parents, preparing for a career, exploring intimacy and relationships, and developing strong peer relationships.[2–4] The physical changes, social isolation, loss of independence, and side effects of treatment that often occur with a cancer diagnosis can be particularly distressing for this age group.[3] AYA-aged survivors may also experience distress as they regain independence, return to normalcy, and are faced with the late effects (e.g., infertility) of treatment.[5]

Clinical screening for distress is recommended throughout the cancer spectrum, from the time of diagnosis through to survivorship.[6–9] Owing to the unique aspects of distress experienced by AYA with cancers, patient-reported outcome measures used in screening should be tailored to this patient population.

The NCCN distress thermometer (DT)[1] and Edmonton Symptom Assessment Scale (ESAS)[10] are commonly used screening tools for distress in cancer care. Some work has been done assessing the validity of the NCCN DT in the AYA

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population. Recklitis et al.[11] compared the widely used NCCN DT with a psychiatric diagnostic interview in a young adult cancer survivor population. This study concluded that the NCCN DT should not be used as a stand-alone screening tool in young adult survivors of cancer because it did not meet the criteria for acceptable sensitivity or specificity, failing to identify 31.8% of survivors who were diagnosed with distress using the gold standard interview process.[11] Although the ESAS is extensively used and validated, most work has been done in adult advanced cancer populations.[12,13]

An Australian tool for psychosocial assessment of on-therapy patients and cancer survivors has been developed for the AYA cancer population.[14] This tool is presented in a checklist format, which limits the ability to use this tool to assess severity, change over time, or for research applications. The Cancer Distress Scales for AYA (CDS-AYA) is a modification of the Australian distress screening tools.[14,15] The CDS-AYA has the potential to address the gap in the availability of cancer distress measures for the AYA population. Further definition of cut-points for distress screening need to be defined before the CDS-AYA is useful for clinical practice. The objective of this study was to determine cut-points for clinical application of the CDS-AYA to screen for distress in the AYA cancer population.

Methods

AYA were defined as individuals between the ages of 15 and 39 years. Age definitions for the AYA cohort vary globally, for the purposes of this study the broadest definition, of 15–39 years of age, was chosen. This age definition for AYA is used by the Canadian Partnership Against Cancer[16] and other organizations.[17]

Data were collected as part of the CDS-AYA field-test study from both AYA undergoing cancer treatment and those who had completed treatment. This group is collectively referred to in this article as ''AYA with cancer.''[15] The survey was conducted at four institutions in Canada, including Princess Margaret Cancer Centre (PMCC) (Toronto, ON), McMaster Children's Hospital (Hamilton, ON), Alberta Children's Hospital (Edmonton, AB), and British Columbia (BC) Women's and Children's Hospital (Vancouver, BC). Approval was obtained from the Research Ethics Boards at each participating institution.

Survey

AYA with cancer were recruited at scheduled clinic visits and were asked to complete a questionnaire package. The self-completed survey contained demographic and clinical questions, along with the CDS-AYA, Hospital Anxiety and Depression Scale (HADS),[18,19] ESAS-revised (ESAS-r),[10,19] and NCCN DT.[1] Patients diagnosed with any type of cancer who were undergoing treatment, in aftercare, or in survivorship were eligible to participate. Questionnaires were completed using iPads or paper booklets. Detailed methods are described in Tsangaris et al.[15]

CDS-AYA

The CDS-AYA is a newly developed set of scales for measuring distress in AYA with cancer. The scales were based on two checklists for AYA-specific psychosocial assessment and care developed in Australia: the AYA oncology screening tool for on-treatment patients and the AYA survivorship oncology screening tool.[14] Cognitive interviews with 45 AYA with cancer aged 15–39 years, and 25 experts, were used to refine the Australian distress screening tools to create the field-test version of the CDS-AYA. Field-test data from 515 participants led to the refinement of five scales that measure distress according to modern psychometric theory.[15] Field-test data were also used to assess reliability and validity of CDS-AYA in the AYA cancer population.[15]

There is no overall score for the CDS-AYA. Instead the CDS-AYA consists of five independently functioning scales: Impact of Cancer (12 items), Physical (12 items), Emotional (11 items), Cognitive (8 items), and Cancer Worry (5 items). Developers recommend the use of the 12-item ''Impact of Cancer'' scale as the primary metric because its content relates to AYA-specific concepts of development (e.g., level of independence, identity, and romantic relationships). The CDS-AYA provides four response options (none, mild, moderate, and severe). For each item, respondents are asked to indicate ''*how much distress they experienced in the past week*.'' For each of the five scales, item scores are summed and transformed onto a scale of 0–100, with higher scores reflecting more distress.

HADS

The 14-item HADS has seven depression and seven anxiety items.[18,19] Respondents are asked to indicate based on how they felt for the past week. Each item consists of four response options and a total score is generated for each of the depression and anxiety subscales that can range from 0 to 21, with higher scores indicating more symptoms of depression or anxiety. The HADS has been described as a screening tool for patients with cancer, with scores of seven and below indicating the absence of anxiety or depression as measured by the two subscales.[18–20] In a review of instruments used in cancer to screen for emotional distress, the HADS received an overall rating of ''Good,'' compared with the other instruments used in the field-test study, ESAS[10,21] and NCCN DT,[1] which received a lower rating of ''Fair.'' Based on the superior rating in the review of screening instruments, HADS was selected to assess cut-points for distress screening in the CDS-AYA scales.[22]

Analysis

All analyses were conducted using Statistical Package for Social Sciences (SPSS) 25.0 (IBM SPSS Statistics, version 25, IBM Corp.).[23] Cases were excluded from the analysis if there was missing data in the CDS-AYA. Missing data for the HADS were imputed using the half rule, with the mean of the scale imputed into missing items if at least half the items were completed in the scale.[24] Differences in the clinical and demographic characteristics between the field-test and the cut-point analysis participants were examined using Chi-square. Statistical significance was $p < 0.05$.

Cut-points CDS-AYA

Methods for determining cut-points for the CDS-AYA scales were adapted from Selby et al.[12] Distress was defined using

Table 1. Participant Demographic and Clinical Statistics

	Field-test sample (n = 515)		*Cut-point sample (n = 453)*	
	n	%	n	%
Gender				
Male	289	56.1	251	55.4
Female	225	43.7	201	44.4
Not reported	1	0.2	1	0.2
Age at the time of survey (years)				
15–19	127	24.7	116	25.6
20–29	226	43.9	205	45.3
30–39	162	31.4	132	29.1
Diagnosis				
Carcinoma	115	22.3	98	21.6
Leukemia	139	27.0	122	26.9
Lymphoma	110	21.4	100	22.1
Sarcoma	28	5.4	27	6.0
Other	107	20.8	91	20.1
Not reported	16	3.1	15	3.3
Province				
Alberta	4	0.8	4	0.9
British Columbia	21	4.1	17	3.8
Ontario	490	95.1	432	95.4
Treatment status				
Active	264	51.3	208	45.9
Completed	213	41.4	212	46.8
No treatment required	16	3.1	15	3.3
Not reported	22	4.3	18	4.0

both the HADS anxiety and depression subscales. Cut-points for defining distress were based on the HADS developer's recommended categories: <8 = normal, 8–10 = borderline abnormal, and 11–21 = abnormal.[18,19] The presence of anxiety or depression for this study was represented by a combination of the borderline abnormal and abnormal HADS categories (score ≥ 8). A receiver operating characteristic curve was generated for each of the five CDS-AYA scales to determine cut-points and suitability of the scales for detecting distress defined by the HADS anxiety and depression scores.

The smallest distance from optimum (DFO) was used to determine the cut-point for the CDS-AYA scale that best maximized sensitivity and specificity. In cases where DFO was equal across scale values, the value that maximized sensitivity was chosen. The smallest scale cutoff value based on the HADS anxiety and depression scores were selected as the final cutoff value for the CDS-AYA scale. This approach ensured that both anxiety and depression cases were captured. Values for area under the curve (AUC) were calculated and assessed using the following categories: 0.5 no discrimination, 0.7–0.8 acceptable; 0.8–0.9 excellent, and >0.9 outstanding.[25]

Results

Participants

In the field test a total of 515 assessments were collected across five sites in Canada, of which 453 participants were included in this study. A total of 62 cases were excluded because either the CDS-AYA scales or HADS could not be scored due to missing data. There were no significant differences in the clinical and demographic characteristics between the field-test participants and cut-point analysis sample ($p \geq 0.373$). All demographic and clinical statistics were self-report and summary statistics are provided in Table 1.

Cut-points

Mean and median CDS-AYA scores are displayed in Table 2 for each of the five scales, by distress status as defined by the normal, borderline abnormal/abnormal categories for the HADS anxiety and depression scores. For the CDS-AYA scales, AUC ranged from 0.75 to 0.85 for HADS anxiety and 0.74–0.81 for HADS depression (Table 3). Table 3 displays the sensitivity and specificity for scale scores, along with the three values associated with the lowest DFO.

Table 2. Mean and Median CDS-AYA Scores by HADS Anxiety and Depression Severity Categories

	HADS anxiety						*HADS depression*					
	Normal (n = 334)			*Borderline abnormal/abnormal (n = 178)*			*Normal (n = 433)*			*Borderline abnormal/abnormal (n = 79)*		
CDS-AYA scale	*Median*	*Valid* n	*Mean (SD)*	*Median*	*Valid* n	*Mean (SD)*	*Median*	*Valid* n	*Mean*	*Median*	*Valid* n	*Mean (SD)*
Impact of Cancer	7	292	13 (16)	37	163	34 (21)	13	383	17 (18)	41	72	41 (21)
Physical	22	334	20 (14)	34	178	34 (13)	25	433	23 (15)	39	79	37 (14)
Emotional	11	332	15 (15)	38	177	39 (18)	17	430	20 (17)	46	79	43 (23)
Cognitive	7	332	11 (14)	28	177	30 (20)	7	431	15 (16)	32	78	32 (22)
Cancer Worry	21	334	22 (19)	48	178	46 (25)	28	433	27 (22)	48	79	48 (25)

Scales are scored on 0–100.
CDS-AYA, Cancer Distress Scales-adolescent and young adults; HADS, Hospital Anxiety and Depression Scale; SD, standard deviation.

Table 3. Summary of Receiver Operating Characteristic Analysis for CDS-AYA Scales

	Anxiety HADS-borderline abnormal/abnormal							*Depression HADS-borderline abnormal/abnormal*						
						95% CI for AUC							*95% CI for AUC*	
CDS-AYA scale	*Scale value*	*Sensitivity (%)*	*Specificity (%)*	*DFO*	*AUC*	*LB*	*UB*	*Scale value*	*Sensitivity (%)*	*Specificity (%)*	*DFO*	*AUC*	*LB*	*UB*
Impact of Cancer	**24**	**70.2**	**71.3**	**0.17**	0.775	0.728	0.822	33	73.2	76.5	0.13	0.801	0.741	0.861
	27	67.1	75.1	0.17				**34**	**71.8**	**78.9**	**0.12**			
	28	67.1	75.4	0.17				36	64.8	81.8	0.16			
Physical	24	79.5	56.4	0.23	0.746	0.699	0.792	**32**	**69.0**	**73.9**	**0.16**	0.785	0.725	0.846
	27	**72.7**	**63.3**	**0.21**				34	69.0	74.1	0.16			
	30	63.4	70.9	0.22				35	64.8	78.9	0.17			
Emotional	24	82.6	71.6	0.11	0.846	0.807	0.884	**30**	**80.3**	**69.7**	**0.13**	0.809	0.747	0.872
	27	**78.3**	**78.9**	**0.09**				32	76.1	72.3	0.13			
	30	73.9	81.7	0.10				34	76.1	72.6	0.13			
Cognitive	**11**	**78.9**	**64.7**	**0.17**	0.782	0.736	0.827	18	76.1	61.2	0.21	0.742	0.673	0.812
	15	71.4	69.9	0.17				**22**	**73.2**	**68.3**	**0.17**			
	18	70.8	69.9	0.18				26	64.8	76.0	0.18			
Cancer Worry	32	72.7	65.4	0.19	0.773	0.725	0.821	36	67.6	66.8	0.22	0.739	0.677	0.802
	36	**68.3**	**77.9**	**0.15**				**41**	**62.0**	**76.3**	**0.20**			
	41	59.6	86.9	0.18				46	56.3	82.1	0.22			

Optimal cutoff based on smallest DFO and maximum sensitivity represented in bold.
AUC, area under the curve; CI, confidence interval; DFO, distance from optimum; LB, lower bound; UB, upper bound.

The CDS-AYA Emotional scale had the largest AUC of the five scales. Based on DFO and maximum sensitivity, the cutoff value for the Emotional scale was determined to be 27 for anxiety (78.3%, 78.9%) and 30 for depression (80.3%, 69.7%). The CDS-AYA Impact of Cancer scale had a cut-point of 24 (70.2%, 71.3%) for anxiety, and 34 (71.8%, 78.9%) for depression based on maximum sensitivity and smallest DFO. The values of 27 for the Emotional scale and 24 for the Impact of Cancer scale were chosen as the optimal screening cutoff values to capture all cases with any anxiety or depression.

Discussion

Initial field testing results by Tsangaris et al.[15] provided evidence of validity and reliability of the CDS-AYA scales in the Canadian AYA cancer population. The cut-point for the identification of borderline abnormal/abnormal cases of distress in this population improves the clinical utility of this new instrument. The Emotional scale had good classification accuracy for both HADS depression and anxiety. The Impact of Cancer scale, which was recommended as the main CDS-AYA scale with content explicitly focused on AYA issues, had similar accuracy in the classification of depression, but had slightly less accuracy in the classification of anxiety than the Emotional Scale. The CDS-AYA cut-points identified in this study should be considered for screening purposes only. The diagnostic value of these cut-points requires further validation.

In general, an AUC of 0.5 or less is considered to be associated with a test that has no better accuracy than chance, and is unable to distinguish between groups. In this study, the AUC of the CDS-AYA based on HADS anxiety and HADS depression was >0.7 in all cases. The CDS-AYA Emotional scale had the greatest AUC of 0.85 considered to be excellent.[25] In comparison with other instruments sensitivity and specificity of cut-points for the CDS-AYA were within the range reported for other commonly used instruments, including the NCCN DT, ESAS, and HADS.[22]

Cutoff values for the NCCN DT based on HADS criterion were found to have variable sensitivity (0.63–0.86) and specificity (0.59–0.81).[22] There was similar variability for ESAS cutoffs also based on HADS with sensitivity ranging from 0.61 to 0.90, and specificity ranging from 0.55 to 0.76.[22] For both ESAS and NCCN DT sensitivity and specificity tended to be lower for cutoff values that were based on HADS depression criterion.[22] The HADS was also found to have high variability in the sensitivity and specificity of cutoff values.[22] In the five studies that used a cutoff of eight for HADS anxiety, sensitivity ranged from 0.34 to 0.94, and specificity from 0.72 to 0.88. Two studies that used a cutoff of eight based on HADS depression criterion had a sensitivity of 0.23 and 0.71, and specificity of 0.95 in both cases.[22]

In the Vodermaier et al.[22] review, the validity of a cutoff value was determined by averaging the reported sensitivity and specificity values, if the average was >0.8 validity was considered high. The cut-point of 27 for the Emotional scale based on HADS anxiety found in this study almost met this metric with a sensitivity of 0.78 and specificity of 0.79.

Given the variability in the sensitivity and specificity for the HADS cutoffs, basing the CDS-AYA cut-points on HADS anxiety and HADS depression criteria could further compound any inaccuracies in the initial HADS cut-point definitions. In a study by Mitchell et al.,[26] the authors performed a meta-analysis to determine the diagnostic validity of the HADS in both cancer and palliative care settings. This study found that the overall HADS score could identify anxiety, depression, or mixed mental disorder in only 6 out of 10 cases, and recommended that the HADS should not be used for case findings.[26] This weak case finding utility of the HADS in the cancer and palliative care settings presents a limitation to applying HADS to identify CDS-AYA cut-points.

Cut-points for HADS scales were also developed primarily for adults, and not specifically for AYA. For HADS, White et al.[27] identified a lower cut-point for the depression scores and higher cut-point for anxiety scores for the 15- to 17-year-old age group than those recommended by the developer. Cut-points from the White et al.[27] study were not used in this study due to the unknown applicability to the 18- to 39-year-old age group. Further research to examine the association between the cut-points for CDS-AYA and clinical diagnosis of distress through gold standard interviews in AYA patients and survivors is warranted.

Psychosocial care is an important aspect of person-centered care, and a priority for AYA with cancer. It is recommended that screening focus on the use of the CDS-AYA Impact of Cancer or Emotional scales, the remaining scales can be administered in the event of a positive screen for higher levels of distress to gather further information. The CDS-AYA fills an important gap in AYA-specific distress screening tools for cancer that captures issues important to this population. To improve the applicability of the CDS-AYA as a screening tool in clinical practice, further study needs to focus on determining referral pathway based on scale scores to facilitate proper care of AYA after screening.

Acknowledgments

This study was conducted with support from C17 Council, and funded by the Childhood Cancer Canada Foundation and the Kids with Cancer Society. We thank Abha Gupta, Dilshan Pieris, Kate Wang, Seline Tam, Nivetha Ramachandran, Colleen Fitzgerald, Sarah McKillop, and Linda Churcher for their contributions. We also thank Pandora Patterson, Michael Osborne, Fiona McDonald developers of the Australian DT AYA on-treatment and survivorship tools.

Author Disclosure Statement

No competing financial interests exist.

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CHAPTER 5: PROMS FOR USE IN DISTRESS PERFORMANCE METRICS

Comparison of Patient-Reported Outcome Measures for Use as Performance Metrics in Adolescent and Young Adult Psychosocial Cancer Care.

Reprinted from *Journal of adolescent and young adult oncology*; Rae, C.S., Tsangaris, E., Klassen, A.F., Breakey, V. and D'Agostino, N.;2020; 9(2);262-270;

doi: 10.1089/jayao.2019.0033

JOURNAL OF ADOLESCENT AND YOUNG ADULT ONCOLOGY
Volume 00, Number 00, 2019

DOI: 10.1089/jayao.2019.0033

Comparison of Patient-Reported Outcome Measures for Use as Performance Metrics in Adolescent and Young Adult Psychosocial Cancer Care

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Purpose: To compare the Cancer Distress Scales for Adolescents and Young Adults (CDS-AYA)—Emotional and Impact scales—with the Edmonton Symptom Assessment Scale–revised (ESAS-r), Hospital Anxiety and Depression Scale (HADS), and the National Comprehensive Cancer Network Distress Thermometer (NCCN-DT) for use as a patient-reported outcome—performance measure (PRO-PM) for AYA cancer care.
Methods: Data were collected as part of the field test study of CDS-AYA. Assessment criteria were based on a National Quality Forum report. Internal and test-retest (TRT) reliability was assessed using Cronbach's alpha and intraclass correlation coefficients, respectively. A content sort of items in each scale was performed to determine AYA-specific content. Two predefined hypotheses for gender and treatment status were assessed using *t*-test.
Results: Four hundred twenty-one participants were included in the analyses. Cronbach's alpha ranged from 0.79 to 0.94, with only the two scales of CDS-AYA achieving >0.90. TRT reliability for HADS was considered excellent (>0.90), with remaining scales having moderate to good reliability (>0.70). Only the Impact scale of CDS-AYA had items that addressed the specific concerns of AYAs (e.g., romantic relationships). In all scales, active therapy patients had higher levels of distress than patients not receiving treatment ($p \leq 0.05$). Distress was greater for females than males for all scales, but nonsignificant for both the ESAS-r ($p=0.07$) and the HADS depression subscale ($p=0.13$). The proportion of AYAs screening positive for distress varied by instrument.
Conclusion: The Impact scale of CDS-AYA met the most criteria for selection of a PROM for use in performance measurement for the AYA cancer population.

Keywords: CDS-AYA, ESAS, HADS, NCCN-DT, distress, screening, performance measure, indicator

Introduction

ADOLESCENTS AND YOUNG adults (AYAs, 15–39 years of age) with cancer require an approach to psychosocial care, unlike that of children or adults, which considers their developmental stage and associated unique needs.[1] Important psychosocial concerns in the AYA cancer population can include: increased reliance on family after gaining independence, isolation from peers, and interference of cancer with education or career development.[1,2] To address these concerns, AYA-specific health care programs that are flexible with AYA-specific support and resources are needed.[1] AYA psychosocial care plans are also necessary to enable routine psychosocial screening and to help patients gain access to AYA-specific psychosocial experts and community resources.[3]

To ensure that newly developed programs and treatments are improving outcomes in this population, it is necessary to have appropriate metrics. A recent report identified a lack of suitable metrics for performance measurement in psychosocial care of AYAs with cancer.[4] Performance measures (PMs) provide a *quantification of health care quality for health care entities such as hospitals or long-term care homes* (e.g., proportion of patients meeting a target wait time for diagnostics). These measures can capture many different types of outcomes, including patient-reported outcomes (PROs) such as quality of life.[5] A PRO-PM is a type of metric captured using a patient-reported outcome measure (PROM) that provides the patient's perspective on aspects of care and well-being that are important to them (e.g., proportion of patients reporting high levels of satisfaction with care).[5] The

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use of PRO-PMs may be particularly important in the area of psychosocial care where many outcomes such as depression, anxiety, and distress are not readily observable. Distress has been recognized as an important issue in the area of psychosocial care of all cancer patients, and screening for distress is recommended.[6] The importance of measuring distress as an outcome in cancer care has been previously described[7,8] along with its significance to AYA-aged cancer patients and survivors.[1–3,9]

There are many different PROMs that measure distress in the cancer population[10]; however, many have not been evaluated for use in AYAs.[11] In Canada, the Edmonton Symptom Assessment Scale–revised (ESAS-r) has been selected for use in cancer distress screening.[7,8] Although the ESAS-r is extensively used and validated, most work has been done in adult cancer populations.[12,13] The National Comprehensive Cancer Network (NCCN) Distress Thermometer (DT) is another instrument commonly used internationally.[14,15] Recklitis et al.[16] compared the NCCN-DT with a psychiatric diagnostic interview in a young adult cancer survivor population. This study concluded that the NCCN-DT should not be used as a stand-alone screening tool in this population because it did not meet the criteria for acceptable sensitivity or specificity.[16]

An AYA-specific tool to measure distress, developed in Australia, comprises a detailed problem checklist (PCL) and modified distress thermometer. This tool served as the basis for the recently developed Cancer Distress Scales (CDS)-AYA, a set of scales designed specifically for this population.[11,17] The CDS-AYA have not yet been extensively used in research or clinical practice.[17] Given the number of PROMs used to measure distress in cancer patients that are not AYA specific, it is important to evaluate PROMs for use in the development of PRO-PMs for the AYA cancer population.

The National Quality Forum (NQF) uses four criteria to endorse a PRO-PM, including importance, scientific acceptability, feasibility, and usability.[18] Patient-centered measurement is a key recommendation from the NQF for developing PRO-PMs to ensure that the selected PROM is both meaningful and valued by the target population.[18–20] In an article commissioned by NQF, Cella et al.[21] further describe the characteristics to consider when selecting an instrument to develop a PRO-PM, including (1) a conceptual and measurement model; (2) reliability (internal consistency and test-retest [TRT]); (3) validity (content, construct, criterion, and responsiveness); (4) interpretability of scores (minimally important differences, reference means, and interpretation guide); (5) burden (time and effort for both respondent and administrator); (6) alternative modes of administration (e.g., phone and touch screen); (7) cultural and language adaptations; and (8) electronic health records (e.g., automated real-time scoring).

The purpose of this study was to assess the CDS-AYA, ESAS-r, Hospital Anxiety and Depression Scale (HADS), and NCCN-DT for use in performance measurement for AYA cancer care.

Methods

Participants

AYAs were defined as persons aged 15–39 years consistent with the LIVESTRONG Young Adult Alliance[22] and Canadian Partnership Against Cancer (CPAC)[4] definitions. Participants were included if they had been diagnosed with cancer and were either undergoing or had completed treatment.

Data collection

This study used data collected for the field test of CDS-AYAs (see Tsangaris et al.[17] for detailed methods). Ethics approval was obtained from all institutions. Questionnaires were completed during a clinic visit and the package included self-complete demographic and clinical information, CDS-AYAs, NCCN-DT, ESAS-r, and HADS.

Measurement instruments

Cancer Distress Scales for Adolescents and Young Adults. CDS-AYA consist of 5 scales: Impact of Cancer (Impact-12 items), Physical (13 items), Emotional (11 items), Cognitive (8 items), and Cancer Worry (5 items).[17] Respondents are asked to indicate how much distress they experienced in the past week for each scale using four response options (none, mild, moderate, and severe). Item scores are summed within each scale and transformed onto a scale of 0–100, with higher scores reflecting more distress. Each scale functions independently (no total score across the five scales). Cut-points for the Impact of Cancer and Emotional scales have the best sensitivity and specificity[23] and were selected for evaluation in this study. The presence of distress is defined in the Impact of Cancer scale as scores ≥ 24 and the Emotional scale as scores ≥ 27.[23]

Edmonton Symptom Assessment Scale–Revised. The ESAS-r is a 9-item symptom scale with 11 response options ranging from 0 (none) to 10 (severe). The questionnaire asks respondents to circle one number based on how they feel at the time of completion. The ESAS along with the Canadian PCL[24] is recommended for distress screening of cancer patients in Canada.[6] According to implementation guidelines, any score ≥ 4 on the anxiety or depression symptom item requires action to address psychosocial distress.[8]

Distress Thermometer. The NCCN-DT[25] asks patients to rate their level of distress in the past week on a scale from 0 (no distress) to 10 (highest level of distress). In the screening process, a response of ≥ 4 should prompt clinicians to ask additional questions.[26] The NCCN-DT is administered along with the PCL, which was not used in this study.

Hospital Anxiety and Depression Scale. The HADS[27,28] was selected because of its use as a screening tool for cancer patients.[29] The HADS has 14 items (7 depression and 7 anxiety items), with 4 response options. The total score ranges from 0 to 21 for each scale, with higher scores indicating more symptoms of depression or anxiety.[27,28] The questionnaire asks participants to answer based on the past week. Recommended categories for identifying anxiety or depression in the subscales are <8 = normal, 8 through 10 = borderline abnormal, and 11 through 21 = abnormal.[27,28] For this study, both the subscales and overall scores were examined. The cut-point for the HADS total score varies in the literature; in this study, a score of >16 was considered to be distressed.[30]

Analyses. Analyses were completed using SPSS 25.0 (IBM SPSS Statistics, Version 25; IBM Corp); statistical significance was $p<0.05$. Only participants with complete clinical information and questionnaire data for the CDS-AYA (Impact and Emotional scales), ESAS-r, imputed HADS, and NCCN-DT were included in analyses. The HADS was imputed using the half-rule, where the mean of the subscale was used if less than 50% of the data were missing. Participants were classified as either distressed or not distressed, according to identified scale cut-points.

Criteria for comparing PROMs for use in performance measurement were adapted from the study by Cella et al. (Table 4).[18] Five of the 8 characteristics presented by Cella et al.[21] are considered required evidence for a PRO-PM.[31] For the purposes of this article, four of these five criteria were assessed, including reliability, validity, interpretability, and burden.[21] The fifth criterion, conceptual and measurement model, refers to the definition and description of concepts and how they are organized into a conceptual framework. This criterion was not evaluated because a detailed literature review would have been required, which was beyond the scope of this study.

Reliability

Internal consistency and TRT reliability were assessed using Cronbach's alpha and the intraclass correlation coefficient (ICC), respectively. ICC values were interpreted as follows: <0.5 poor, 0.5–0.75 moderate, 0.75–0.90 good, and ≥0.9 excellent.[32]

Validity

Participant characteristics for development of each scale were collected from the literature. A concept sort was conducted by two researchers to assess content validity for AYA cancer patients. The items in each scale were categorized by major and minor themes. Examples of major themes included emotional, impact of cancer, and physical.[17] These themes were elicited from the cognitive development interview process of CDS-AYA.[17] Minor themes were developed from scale items. AYA-relevant content was based on concepts described in the literature relating to psychosocial care.[1,33,34] The following concepts were considered to be AYA relevant: appearance changes, relationships (peer, family, and romantic), participation (returning to social roles and normalcy), identity, independence, health literacy, fertility, education, and finance. The proportion of AYA-relevant content in each scale was calculated.

To assess construct validity, differences between factors known to be associated with distress, including gender (male or female) and treatment status (on or off treatment), were assessed using a *t*-test. Based on the literature, it is expected that females[35] and those currently on treatment should have poorer outcomes on the measurement scales.[36–40]

Interpretability and burden

Literature values for cut-points were reported for interpretability of the scale. The number of items in each scale was also summarized to provide an indication of respondent burden.

Comparison of PROMs

The proportion of patients screening positive for distress was calculated by gender and treatment status for each scale, and differences were assessed using a chi-square test. Variables for stratification were chosen because of known differences in distress by gender[35] and treatment status.[36–40]

Results

There were 515 participants in the field test of CDS-AYA, of which 86 completed the TRT. From the field test participants, 421 had complete clinical and scale data and were included in analyses. Cancer diagnoses of participants were heterogeneous with most classified as carcinoma, leukemia, lymphoma, or sarcoma. For TRT, 81% participants had complete data for all the scales and were included in reliability analyses. Clinical and demographic statistics are displayed in Table 1.

A summary of characteristics for evaluation of PROMs for use in performance measurement is provided in Table 2.

Reliability

For internal consistency, Cronbach's alpha ranged from 0.79 to 0.94, with only the two scales of CDS-AYA, Emotional and Impact of Cancer, achieving above the recommended >0.90 cut-point. The TRT reliability for the HADS overall was considered excellent (>0.90), with remaining scales having good reliability (>0.75), except for the NCCN-DT (0.73) with an ICC slightly below 0.75.

Validity

A summary of scale content by major and minor themes is displayed in Table 3. The majority of items in the scales fell under the emotional theme with most under the minor theme of anxiety. These included items such as feeling worried (CDS-AYA—Emotional) and sudden feeling of panic (HADS—anxiety). The ESAS-r primarily focused on the physical theme with items associated with the minor theme, symptoms, such as pain, nausea, and tiredness. Only the Impact scale of CDS-AYA and HADS depression subscale had items that were associated with the impact theme such as enjoyment of things (HADS—depression). All scales, except

TABLE 1. DEMOGRAPHIC AND CLINICAL STATISTICS

	Field test (n=515)		*Analysis sample (n=421)*	
	N	%	n	%
Age at survey				
15–19 years	127	24.7	103	24.5
20–29 years	226	43.9	194	46.1
30–39 years	162	31.4	124	29.5
Gender				
Male	289	56.1	234	55.6
Female	225	43.7	187	44.4
Treatment status				
Active treatment	277	53.8	202	48.0
Treatment complete or not required	229	44.5	219	52.0

TABLE 2. CHARACTERISTICS FOR EVALUATION OF PATIENT-REPORTED OUTCOMES FOR USE IN PERFORMANCE MEASUREMENT (ADAPTED FROM TABLE 4 OF CELLA ET AL.[18])

Criteria (N = *421*)		*CDS-AYA Emotional (0–100)*[a]	*CDS-AYA Impact of cancer (0–100)*[a]	*ESAS-r (0–100)*	*NCCN DT (0–10)*	*HADS overall (0–42)*	*HADS anxiety (0–21)*	*HADS depression (0–21)*
Reliability—Internal consistency	*Cronbach's alpha ≥ 0.90 individual level*	0.936	0.940	0.880	N/A	0.876	0.851	0.793
Reliability—Test retest	ICC (95% confidence intervals)	0.853*** (0.763, 0.908)	0.855*** (0.768, 0.910)	0.836*** (0.736, 0.898)	0.728*** (0.562, 0.831)	0.910*** (0.856, 0.944)	0.862*** (0.769, 0.916)	0.864*** (0.773, 0.917)
Content validity—*How well the scale captures all aspects of a construct for the target population of AYA cancer patients*	Age range in the development process (years)	15–39[17]	15–39[17]	Median age 56—interview 61—field test[24]	52–88[25]	16–65[28]	16–65[28]	16–65[28]
	Target condition in development	Cancer active treatment and survivorship[17]	Cancer active treatment and survivorship[17]	Advanced cancer[24]	Prostate cancer[25]	General outpatient clinics[28]	General outpatient clinics[28]	General outpatient clinics[28]
	AYA cancer patients involved in content development	Exclusively	Exclusively	AYAs not excluded, mostly older adults involved	Older adults in the original phase of development	AYAs involved not cancer patients	AYAs involved not cancer patients	AYAs involved not cancer patients
	Patient-centered questions (proportion of items relevant to AYAs)	0%	75%	0%	0%	0%	0%	0%
Construct Validity—*Support of predefined hypotheses for differences in scores between known groups*	*Females score poorer than males [mean diff (SE)] Males–females*	–6.2 (1.9)***	–5.1 (1.9)**	–2.6 (1.4) ($p = 0.068$)	–0.55 (0.24)*	–1.6 (0.67)*	–1.1 (0.41)*	–0.52 (0.35) ($p = 0.133$)
	Active treatment patients score poorer than patients who have completed treatment Active-completed	9.0 (1.9)***	16.6 (1.8)***	6.9 (1.4)***	0.67 (0.24)**	2.7 (0.66)***	0.84 (0.41)*	1.8 (0.33)***
Interpretability—*Are there ways to interpret what scores and differences mean?*	*Cut-points*	≥27	≥24	≥4 on the anxiety or depression symptom item	≥4	>16	>8	>8
Burden—*How much time and effort does it take for respondents or administrators to complete?*	*Number of items*	11	12	10	1	14	7	7

[a]Slight deviations may occur from values reported in the development article[17] due to the use of a smaller sample size to ensure complete data for all scales.
***$p < 0.001$.
**$p < 0.01$.
*$p < 0.05$.
HADS, hospital anxiety and depression scale; SD, standard deviation; SE, standard error; N/A, not applicable; CDS, cancer distress scale; AYAs, adolescents and young adults; ESAS-r, edmonton symptom assessment scale-revised; NCCN, national comprehensive cancer network; DT, distress thermometer.

TABLE 3. SUMMARY OF SCALE CONTENT BY MAJOR AND MINOR THEMES

	Emotional								*Impact*				*Physical*		*Other*	*Summary*	
	Anger/frustration	*Anxiety*	*Depression*	*Grief/loss*	*Guilt*	*Helpless*	*Hopeless*	***Total***	*Wellbeing*	***Total***	*Self-perception*	*Relationships*	*Participation*	*Enjoyment*	*Total*	*Total number of items*	*Number of AYA-specific items*
CDS-AYA—Emotional	1	3	2	1	1	1	1	11	1	0					0	11	0
CDS-AYA—Impact								0		12	5	4	3			12	9
ESAS-r		1	1					2		0					6	10	0
HADS—Anx		7						7		0						7	0
HADS—Dep			1					3	2	3				3	1	7	0
NCCN-DT																1	0

HADS-Anx, HADS Anxiety; HADS-Dep, HADS Depression.

the Impact scale of CDS-AYA, lacked items considered relevant to unique concerns of AYAs. In the Impact scale of CDS-AYA, items relevant to AYAs included the impact of cancer on identity, level of independence, family relationships, keeping up with peer achievements, ability to do normal activities, participating fully in life, making new friends, and romantic relationships. Many of the scales captured more general concepts such as feeling tense or wound up (HADS—anxiety), pain (ESAS-r), and feeling sad (CDS-AYA—Emotional), which are more broadly applicable.

For construct validity, all the scales supported the hypothesis that active therapy patients have higher levels of distress than patients not receiving treatment ($p \leq 0.05$). More distress was observed in female than male participants for all scales; however, differences were not significant for the ESAS-r ($p=0.068$) and HADS depression ($p=0.133$) scales.

Interpretability and burden

For interpretability, all scales had defined cut-points. The length of the scales ranged from 1 to 14 items, with all scales viewable on a single page.

Comparison of PROMs

The proportion of AYAs who were on treatment and screened positive for distress ranged from 20.9% to 61.8% and 23.9% to 70.6% in males and females, respectively (Fig. 1). For off-treatment patients, the proportion that screened positive for distress ranged from 9.7% to 27.4% for males and 10.5% to 43.2% for females. The CDS-AYA (Emotional and Impact scales) classified a larger proportion of on-treatment patients as distressed compared with the ESAS-r, NCCN-DT, and HADS for both females and males ($p \leq 0.001$; Fig. 1). For off-treatment males and females, the HADS overall score and HADS depression subscale classified a smaller proportion of patients as distressed compared with CDS-AYA (Emotional and Impact scales), ESAS-r, and NCCN-DT ($p \leq 0.006$; Fig. 1).

Discussion

Overall, the majority of scales examined in this study met the Cella et al.[21] characteristics for selection of a PROM for PM. The scales had good internal consistency and reliability and were generally brief and interpretable. The greatest difference among the scales was related to content validity. The CDS-AYA scales were the only metrics explicitly designed for the AYA cancer population,[17] using patient interviews to ensure content validity.

AYA-relevant psychosocial concerns[1,32,33] were not predominant in the scales examined. Many areas of distress important to AYAs with cancer were not represented, such as distress related to cancer worry, cognitive problems, employment, and education.[17] For the three major themes (emotional, impact, and physical) observed in this article, most of the scale's items were limited to just one major theme. By not capturing all areas of distress experienced by patients, it is possible that some patients with distress may be missed in screening. Clinically, this gap could be overcome using checklists such as those included in the ESAS-r and NCCN-DT. However, checklists have important limitations

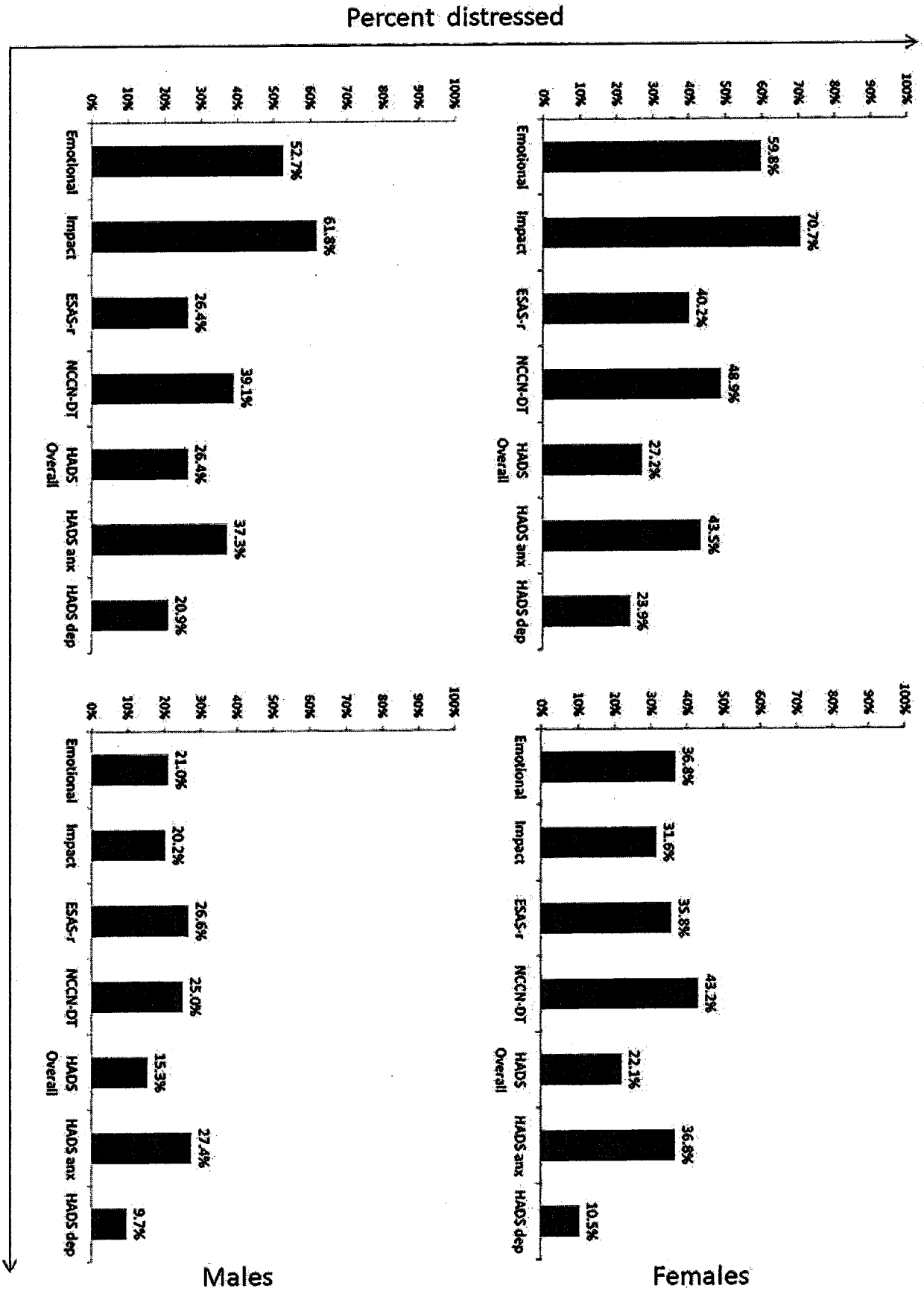

FIG. 1. Proportion of AYAs who screened positive for distress by instrument. AYAs, adolescents and young adults.

and do not have the same psychometric properties as scales. An important aspect of a scale is that it can be used to examine change over time in varying degrees of distress rather than just the presence or absence of symptoms of distress. CDS-AYA have additional scales[17] covering other areas of distress that are important to AYAs, although administration of all the scales may be burdensome for screening purposes.

Many of the items in the scales described concepts such as worry, fatigue, and pain that could be considered more broadly applicable in the cancer population. Most issues in the psychosocial care of AYAs with cancer relate to their stage of development. During the AYA period, individuals are reaching key milestones, including developing an identity, self-image, independence, increased involvement in relationships and dating, and important decisions regarding education, career, and family.[2]

The Impact of cancer scale of CDS-AYA was the only scale that specifically captured some of these key concepts. This included items on keeping up with achievements of peers and normalcy. These are both important issues to AYAs with cancer who are missing out on the experiences of their peers such as going to the prom, attending higher education, and starting careers and families.[1,32,33] Aspects of identity and level of independence captured by the Impact scale are also very important to AYAs who become more reliant on family during their illness and are missing out on key experiences that help them form their self-identity (going away to university).[1,32,33] The Impact scale of CDS-AYA also has relationship items (e.g., impact of cancer on romantic relationships). This is important to AYAs because cancer can interfere or change relationships with both family and peers. Relationship concerns can include making friends, protecting parents, and developing romantic relationships (disclosure of cancer or fertility).[2,10,41] Having specific content that captures the unique concerns of AYAs with cancer may help to better measure distress in this population.

There was substantial variation in the prevalence of distress identified when using different PROMs in this study. Literature reports of distress in AYAs with cancer have been previously described and are also highly variable.[42] Enskar and von Essen[38] reported that more than 50% of AYA cancer patients and survivors reported psychosocial distress in 12 of 13 aspects that were measured. Recklitis et al.[16] found that 49.4% of AYA cancer survivors had moderate or high distress levels on the NCCN-DT. Clinical levels of distress in AYA cancer, where a patient meets the criteria for diagnosis of a mental disorder such as post-traumatic stress disorder, have also been found to be variable, ranging from 5.4% to 56.5% in a 2013 review.[43] The variations between scales in this study are likely related to differences in the distress construct measured. Given the variability in estimates produced by different scales, it is unlikely that distress as a performance measure would be comparable across institutions, provinces, or countries using different PROMs. In the selection of a scale for a distress PRO-PM, it is important to consider the patient-centered nature of the PROM to ensure that it captures the aspects of distress most important to the target population.

A limitation of this study is that clinical interviews were not conducted to definitely diagnose distress, therefore scales could not be compared with gold standard diagnostics. Further work is needed to compare screening scales used in the AYA cancer population with gold standard interviews to determine how accurately these instruments classify distress in this age group. In addition, examining changes in distress is an important aspect for a performance measure and the inability to assess responsiveness is a limitation. This study also did not include the PCL, a component of the NCCN-DT. A protocol for use of the NCCN-DT with a modified PCL in the AYA cancer population has been developed and is currently being validated in Australia for use in distress screening.[44] However, the PCL does not contribute to the scoring of the NCCN-DT.

Given that the Impact scale content of CDS-AYA is highly relevant to AYA cancer patients, this scale met the most criteria for selection of a PROM for use in performance measurement. However, this scale has limitations because it does not capture aspects of distress outside of the impact of cancer theme. Domains such as physical and emotional distress are also highly relevant to AYAs with cancer, and the effect on screening within a single theme is unknown. Further work could look at the application of all the CDS-AYA in distress screening through the use of computer adaptive testing (CAT). A recent study of a PROM for patients with a cleft lip and/or palate was able to use CAT to reduce the 12-scale 110-item CLEFT-Q to a mean of 43 items.[45] Using CAT with CDS-AYAs may allow administration of all five scales using fewer items to greatly reduce respondent burden. Development of benchmarks for CDS-AYA is also necessary before it can be used in performance measurement.

Acknowledgments

This study was conducted with support from the C17 Council and funded by the Childhood Cancer Canada Foundation and the Kids With Cancer Society. The authors would also like to acknowledge Abha Gupta, Dilshan Pieris, Kate Wang, Seline Tam, Nivetha Ramachandran, Colleen Fitzgerald, Sarah McKillop, and Linda Churcher for their contributions. The authors would also like to acknowledge Pandora Patterson, Michael Osborn, and Fiona McDonald—developers of the Australian DT AYA on-treatment and survivorship tools.

Author Disclosure Statement

The authors have no conflicts of interest.

Funding Information

Support provided by the C17 Council through funding from Childhood Cancer Canada Foundation and the Kids with Cancer Society.

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CHAPTER 6: DEVELOPMENT OF AN INDICATOR FOR ONCOFERTILITY CARE

Development and validation of an indicator for oncofertility care in Ontario, Canada for adolescents and young adults with cancer

This study was supported by the Institute for Clinical Evaluative Sciences (ICES) which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred.

ABSTRACT

Introduction: Fertility is an important issue facing adolescents and young adults (AYA) (15-39 years of age) with cancer. However, there is a lack of metrics to monitor and evaluate fertility care in this population. A recent panel proposed the indicator "*proportion of cancer patients who attend a fertility consultation before the start of treatment*" for use in AYA cancer care. The objective of this study was to evaluate a proposed indicator for oncofertility using the National Quality Forum (NQF) criteria: importance to measure and report, scientific acceptability of measure properties (validity and reliability), feasibility, usability and use, and related and competing measures.

Methods: This was a retrospective cohort study using administrative data available through the Institute of Clinical Evaluative Sciences (ICES) in Ontario, Canada. Cases were included if they were diagnosed with a cancer between April 2001 and September 2019, and aged 15-39 years. Fertility consultations were identified by OHIP billing codes 628 (female) and 606 (males).Validity was assessed by examining expected differences in the proportion of fertility consults within clinical and demographic factors using Chi-square tests. Reliability of the indicator was assessed using Pearson's correlation co-efficient. Comparing the primary method of identifying fertility consults visits using OHIP billing codes 628 and 606 with a secondary method using visits to physicians in a registered speciality associated with providing fertility preservation services.

Results: The population was comprised of 49,425 unique individuals, with 7739 (15.7%) identified as having attended a fertility consult. Of the population 28.6% had no record of treatment, mostly within diagnostic years 2000 to 2004. Therefore the primary indicator was redefined as "*proportion of cases attending a fertility consult visit ≤ 30 days from diagnosis of cancer*". For diagnostic years 2016-2019, differences in the proportion of cases receiving their first fertility consult within 30 days of diagnosis were observed for sex, age, cancer type, hospital type, LHIN and region ($p<0.001$). There was a negligible correlation between the time from diagnosis to fertility consult and time from diagnosis to first visit to fertility related speciality ($r=0.11$; $p=0.002$).

Conclusions: The indicator examined in this paper adhered to the five criteria described by the NQF, providing a possible metric for reporting on oncofertility care in system performance reports, with applicability to evaluations of interventions and models of care.

INTRODUCTION

Approximately 7600 adolescents and young adults (AYA), between the ages of 15 and 39 years, are diagnosed with cancer every year in Canada.[1] This age group has unique challenges associated with a diagnosis of cancer due to various factors, including the biology of their disease, delayed diagnosis and psychosocial challenges such as the immense life changes which occur over this time period (e.g. gaining autonomy from parents, career development and starting families).[2-4] However, one of the most important issues for this age group is fertility. During treatment for cancer many children, adolescents and young adults will receive therapies which are damaging to the reproductive organs, potentially leading to future problems with fertility.[5] The emotional and financial impact of the inability to become biological parents can be devastating to young cancer survivors and their families. As many individuals are now delaying the decision to have children until their 30s, there is a growing number of cancer patients at risk for compromised fertility prior to family planning.[6] Due to the increasing awareness of this issue, a new field, Oncofertility, was created to address reproductive matters in cancer survivors in 2006.[7] Oncofertility has been a key priority for many nations, including Canada where this topic has been addressed in national workshops[8,9] and a 2017 national systems performance report on AYA cancer care.[1]

In order to better evaluate interventions and monitor outcomes for Oncofertility meaningful metrics are needed. Currently there are gaps in metrics for examining system performance in fertility preservation services for AYA with cancer.[10] A recent scoping review[10] only identified two indicators pertaining to fertility in this population: ‘‘*number*

of referrals to fertility preservation services for adolescents and young adults with a cancer diagnosis''[11] and "*ratio of incident cases (2015) of cancer in adolescent and young adult women (15–39 years of age) to number of in vitro fertility centers, by province, all cancers*".[1] The latter indicator regarding in vitro fertilisation (IVF) centers was reported on in 2017, as part of a special feature in the Person-Centred Perspective Indicators in Canada: a reference report for AYA with cancer produced by the Canadian Partnership Against Cancer (CPAC).[1] The report highlighted limitations with the indicator as it only provides a perspective on access rather than whether patients were actually being referred for fertility consultations.

Understanding referrals for fertility consultations is important because a key recommendation within 'active and supportive care,' from an international stakeholder's workshop on AYA cancer care, was that "*Fertility risks and options for considering or not considering fertility preservation must be discussed with each patient".* [8] To address this recommendation from Fernandez et al.[8] a Delphi process on indicators for AYA cancer care identified the metric "*proportion of cancer patients who attend a fertility consultation during treatment*".[12] This indicator is also similar to the proposed Australian indicator examining the number of fertility referrals.[11] The importance of this indicator was highlighted in a recent survey looking at fertility options for patients with cancer around the world which identified issues with referrals along with lack of fertility care providers, and dissemination of information as barriers for cancer patients in Canada.[13] Utilizing an indicator to monitor how many AYA attend fertility consultation visits is likely more feasible in Canada than the numbers of patients referred, given

current data availability in administrative databases in which information on physician referrals is not captured readily.

Administrative databases in Ontario have been used previously to describe referral patterns for fertility preservation in a sub-population of AYA aged women with breast cancer and lymphoma.[14,15] The current study will build upon this work to both define and evaluate the proposed indicator the "*proportion of cancer patients who attend a fertility consultation before the start of treatment*," described by the system performance working group of the Canadian Task Force on AYA with Cancer for use in Ontario, Canada.[12] Evaluation of the indicator was based upon the "*Measure Evaluation Criteria and Guidance for Evaluating Measures for Endorsement*" provided by the National Quality Forum (NQF).[16] The NQF is a non-profit based in the United States which endorses healthcare measures as well as recommends measures for use in reporting programs.[17] This paper will assess and discuss the indicator based upon the following five NQF criteria: importance to measure and report, scientific acceptability of measure properties (validity and reliability), feasibility, usability and use, and related and competing measures.

METHODS

We conducted a retrospective cohort study using administrative data available through the Institute of Clinical Evaluative Sciences (ICES) between April 1, 1988 and November 30, 2020. Databases accessed were Ontario Cancer Registry (OCR), Ontario Health Insurance Plan Claims Database (OHIP), ICES Physician Database (IPDB), Registered Persons Database (RPDB), and Cancer Activity Level Reporting (ALR). An overview of study

timeline definition is provided in Figure 1. All analyses were conducted in SAS, through the remote iDAVE server provided by ICES. Ethics approval was obtained from the Hamilton Integrated Research Ethics Board (HiREB).

Population

Eligible participants included those diagnosed with cancer between April 2001 and September 2019, who were 15 to 39 years of age at diagnosis. Participants were excluded if the diagnosis was a secondary cancer, they had a fertility consult anytime preceding 30 days prior to official diagnosis, they were a non-Ontario resident or had a prior sterilization procedure before the diagnosis of cancer. The timeframe included 30 days prior to diagnosis to account for any delays in the formal date of diagnosis. Sterilization procedures included hysterectomy, oophorectomy, and tubal ligation which were identified using OHIP billing codes (See Table 1).

Data

Cancer cases were obtained from the Ontario Cancer Registry (OCR). Cancer type was defined using the scheme developed by Barr et al[18] for AYA cancers based on ICD O-3 for morphology, topology and behaviour obtained from OCR. Fertility consults were identified in OHIP using diagnostic code ICD-9 628 for female infertility and 606 for male infertility. Secondarily, fertility visits were identified by a visit to a specialist who is associated with providing fertility services. A cohort of physicians whose main speciality was listed as Endocrinology, Gynaecology-Oncology, or Urology was created from IPDB to identify visits for a fertility consult in OHIP between April 1 2013 and March 31st 2017, the time period in which IPDB is valid. Clinical data were obtained from OCR and ALR, including age at diagnosis, sex, diagnosis year, hospital type, Local Health

Integration Network (LHIN). Regions were classified according to LHINs as follows: North, Central, South west, South east, South. Treatment information collected included the first date present in ALR for radiation and chemotherapy. ALR is mainly focused on systemic and radiation therapy services and only captures surgical data from Regional Cancer Centers (RCCs). Most cancer surgeries do not have a direct impact on fertility and were excluded from these analyses. However surgery for reproductive organ cancers can have a significant impact and therefore were included in analyses. These procedures were identified using OHIP billing codes which have been described previously for gynecological cancers (Table 1).[19] A review of OHIP billing codes for surgical procedures related to testicular cancers (excluding biopsies) found two codes for orchidectomy and one code for radical orchidectomy for malignancy with retroperitoneal lymph node dissection (See Table 1). These codes were used to identify the first surgical visit with potential to impact fertility which occurred between 30 days prior to the diagnosis date and 2 years after diagnosis.

Indicator

The indicator proposed by Rae et al[12] was modified slightly to examine the proportion of visits which occur before the start of treatment (i.e. chemotherapy, radiation, or surgery related to reproductive organs), which is the optimal time window to begin fertility preservation to ensure any harmful effects of treatment are avoided. The indicator examined in this study is "*proportion of cancer patients who attend a fertility consultation before the start of treatment (reproductive related surgery, radiation, or chemotherapy)*". This is considered a process indicator based upon resource use

(attendance of a fertility consult visit with a physician). The numerator included cases which had a service visit to a physician billed as diagnostic code ICD-9 628 for female infertility or 606 for male infertility that occurred before the earliest date of treatment recorded in ALR as described above. The denominator comprised all diagnoses of AYA cancers in the time period. Those with secondary cancers, prior sterilization procedures, or a fertility consult 30 days before diagnosis were excluded because fertility in these patients may have been compromised, so influencing their decision to attend a fertility consult. An overview of the framework of the use of the indicator in clinical practice is provided in Figure 2.

Analysis

Data Quality & Sample Characteristics

Descriptive statistics were calculated for clinical and demographic variables for the population, including percent missing data. Proportions of AYA with cancer who attended a fertility consult before, during, and after treatment were also calculated. The available administrative data do not provide an end of treatment date for patients, therefore "after treatment" was considered any date occurring two years or longer after the date of diagnosis.

Validity

Differences in the proportion of fertility consults occurring before treatment by sex, year of diagnosis, age at diagnosis, cancer diagnosis, institution type, region, and LHIN were assessed using Chi-square tests. These variables were selected to determine if differences exist in important clinical or system factors to which quality initiatives could be focused. Hypotheses for expected differences by factor are provided in Table 2.

Reliability

Reliability of the indicator was assessed using a secondary method of identifying fertility consult visits through the use of visits to physicians in a registered speciality associated with providing fertility preservation services, namely Endocrinology, Gynaecology-Oncology, or Urology. The specialities were identified in IPBD and linked to OHIP to identify visits starting 30 days prior to diagnosis onwards. The Pearson correlation coefficient was calculated to examine the association between the two methods of identifying fertility consult visits. Correlation coefficients were interpreted as follows: 0-0.1 negligible, 0.11-0.39 weak, 0.40-0.69 moderate, 0.70-0.89 strong, and 0.90-1.00 very strong.[20] Also, the distribution of the sex-specific diagnostic code ICD-9 for fertility consults visits was assessed by sex, to determine the occurrence of misclassification.

RESULTS

Demographics and Data Quality

The entire sample was comprised of 49,425 unique individuals, with 7739 (15.7%) identified as having the outcome of interest, attending a fertility consult (Table 3). In the sample, 14,144 (28.6%) had no treatment data (chemotherapy or radiation or surgery at an RCC) in ALR or a record of reproductive related cancer surgery in OHIP. Of the remaining cases, 3587 (11.5%) had values for a first treatment visit outside a plausible treatment window of 30 days prior to diagnosis or two years after diagnosis (Table 4). The percentage of cases with no treatment data varied by diagnosis, with <10% missing for reproductive cancers, Hodgkin lymphoma, and breast cancers. All other cancer diagnoses had greater than 20% of cases with no record of chemotherapy, radiation, surgery at RCC or surgery for reproductive cancer (OHIP). This was considered not

plausible for the majority of cancers which are likely to receive at least some chemotherapy. Therefore, it was decided to exclude cases with no treatment record. Also values outside a plausible treatment window of 30 days prior to diagnosis or two years after diagnosis were excluded from analyses. This left 35,715 cases with valid values for treatment data in the analysis. The percentage of cases with no treatment data was greatest for diagnosis years 2000-2004, ranging from 31.2% to 44.3%, which is likely attributable to RCCs not starting to submit directly to ALR until 2005/2006. So it was decided to remove this time period from the remainder of analyses. Given the loss of the sample due to missing treatment data, it was decided to analyze a second indicator based on the time from diagnosis to fertility consult as a proxy for start of treatment. The diagnosis date was available for the entire sample. The new indicator was defined as the "*proportion of cases attending a fertility consult visit ≤ 30 days from diagnosis of cancer*". Thirty days from diagnosis was chosen as a cut-off as it is expected that some treatment should begin within this window. This was considered the primary indicator for analyses, and the indicator "*proportion of cancer patients who attend a fertility consultation before the start of treatment (reproductive related surgery, radiation, or chemotherapy)*" was used for purposes of comparison.

Outcome

The majority of cases did not have any recorded visit for a fertility consult in OHIP (84%). Overall 7% of cases attended their first fertility consult within 30 days of diagnosis, and 10% beyond 30 days from diagnosis. A 6% increase in the proportion of first fertility consults within 30 days of diagnosis was observed between the earliest time

period (2004-2010) and the most recent diagnosis years (2016-2019) (Figure 3). Similar results were observed for the comparative indicator examining the proportion of first fertility consults before the start of treatment (Figure 3).

Validity

There was a significant increase in the proportion of first fertility consults attended in later diagnostic years (X^2 =789.7; df 3; p<0.0001) (Figure 4). Therefore, all validity analyses testing hypotheses proposed in Table 2 were performed in the most recent diagnosis year group, '2016-2019'. Differences in the proportion of cases receiving their first fertility consult within 30 days of diagnosis were observed for sex, age, cancer type, hospital type, LHIN and region (p<0.001; Table 5). The predefined hypotheses were all met. Overall the proportion attending fertility visits was greatest among males, younger age groups, pediatric hospitals, and central regions (p<0.001). Results did not differ for the comparator indicator, except for sex for which there were no differences in the proportions of males and females attending a fertility consult before the start of treatment (X^2=1.8; df 1; p=0.17). However, when comparing percentages between indicators, values tended to be greater in the indicator examining the proportion attending visits within 30 days of diagnosis, with most notable differences by cancer diagnosis. Trends over time for each indicator are shown in Figure 5 for sex, and Figures 6 and 7 for males and females, respectively, by age group. Overall trends were similar; however, some decreases in proportions attending fertility consults were observed in later diagnosis years for the indicator examining visits before treatment.

Reliability

There were misclassifications based on sex for both the male and female OHIP billing codes for a Fertility consult. In the full dataset (n=49,425), for females 0.3% of visits were incorrectly assigned the OHIP billing code for males 606, while 48% of males were assigned the OHIP billing code for females of 628. After removal of the '2000-2004' diagnosis group, misclassification was similar with 0.2% and 50.5% for females and males, respectively.

Correlations were examined on the entire dataset for the time period between April 1st, 2013 and March 31st, 2017. There was a negligible correlation between the time from diagnosis to fertility consult and time from diagnosis to first visit to fertility related speciality (r=0.11). Examining each speciality separately, there was no correlation between the number of days from diagnosis to fertility consult for either the number of days from diagnosis to a visit to an Endocrinologist (p=0.54) or Urologist (p=0.22). There was a weak correlation between time to fertility consult and time to a visit with Gynaecology-Oncology specialist (r=0.31; p<0.001).

DISCUSSION

This paper examined the indicator "*proportion of AYA with cancer who attend a fertility consultation ≤30 days from diagnosis of cancer*". The originally proposed indicator "*proportion of AYA with cancer who attend a fertility consultation before the start of treatment*" was used as a comparator due to the problem of a high proportion of missing treatment data. The technical definition for each indicator is provided in Table 6. Overall the results for the two indicators were similar, suggesting that *≤30 days from*

diagnosis of cancer may serve as a suitable proxy for the start of treatment. The small differences observed between results for the two indicators may be attributable to incorrect or incomplete treatment data. The 5 NQF criteria - importance to measure and report, scientific acceptability of measure properties (validity and reliability), feasibility, and usability and use, and related and competing measures, for this indicator in the context of the results are discussed below.[16]

IMPORTANCE TO MEASURE AND REPORT

In order for a metric to help make gains in the quality of care provided, it needs to demonstrate variation in the care across patient sub-groups or services, or overall less than optimal performance. This concept is "the importance to measure and report" the first criterion of NQF.[16] The potential effects of cancer treatment on future fertility are well documented.[21-25] Ensuring that patients are well informed about potential risks and are provided with options for fertility preservation in a timely manner is an important focus for the quality of cancer care for AYA.[26] Studies have found that fertility preservation is an important issue for cancer patients with the potential to improve long-term quality of life. A study of 560 women undergoing cancer treatment found that specialized counseling about fertility preservation options reduced regret and improved overall quality of life.[27] Fertility was also identified as top priority in terms of a life goal in a small sample of adolescent males.[28] Further, in a recent systematic scoping review, Anazodo et al[26] concluded that, despite the existence of multiple guidelines and models of care for oncofertility, the use of fertility preservation services in cancer patients was still low and that there was variability in the quality of fertility care provided. This supports

the need for metrics to aid in quality improvements and evaluate patient outcomes in this area.

Because the discussion of fertility risks or the utilization of fertility preservation services is not a data element captured readily in administrative databases for cancer patients, we need to look at a secondary measure which could capture related events such as those patients who have a fertility consult with a specialist. The results of this study found relatively low rates of fertility consultations for males (2.2%-17.9%) and females (2.4%-12.3%) which have increased over time. These results are consistent with a recent study which surveyed AYA with cancer across Canada and found that uptake of fertility preservation remained low, with only 13% of respondents reporting that they undertook fertility preservation options after the diagnosis of cancer.[29] Also, two recent studies in Ontario, using administrative data, reported fertility consult rates of 8% and 10.7%, for women with lymphoma and breast cancer respectively.[14,15] Yee et al[30] reported in 2013 that the use of sperm banking for male cancer patients was low in Canadian fertility clinics. These low rates support the less than optimal performance in this metric. This study also identified variations in both regions and LHINs, most notably between patients treated in northern (5%) and central (15%) regions, providing areas on which to focus improved efforts, such as increasing access to fertility services which may be lacking in northern regions, especially for women. There were also variations by cancer type with breast cancer having some of the highest rates of referral. Some variation may be related to the risk to fertility posed by the cancer type. However, patients with breast cancer had a greater proportion attending fertility consultations than both females and males with

reproductive organ cancers. This may be attributed to work which has focused specifically on the breast cancer population. In a recent review[31] of fertility preservation, patient decision aids for cancer patients identified 11 papers and 9 decision aids. Of the 9 decision aids available two were specific to breast cancer. No other decision aid was specific to a particular cancer type. There is also a breast cancer specific decision aid developed in Toronto which is breast cancer specific and not identified in the previous review.[32,33] It is possible that disease specific approaches at some of the larger health care institutions in Ontario may contribute to greater uptake in fertility consultation services in this population observed in this study, creating an opportunity for improvement related to other cancers associated with a high risk to fertility. Overall, the findings of this study support the "Important to measure" criteria with less than optimal performance related to attendance for fertility consultations by cancer patients, as well as variability in rates by multiple factors.

SCIENTIFIC ACCEPTABILITY OF MEASUREMENT PROPERTIES

The scientific acceptability of an indicator is defined as the "*extent to which the measure, as specified, produces consistent (reliable) and credible (valid) results about the quality of care when implemented*."[16] This study assessed the validity of results by examining the indicator to look for expected differences in clinical factors. An important aspect of quality is that the metric will improve with interventions aimed at enhancing the process or outcome of interest. In Ontario many initiatives have been undertaken which should lead to increases in the rate of fertility consults by cancer patients. In the earliest timeframe examined by this study most interventions centered around awareness, starting

with the creation of the field of Oncofertility in 2006.[7] The Canadian National Task Force on AYA with Cancer was established in 2008, holding international stakeholder workshops in 2010 and 2012.[8,9,34] Other notable occurrences include the start of the charitable organization Fertile Future in 2008, that provides support to cancer patients for fertility preservation, as well as oncofertility related information.[35] Further improving options for female cancer patients, oocyte cryopreservation became non-experimental in 2013 with the publication of the first guideline for mature oocyte cryopreservation.[36] This removed the need for a partner or sperm bank donation required for women to undergo embryo cryopreservation, which limited choices especially for younger women who may not be in a long-term relationship at the time of diagnosis. The biggest change in Ontario came in December 2015 with the establishment of the Ontario Fertility Program which provides government funding for one cycle of fertility preservation and IVF for patients with a condition for which planned treatment may lead to infertility.[37] However, the program does not cover the cost of fertility drugs, genetic testing or storage of sperm, eggs and/or embryos, with these costs disproportionately impacting women, for IVF drugs cost upwards of $5000 per cycle and storage costs for both eggs/embryos $250-$500 per year versus just storage costs for banked sperm of $250-$500 per year.[38] Our results appear to improve with the implementation of these various initiatives showing rates of consultations increasing steadily over time, and the most substantial increase occurring in the 2016-2019 time period in which the provincial government started to provide funding. This enhancement was much larger for males, possibly reflecting cost differences, or other considerations such as potential treatment delays for females (8-14 days) while

waiting for fertility preservation procedures which are not as problematic for males who can undergo sperm banking quickly.[39,40] Furthermore, the proposed indicators found regional and LHIN differences which likely reflect differential access to specialized fertility care, with northern regions having the lowest consultation rate. The regional differences have been discussed previously when examining the effect of the Ontario Fertility Program in women, finding the greatest impact in the Greater Toronto Area, attributed to access to fertility care which is more readily available in this region.[41] There was also a decreasing uptake of fertility consultations with age, which may reflect parity, with older individuals who have existing children being less likely to attend a fertility consult. Parity was found to be an important factor in women diagnosed with breast cancer or lymphoma attending fertility consultations.[14,15]

Another important aspect of an indicator is an evidence-based risk-adjustment strategy, adjusting for factors which are present at the start of treatment that may influence the metric. This is important in order to ensure that any comparisons made between regions or sites relate to the quality of care, and not another factor. A strategy to adjust for risk was not proposed in this study because of the current low rates of fertility consultation, given the recommendation that all AYA patients diagnosed with cancer undergo fertility preservation consultation before treatment. However, as rates improve risk-adjustment strategies should be further explored. An important factor that may be considered is the risk to fertility associated with the cancer diagnosis. This could impact comparison of an indicator between hospitals, because some hospitals may only treat

cancers which have lower risks to fertility, such as melanoma which may require surgery only and therefore patients may decide not to pursue fertility consults.

The NQF reliability criterion relates to the consistency of results and is described as "*the measure is well defined and precisely specified so it can be implemented consistently within and across organizations and allows for comparability*".[16] A major issue contributing to reliability of the metrics in this study was the tendency for the OHIP diagnostic code which is sex specific, 628 for females and 606 for males, to be misclassified. This was a greater problem for male visits with almost half of these coded as a female fertility consultation. Some misclassification of these codes may relate to using gender rather than sex when billing. However, rates of misclassification for males were remarkably high, making it unlikely that this is the sole reason for the discrepancy. If both codes are not used when selecting fertility visits the proportion of consults could be underestimated. The OHIP diagnostic codes were also compared to a secondary method of identifying fertility visits which used the first visit to a fertility related specialist. Education programs or further training should be provided to those submitting OHIP codes to help clarify the difference between these codes in order to improve correct use of the codes. This approach only found a weak correlation between fertility visits and visits to gynaecology-oncologists. This method was limited because reproductive endocrinologists are not included in the speciality list available in the IPDB database, and it was not possible to determine if the visit was cancer rather than non-cancer related. Originally it had been proposed to use identification numbers from the College of Physicians and Surgeons of Ontario (CPSO) for physicians who work at fertility clinics

or were registered as reproductive endocrinologists as a secondary method to verify the OHIP diagnostic codes. However, approval to import the list of CPSO numbers into ICES could not be obtained within the timeframe of this study. This should be the focus of future work to ensure the that OHIP diagnostic codes are capturing all fertility consults. Another issue with reliability was the high percentage of missing treatment data in the ALR database which prevented a primary examination of the proportion of first fertility consultations before the start of treatment. A large proportion of patients did not have a single visit for chemotherapy or radiation. The greatest proportion of missing treatment data was for thyroid and melanoma diagnoses. This may be plausible, given that melanoma may be removed by a dermatologist in their office then a referral made to an oncologist with no further cancer treatment required. Thyroid cancer has been the subject of over diagnosis, and it is possible that a large proportion of these cases did not need treatment. Research has looked into the quality of ALR data for breast cancer cases diagnosed between 2006 and 2009, comparing these data to gold standard medical chart abstraction.[42] The study found that 98.8% radiotherapy, 95.5% chemotherapy and 99.9% surgery data for 2,401 women were complete. Missing treatment data was also minimal for this population in our study. There was also a proportion of data for which the timeframe was outside of a plausible window to start treatment, possibly due to an entry error. Further work needs to be done to assess the quality of treatment data for different cancer types and centers before an indicator utilizing treatment dates could be considered reliable. It would also be helpful for ALR to capture all cancer-related surgery data in the province of Ontario, rather than just those surgeries which occur at RCCs. The diagnosis

date was very reliable and available for all participants. Adopting a within 30 day window of diagnosis produced similar results to the indicator looking at visits before the start of treatment. Using the time between diagnosis date and fertility visit is likely more comparable across sites and diseases given the variability in missing treatment data.

FEASIBILITY

Feasibility is defined by the NQF as the "*extent to which the specifications, including measure logic, require data that are readily available or could be captured without undue burden and can be implemented for performance measurement*."[16] Both indicators examined here can be calculated using data readily available through ICES in Ontario, and it is likely that similar data sources would be available across Canada to calculate comparable measures. Looking at fertility consults within 30 days of diagnosis is much more straightforward, requiring the use of only the cancer registry and OHIP database. Also, given that diagnosis date is a common element in most administrative cancer databases, using fertility visits within 30 days of diagnosis as an indicator is likely more feasible at an international level. Using treatment data also required a greater number of steps to process the data in order to calculate the indicator, and resulted in the loss of some of the sample due to missing data. In order to improve the feasibility of using treatment data for this indicator it would be important to capture patients who receive no treatment, as well as a start date of treatment, in administrative databases.

USABILITY AND USE

Part of the NQF criteria includes the usability and use of the indicator for accountability and performance improvement of care at both the patient and population level. The lack of an oncofertility indicator was highlighted as a gap in a Canadian 2017

system performance report which focused on AYA with cancer. The indicator discussed in this paper could be utilized in this capacity to help monitor progress in oncofertility services over time,[1] as well as improving awareness of the issue on a national level. Internationally, there are efforts to improve oncofertility care for AYA with cancer,[43] and a consequent need to monitor progress in oncofertility outcomes. Recently, Anazodo et al,[26] performed a scoping review of oncofertility care internationally looking at both practices and models of care. This found 8 different models of care for oncofertility, but noted none which had provided any measurement criteria for success for their model implementation. The indicator presented in this paper could be used as one measure to help evaluate models of care and ensure that interventions are working to improve oncofertility care in this patient group.

COMPARABILITY TO OTHER MEASURES

Another metric for oncofertility has been developed which could potentially complement the indicators proposed in this paper. In 2017, an outcome indicator, the Global Oncofertility Index, which would estimate the reproductive loss due to cancer, was proposed.[44] It was defined as "*the number of individuals per100 000 in a given year within a specified region or country whose reproductive health is at risk due to cancer diagnosis/gonadotoxic treatment*".[44] The development of this indicator was challenged by data issues and information gaps such as the risk of loss of fertility by cancer diagnosis. This metric could have helped identify areas globally with high and low risks for cancer-related fertility loss, informing interventions to improve care in these areas, as well as highlight areas where best practices may exist.[44] The indicator developed in this study captures a process (attendance of a fertility consult) rather than an outcome, but may

present fewer challenges for data collection in many countries with administrative databases. However, it would likely face similar data challenges in some countries where detailed administrative data are not collected.

LIMITATIONS

The examination of the fertility consult indicator in this study was limited to a single province, which comprises approximately 40% of the Canadian population. In order to strengthen the utility of the indicator it is important that future work focus on examining the feasibility and comparability of this indicator in other provinces across Canada, as well as internationally. Given that AYA with cancer represent a small population, having nationally and internationally comparable metrics would greatly facilitate evaluations of process of care models. Also, this indicator does not capture the initial discussions of fertility risks before the start of treatment or the uptake of fertility preservation for patients wanting this option. In Ontario, much of the data related to fertility preservation is housed within private clinics and not easily accessible through administrative databases, thereby limiting its utility for development of metrics. Recent efforts by the Australasian Oncofertility Registry, which started a pilot project that captures data from cancer and fertility centers in both Australia and New Zealand for patients 0-44 years of age, is a potential model which could be replicated in other countries to address data gaps and ensure comparability of metrics internationally.[45] A similar initiative was undertaken in Canada in 2015 by the Cancer Knowledge Network creating a database focused on tracking referrals of cancer patients and monitoring patient decision making regarding fertility preservation services.[46] However, funding support was limited and data collection has ceased. Supporting these types of databases will be essential for developing targeted

metrics to help further monitor progress, evaluate interventions, and improve oncofertility care and related outcomes.

CONCLUSIONS

The indicator examined in this paper adhered to the five criteria described by the NQF. It is likely that the primary indicator "*proportion of cases attending a fertility consult visit ≤ 30 days from diagnosis of cancer"* provides the greatest comparability across Canada and internationally, given the variability in access to services and reliability of treatment information. Further work needs to be done to assess the applicability of this metric internationally, as well as developing other types of metrics for use in oncofertility care. The indicator presented here provides a basis for reporting on oncofertility care in system performance reports, with applicability to evaluations of interventions and models of care.

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TABLES AND FIGURES

Figure 1. Study timeline definition for retrospective cohort of adolescent and young adults (15-39 years of age) diagnosed with cancer in Ontario, Canada

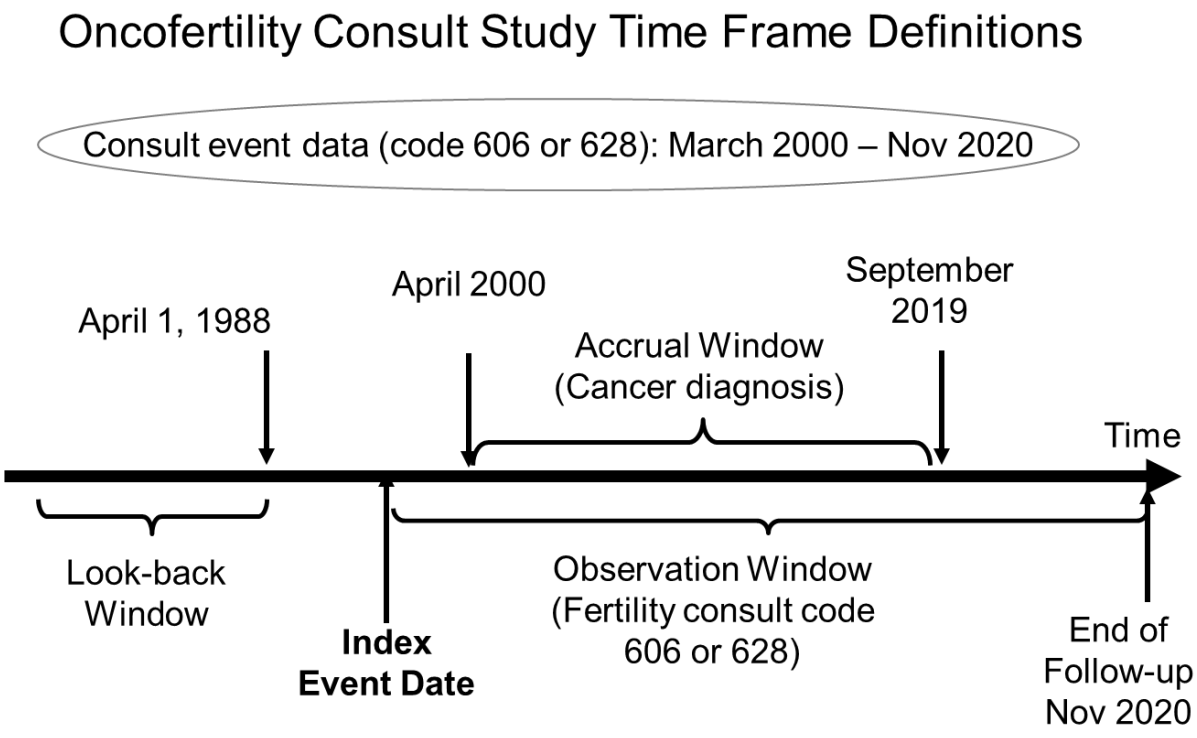


Table 1. OHIP Billing Codes to identify fertility consultations, sterilization procedures, and reproductive related cancer surgeries for males and females

Sex	Fertility consultation	Sterilization procedures	Reproductive related cancer surgeries
Female	**628**	S816, S781, S776, S763, S762, S759, S758, S757, S727, S710, P042, E090, S799, S782, S750, S747, S745, S73, S727, S714, E853, S741, P041, S783	R912, R913, S213, S312, S704, S705, S710, S714, S738, S744, S745, S750, S754, S757, S758, S759, S762, S763, S764, S765, S766, S767, S776, S781, S782, S810, Z553, Z563, Z583, Z720, Z723, Z729, Z730, Z731, Z735, Z766, Z769
Male	**606**	S626, E545	S589, S590, S598

Figure 2. Indicator for attendance of a fertility consultation before cancer treatment in the context of the clinical referral pathway

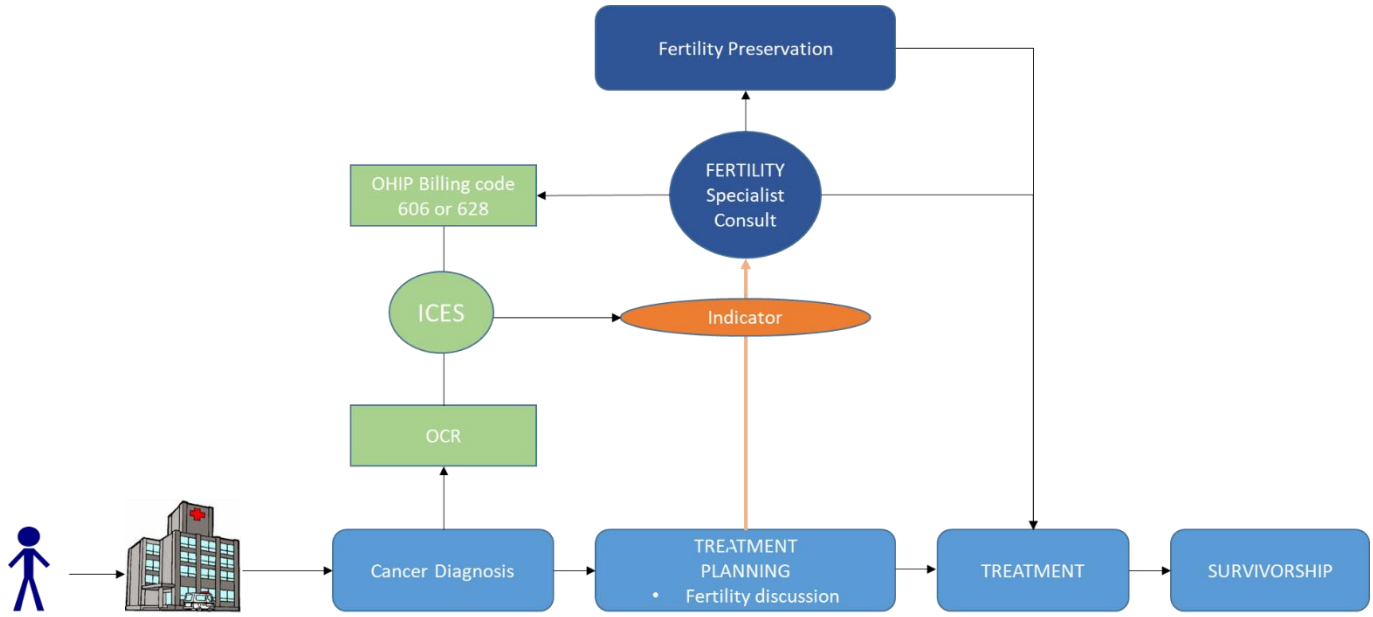


Table 2. Predefined hypotheses to test validity of an indicator for monitoring the proportion of adolescent and young adults diagnosed with cancer attending a fertility consultation before treatment

Variable	Hypothesis	Evidence
Year of Diagnosis	*Fertility consultations will increase over time*	Awareness and resources for oncofertiltiy have increased over time 2005 to 2010 – Oncofertilty defined 2011 to 2015 – Gaining awareness among patients and clinicians 2016-2019 – Ontario government provides cancer patients with funding for fertility preservation <u>Key dates</u> 2006 Oncofertility introduced 2008 Canadian Task Force on AYA with Cancer 2010 First AYA cancer stakeholder workshop 2012 Second AYA cancer stakeholder workshop 2013 Oocyte cryopreservation became non-experimental 2015 Funding for fertility preservation by Ontario government
Sex	*Males will have a higher fertility consultation rate than females*	Ease of fertility preservation in this group may make fertility consultation more likely to be undertaken
Age at diagnosis	*Lower ages will have the highest rate of attending fertility consults*	Parity is a known factor influencing choice, older age groups more likely to have kids;15-19 year age group most likely treated in pediatric hospital with resources and knowledge base to support oncofertility
Cancer diagnosis	*Variations in rates will occur by diagnosis with cancers with high risks to fertility having greater rates of attending a consult*	• Low (melanoma, thyroid cancer, other) • Moderate (brain tumours, bone and soft tissue sarcomas, breast cancer, colorectal cancer), and • High risk (cancers of the reproductive tract, Hodgkin and non-Hodgkin lymphoma, Leukemias)
Institution type	*Teaching and Pediatric hospitals will have the highest rate of patients attending fertility consults within the specified time period*	Teaching and pediatric hospital tend to be in major centers improving access, also generally have more expertise in oncofertility available within center than smaller institutions
Region	*Remote regions will have the lowest proportion of cancer patients attending fertility consults within the specified time period*	Availability of fertility preservation services varies across the province especially for women. IVF clinics are generally limited to large urban centers.
LHIN	*There will be variations in the proportion of cancer patients attending fertility consults in the specified time period based on LHINs*	Health unit variation would evidence areas for improvement for this indicator across the province. We expect differences by LHIN because of types of institutions servicing LHIN and access to fertility services.

Table 3 Clinical and demographic summary statistics by dataset for adolescent and young adults diagnosed with cancer in Ontario, Canada

		Full dataset		≤30 days before diagnosis		Before the start of treatment	
Factor	**Sub-group**	**N=49,425**		**N=39,977**		**N=26,267**	
		n	**%**	**n**	**%**	**n**	**%**
Treatment	**No**	14,144	28.6	10,555	26.4	0	0.0
	Yes	35,281	71.4	29,422	73.6	26,267	100.0
Fertility consult	**No**	41,686	84.3	33,453	83.7	21,301	81.1
	Yes	7739	15.7	6524	16.3	4966	18.9
Sex	**Female**	29,772	60.2	24,079	60.2	15,172	57.8
	Male	19,653	39.8	15,898	39.8	11,095	42.2
Age group (years)	**15-19**	3715	7.5	3040	7.6	1852	7.1
	20-24	6037	12.2	4999	12.5	3377	12.9
	25-29	9024	18.3	7457	18.7	4924	18.8
	30-34	13,078	26.5	10,578	26.5	6923	26.4
	35-39	17,571	35.6	13,903	34.8	9191	35.0
Cancer	**Bone tumours**	548	1.1	436	1.1	288	1.1
	Breast cancer (female)	5915	12.0	4727	11.8	4093	15.6
	Brain tumour	886	1.8	719	1.8	546	2.1
	Colorectal cancer	2600	5.3	2210	5.5	1459	5.6
	Female reproductive tract	3872	7.8	3101	7.8	2858	10.9
	Hodgkin	2899	5.9	2325	5.8	1985	7.6
	Leukemia	1017	2.1	857	2.1	672	2.6
	Male reproductive	4084	8.3	3315	8.3	3128	11.9
	Melanoma	3845	7.8	3010	7.5	1596	6.1
	Non Hodgkin Lymphoma	3105	6.3	2488	6.2	1905	7.3
	Soft tissue sarcoma	1536	3.1	1219	3.1	818	3.1
	Thyroid	9082	18.4	7631	19.1	1827	7.0
	Other	10,036	20.3	7939	19.9	5092	19.4
Diagnosis year	**2000-2004**	9448	19.1				
	2005-2010	15,290	30.9	15,290	38.3	9756	37.1
	2011-2015	13,800	27.9	13,800	34.5	9172	34.9
	2016-2019	10,887	22.0	10,887	27.2	7339	27.9
Hospital type	**Community**	16,326	33.0	13,470	33.7	7847	29.9
	Pediatric	891	1.8	704	1.8	360	1.4
	Small	3131	6.3	1470	3.7	798	3.0

	Teaching	12,543	25.4	9914	24.8	6575	25.0
	Missing	16,534	33.5	14,419	36.1	10,687	40.7
Region	**Central**	21,319	43.1	17,474	43.7	11,022	42.0
	North	4032	8.2	3221	8.1	2382	9.1
	South East	11,107	22.5	8924	22.3	5995	22.8
	South West	5300	10.7	4208	10.5	2743	10.4
	Southern	7667	15.5	6150	15.4	4125	15.7
LHIN	**1) Erie St. Clair**	2165	4.4	1715	4.3	1127	4.3
	2) South West	3135	6.3	2493	6.2	1616	6.2
	3) Waterloo Wellington	2893	5.9	2349	5.9	1539	5.9
	4) Hamilton Niagara Haldimand Brant	4774	9.7	3801	9.5	2586	9.9
	5) Central West	3131	6.3	2576	6.4	1527	5.8
	6) Mississauga Halton	4594	9.3	3779	9.5	2373	9.0
	7) Toronto Central	6366	12.9	5224	13.1	3412	13.0
	8) Central	7228	14.6	5895	14.8	3710	14.1
	9) Central East	5599	11.3	4504	11.3	2860	10.9
	10) South East	1424	2.9	1117	2.8	827	3.2
	11) Champlain	4084	8.3	3303	8.3	2308	8.8
	12) North Simcoe Muskoka	1498	3.0	1208	3.0	854	3.3
	13) North East	1773	3.6	1407	3.5	1061	4.0
	14) North West	761	1.5	606	1.5	467	1.8

Table 4. Proportion of first treatment dates that occurred outside a plausible range of between 3 months prior to official diagnosis and two years post-diagnosis. Highlighting indicates values outside range

	Time to Treatment	N	%
Before diagnosis	**>2 years**	328	0.99
	1-2 years	99	0.30
	9 months-1 year	95	0.29
	6-9 months	87	0.26
	3-6 months	138	0.42
	Diagnosis -3 months	1131	3.42
After diagnosis	**Diagnosis -3 months**	15436	46.61
	3-6 months	6987	21.1
	6-9 months	2553	7.71
	9 months-1 year	1621	4.89
	1-2 years	1663	5.02
	>2 years	2978	8.99

Figure 3. Distribution of fertility consult visits for adolescent and young adults with cancer before the start of treatment by indicator

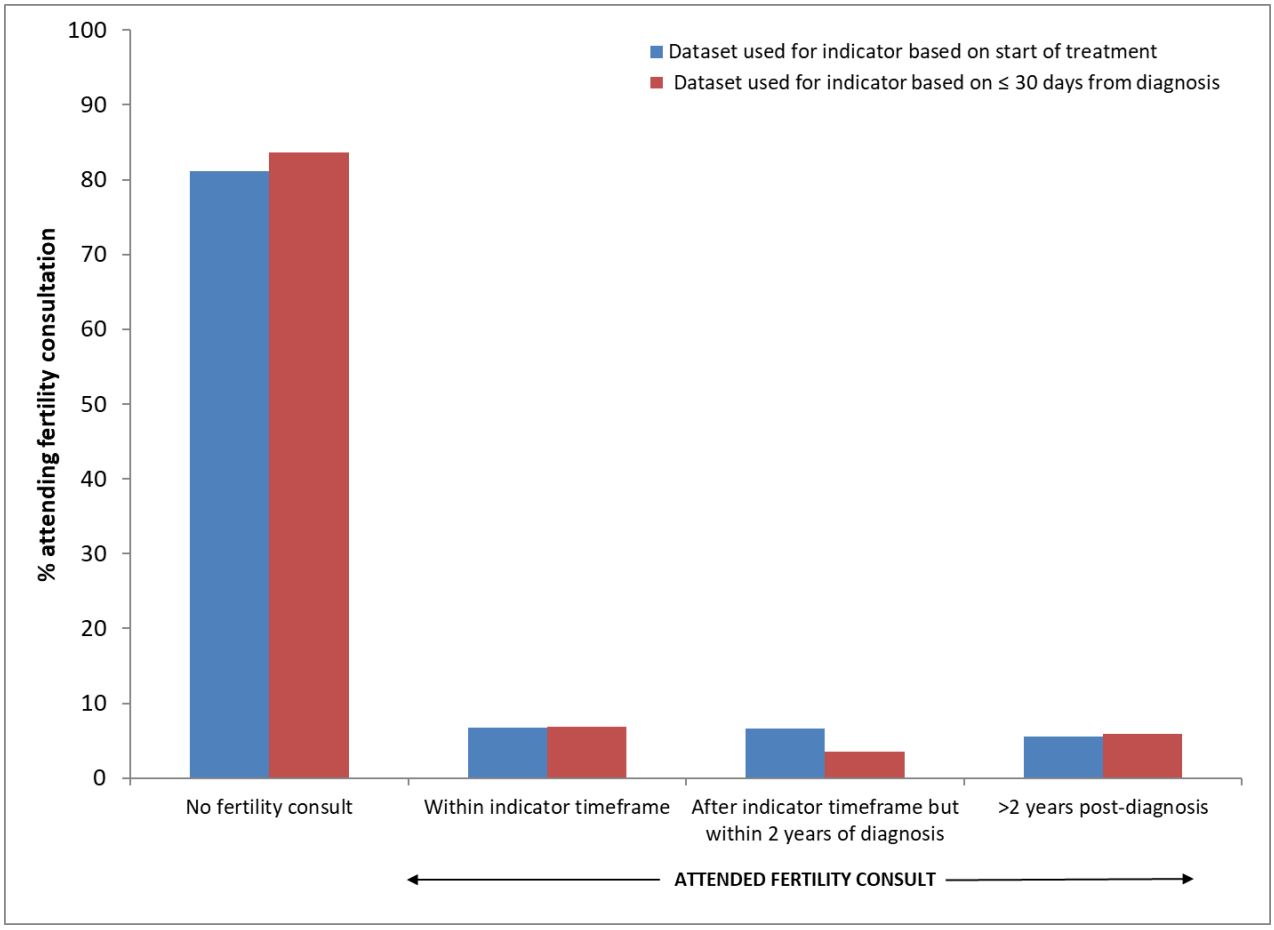


Figure 4. Proportion of adolescent and young adults with cancer attending fertility consult before treatment by indicator across year of diagnosis grouped

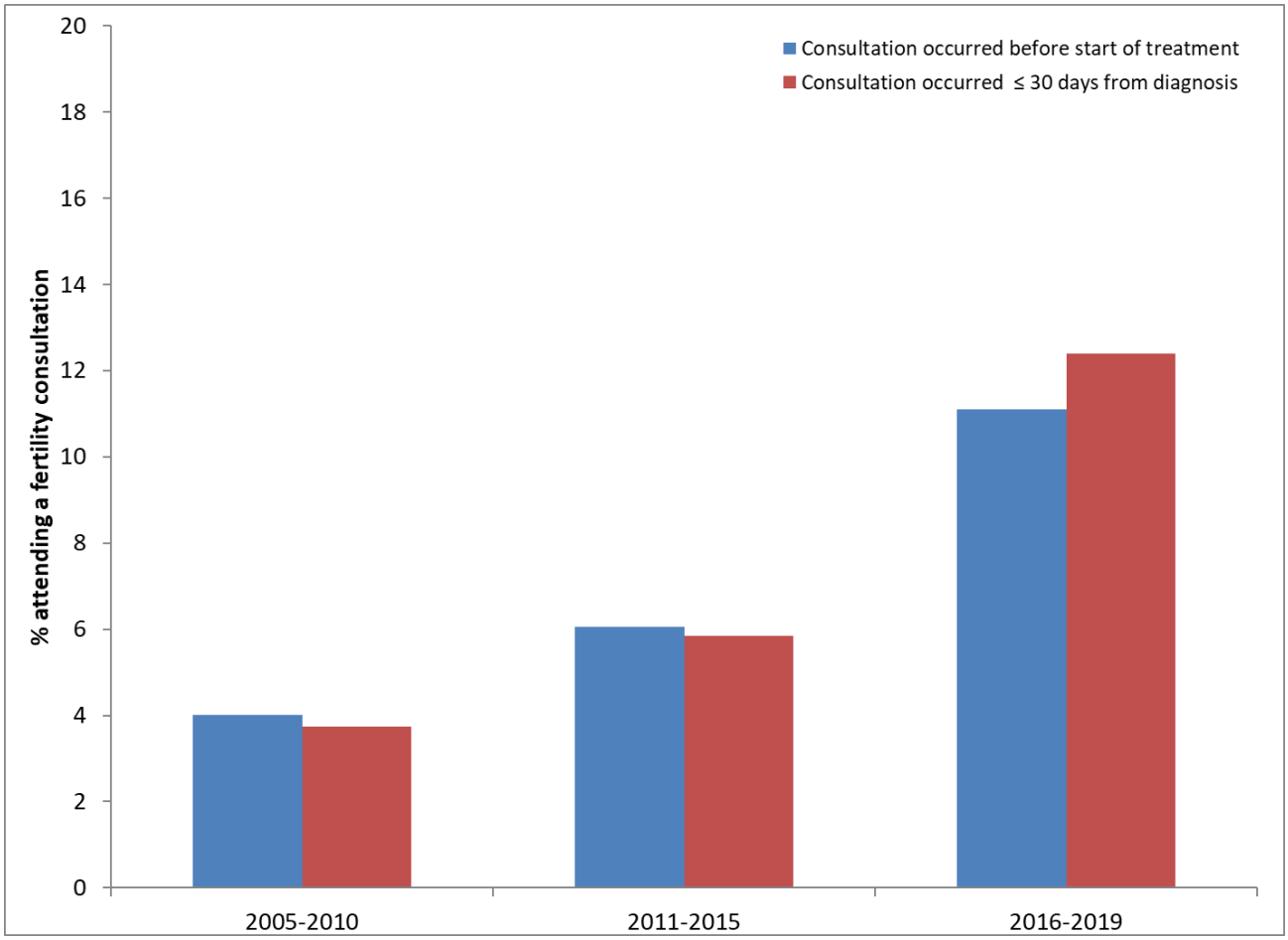


Table 5. Proportion of adolescent and young adults with cancer attending fertility consults before treatment by clinical and demographic factors for each indicator definition

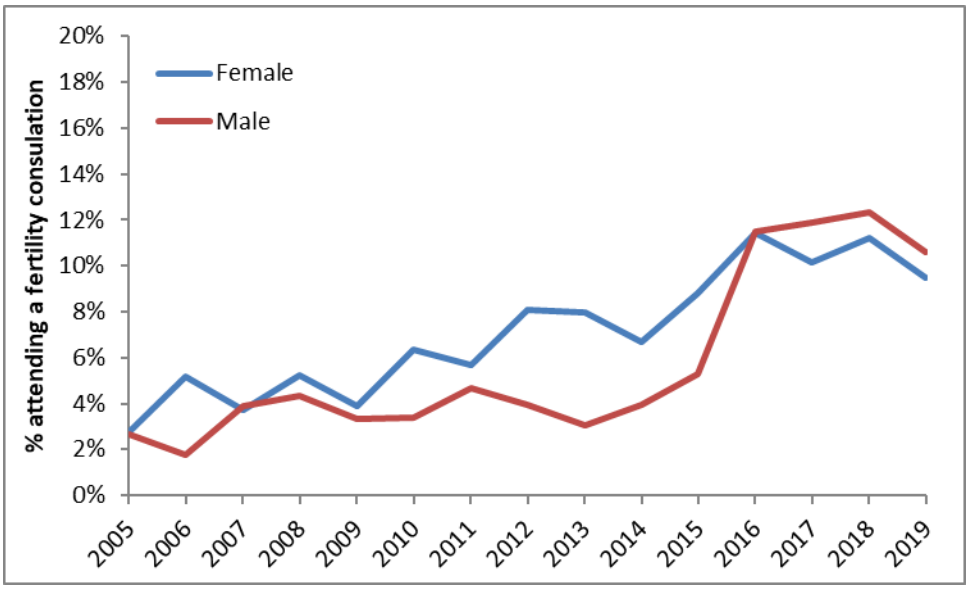
		Consultation before treatment starts (n=7339)			Consultation <=30days dx (n=10,887)		
Data for diagnoses from 2016 to 2019		N			N		
Factor	Sub-group	No	Yes	% attending	No	Yes	% attending
Sex	Female	3797	454	10.7	5888	651	10.0
	Male	2727	361	11.7	3650	698	16.1
Age group	15-19	378	66	14.9	622	162	20.7
	20-24	799	108	11.9	1106	246	18.2
	25-29	1218	212	14.8	1784	338	15.9
	30-34	1777	267	13.1	2628	372	12.4
	35-39	2352	162	6.4	3398	231	6.4
Cancer	Bone tumours	65	12	15.6	78	21	21.2
	Breast cancer	913	261	22.2	949	318	25.1
	Colorectal cancer	428	53	11.0	653	76	10.4
	Female reproductive tract	794	61	7.1	793	87	9.9
	Hodgkin	468	96	17.0	424	209	33.0
	Leukemia	185	28	13.1	217	64	22.8
	Male reproductive	730	150	17.0	669	231	25.7
	Melanoma	348	11	3.1	713	9	1.2
	Non Hodgkin	514	60	10.5	580	126	17.8
	Soft tissue sarcoma	210	17	7.5	287	33	10.3
	Thyroid	318	8	2.5	1981	17	0.9
	*Other+Brain tumours	1551	58	3.6	4175	175	4.2
Hospital Type	Missing	3348			4347		
	*Community + small	1997	220	9.9	3458	377	9.8
	Pediatric	64	21	24.7	129	48	27.1
	Teaching	1431	258	15.3	2153	375	14.8
Region	Central	2675	451	14.4	4023	704	14.9
	North	667	24	3.5	855	49	5.4
	South East	1500	173	10.3	2214	299	11.9
	South West	667	60	8.3	980	103	9.5
	Southern	1015	107	9.5	1466	194	11.7
LHIN	1) Erie St. Clair	261	17	6.1	405	26	6.0
	2) South West	406	43	9.6	575	77	11.8
	3) Waterloo Wellington	391	33	7.8	578	70	10.8
	4) Hamilton Niagara	624	74	10.6	888	124	12.3

	Haldimand Brant						
	5) Central West	446	55	11.0	659	106	13.9
	6) Mississauga Halton	594	62	9.5	890	115	11.4
	7) Toronto Central	758	180	19.2	1131	254	18.3
	8) Central	877	154	14.9	1343	229	14.6
	9) Central East	744	75	9.2	1111	141	11.3
	10) South East	227	17	7.0	287	31	9.7
	11) Champlain	529	81	13.3	816	127	13.5
	12) North Simcoe Muskoka	212	11	4.9	293	21	6.7
	***13) North East & 14) North West**	455	13	2.8	562	28	4.7

*Values merged due to small cell size <6

Figure 5. Proportion of adolescent and young adults with cancer attending fertility consult before treatment by diagnosis year

a. Fertility consultation before start of treatment



b. Fertility consultation ≤ 30 days from diagnosis

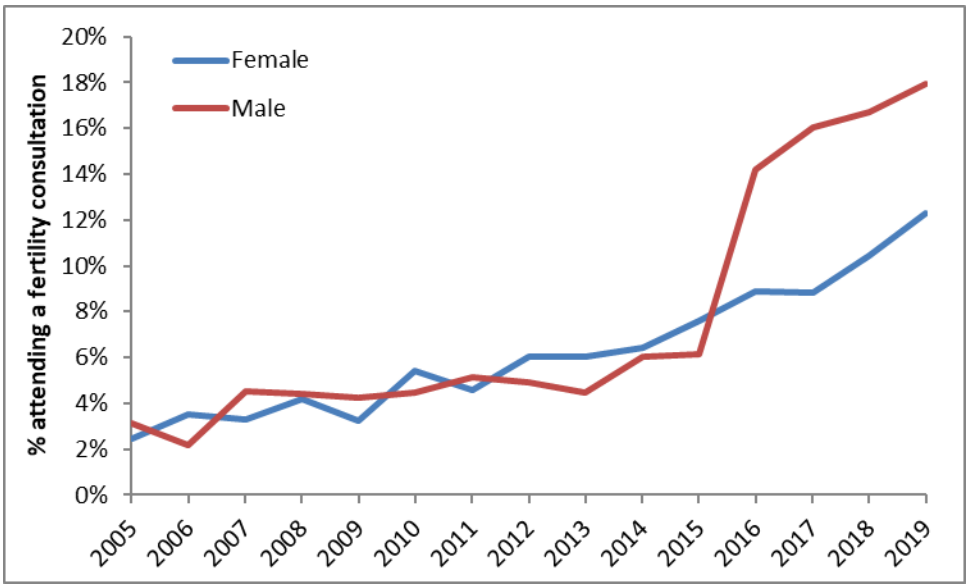
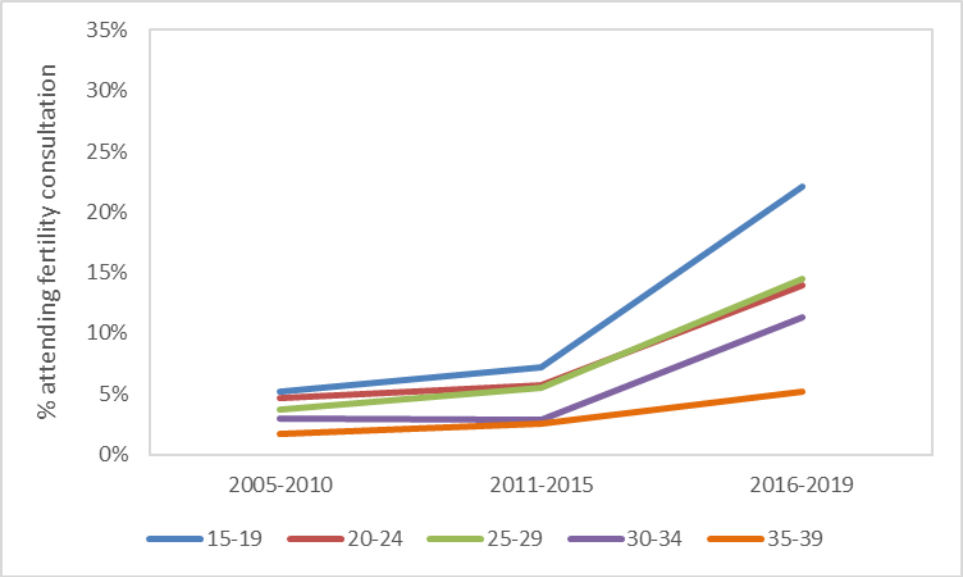


Figure 6 – Males: Proportion of adolescent and young adults with cancer attending fertility consult before treatment by age group across year of diagnosis grouped

a. Fertility consult before start of treatment



b. Fertility consult ≤ 30 days from diagnosis

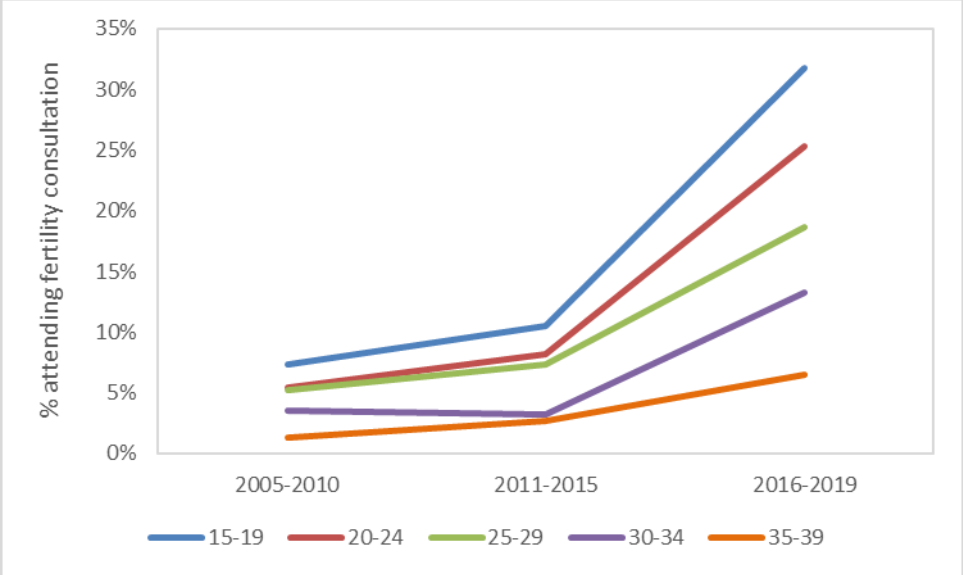
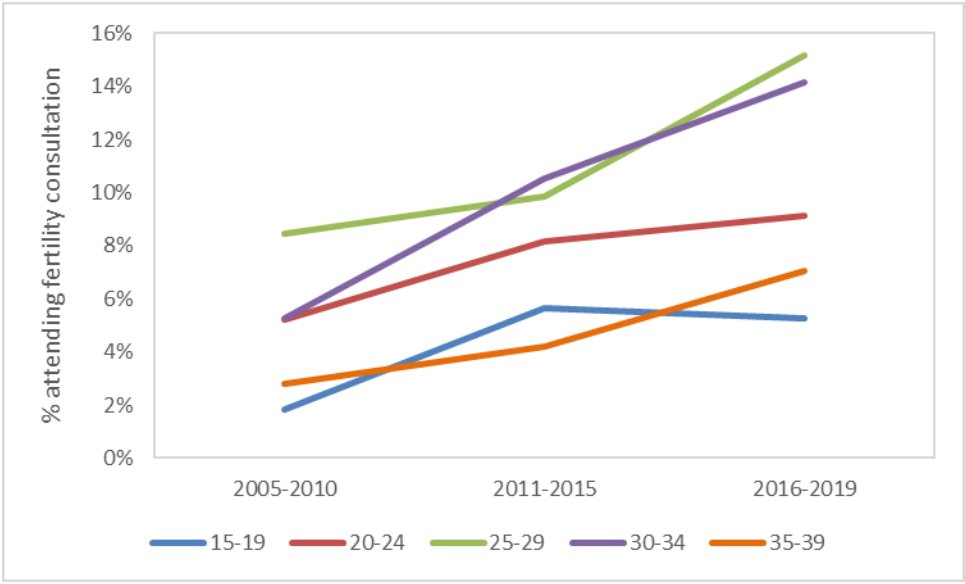


Figure 7 – Females: Proportion of adolescent and young adults with cancer attending fertility consult before treatment by age group across year of diagnosis grouped

a. Fertility consult before start of treatment



b. Fertility consult ≤ 30 days from diagnosis

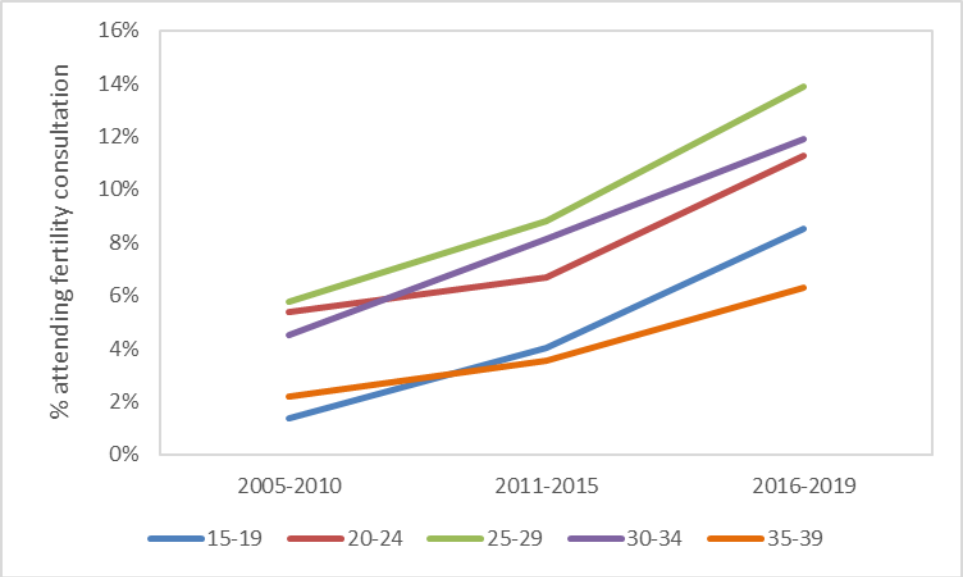


Table 6. Indicator definitions for the monitoring of adolescent and young adults with cancer attendance of fertility consultations before the start of treatment

Definition	*Proportion of AYA with cancer who attend a fertility consultation before the start of treatment*
Measurement Timeframe	By year 2005-2019
Data Source(s)	Ontario Cancer Registry (OCR), Ontario Health Insurance Plan Claims Database (OHIP), Cancer Activity Level Reporting (ALR).
Stratification Variables	1. Sex 2. Age group (15-19,20-24,25-29,30-34,35-39)
Denominator	Number of patients diagnosed with cancer <u>Inclusion</u> • 15-39 years of age at diagnosis <u>Exclusion</u> • diagnosis with a secondary cancer, • had a fertility consult (OHIP Billing code 606 or 628) anytime preceding 30 days prior to official diagnosis, • were a non-Ontario resident or • had a prior sterilization procedure prior to cancer diagnosis.
Numerator	Number of patients diagnosed with cancer attending a fertility consultation identified as OHIP billing code 628 female infertility or 606 male infertility before the start of treatment Start of treatment defined as minimum value of one of the following: • Chemotherapy – First visit date in ALR • Radiation – First visit date in ALR • Reproductive surgery – First service date (within 30 days before diagnosis and 2 years post diagnosis) defined by billing codes Males: S590, S598, S589 Females: R912, R913, S213, S312, S704, S705, S710, S714, S738, S744, S745, S750, S754, S757, S758, S759, S762, S763, S764, S765, S766, S767, S776, S781, S782, S810, Z553, Z563, Z583, Z720, Z723, Z729, Z730, Z731, Z735, Z766, Z769
Notes	• OHIP billing codes for male and female infertility can be incorrectly used by sex and both are required to capture all infertility visits within a sex • Diagnosis date timeframe includes 30 days prior to diagnosis to account for any delays in official diagnosis date

Definition	*Proportion of AYA with cancer who attend a fertility consultation ≤30 days from diagnosis of cancer*
Measurement Timeframe	By year 2005-2019
Data Source(s)	Ontario Cancer Registry (OCR), Ontario Health Insurance Plan Claims Database (OHIP)
Stratification Variables	1. Sex 2. Age group (15-19,20-24,25-29,30-34,35-39)
Denominator	Number of patients diagnosed with cancer <u>Inclusion</u> • 15-39 years of age at diagnosis <u>Exclusion</u> • diagnosis with a secondary cancer, • had a fertility consult (OHIP Billing code 606 or 628) anytime preceding 30 days prior to official diagnosis, • were a non-Ontario resident or • had a prior sterilization procedure prior to cancer diagnosis.
Numerator	Number of patients diagnosed with cancer attending a fertility consultation identified as OHIP billing code 628 female infertility or 606 male infertility within 30 days of diagnosis
Notes	• OHIP billing codes for male and female infertility can be incorrectly used by sex and both are required to capture all infertility visits within a sex. • Diagnosis date timeframe includes 30 days prior to diagnosis to account for any delays in official diagnosis date.

CHAPTER 7: FERTILITY REFERRAL PATTERNS FOR MALE AND FEMALE CANCER PATIENTS IN ONTARIO, CANADA

Factors associated with adolescent and young adults attending a fertility consultation within 30 days of a cancer diagnosis in Ontario, Canada.

Part A. Males
Part B. Females

Acknowledgements

This study was supported by the Institute for Clinical Evaluative Sciences (ICES) which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred.

PART A. FERTILITY REFERRAL PATTERNS IN MEN WITH CANCER

ABSTRACT

Introduction: Cancer and its treatment can impair fertility in men who should be referred for fertility consultation before the start of therapy. This study examined factors associated with men attending a fertility consultation within 30 days of diagnosis.

Methods: Males 15 to 39 years of age, diagnosed with cancer in Ontario, Canada between 2006 and 2019, were identified from the Ontario Cancer Registry. Administrative data from the Institute of Clinical and Evaluative Sciences were used to obtain clinical and sociodemographic variables. A backwards selection multivariate logistic regression was performed.

Results: Of 13,720 cases identified 8.5% had attended a fertility consultation within 30 days of diagnosis. A more recent year of diagnosis (OR=5.5, 95% CI [4.6,6.6]), living in an urban area (OR=1.3 [1.0,1.8]), receiving radiation therapy (OR=1.4 [1.2,1.6]), chemotherapy (OR=1.9 [1.6,2.2]), and reproductive organ-related cancer surgery (OR=1.5 [1.2,1.7]) were associated with a greater likelihood of attending such a fertility consultation. Older age (OR=0.2 [0.1,0.2]), living in a northern region (OR=0.3 [0.2,0.5]), having a cancer with low (OR=0.3 [0.2,0.4]) or moderate risk to fertility (OR=0.6 [0.5,0.7]), and residing in a neighbourhood with lower income (OR=0.4 [0.3,0.5]) or residential instability quintile (OR=0.8 [0.6,1.0]) were associated with being less likely to attend a fertility consultation.

Conclusion: Although rates of fertility consultation have increased over time, these remain low in various clinical and demographic groups. Funding for fertility preservation has had the greatest impact on improving rates of referral in this population of young men with cancer.

INTRODUCTION

Adolescent and young adults (AYAs), 15 to 39 years of age, with cancer have many unique challenges related to their age, their healthcare system and the nature of their disease.[1,2] Fertility is one of the most important issues facing this population.[3-5] Approximately 15 % to 30% of males who survive cancer will experience problems with fertility.[6,7] The psychosocial issues are well documented with fertility concerns impacting many aspects of life including well-being and relationships.[8-11] In order to ensure that young people with cancer are aware of the risks to fertility, as well as the options for preservation, it is recommended that they are referred for fertility counselling before treatment.[12] It is important to better understand the uptake of fertility preservation services in this population, to ensure that AYAs diagnosed with cancer have future choices regarding their family planning.

There are many factors related to cancer and its treatment which may lead to lower fertility rates in males.[13] Fertility sparing strategies and gonadal protection can be used in male cancer patients such as alternative regimens of chemotherapy and gonadal shielding.[14,15] However, sperm cryopreservation is the main method used to preserve fertility in post-pubertal males with cancer.[14] Sperm banking should be undertaken before chemotherapy because a single treatment can impact the DNA integrity of the sperm.[14]

Barriers to fertility preservation in males diagnosed with cancer have been discussed in detail, including patient awareness of the impact of treatment on fertility and of preservation options before treatment, and lack of knowledge among oncologists.[16,17-19] Yee et al[16] found that most fertility centers in Canada had a relatively low volume of referrals of men with cancer, with only 8% of centers surveyed having a large referral

volume per month. A retrospective study at a single site found that 18% of patients 14 to 30 years of age, diagnosed between 1995 and 2005, utilized sperm banking,[20] while a study in 12 institutions over a two year period found that 19% of adolescents were able to successfully bank a specimen.[19] In the United States, another study found 11% uptake of sperm banking in patients 13-50 years of age who were planning to undergo chemotherapy.[21] These rates show an underutilization of fertility services in this population.

Sperm banking is an accessible method for males diagnosed with cancer to preserve their fertility before treatment. In order for them to do so a series of steps must take place. First, an initial discussion regarding fertility risks by the oncologist must occur, which can lead to a referral to a fertility specialist if the patient would like further information. Second, the referral appointment is made, and the patient chooses to attend. The fertility specialist then can arrange the necessary appointments for fertility preservation, if the patient chooses to proceed. In order to improve the uptake of fertility preservation services in males diagnosed with cancer, it is important to better understand factors influencing the second step in the process, attendance at fertility consultations. This information could be used to help inform interventions and programs in oncofertility care. The objective of this study was to examine factors associated with attending a fertility consultation within 30 days of diagnosis for males aged 15 to 39 years when diagnosed with cancer. Thirty days after diagnosis was chosen as a proxy for the start of treatment, as suggested by a recent indicator development study for oncofertility care.[22]

METHODS

We conducted a retrospective cohort study using administrative health data housed at the Institute of Clinical and Evaluative Sciences (ICES) in Toronto, Ontario, Canada. All analyses were performed through a remote access server, iDAVE, using SAS. This secondary data analysis was approved by the Hamilton Integrated Research Ethics Board (HiREB).

Population

We included all males, 15 to 39 years of age at time of diagnosis of cancer in Ontario, Canada between January 1, 2006 and September 30, 2019. Exclusion criteria were a secondary cancer diagnosis, fertility consult preceding 30 days prior to cancer diagnosis, non-Ontario resident status or prior sterilization procedure. Sterilization procedures were identified using Ontario Health Insurance Plan (OHIP) Claims Database billing codes S626 and E545 for vasectomy.

Data

Data were extracted between April 1, 1988 and October 31, 2020 from administrative databases of Ontario Cancer Registry (OCR), OHIP, Registered Persons Database (RPDB), and Cancer Activity Level Reporting (ALR). A service visit for a male fertility consult was identified using the diagnostic billing code ICD-9 606 in the OHIP database. Because errors in billing code by sex have been identified, the code for female infertility ICD-9 628 was also applied.[22]

Factors included in the modelling were informed by previous work of referral patterns in female cancer patients. Demographic factors were obtained from RPBD, including rurality, quintiles for residential instability, material deprivation, dependency

and ethnic concentration. Quintiles are interpreted on an ordinal scale from one (least marginalized) to five (most marginalized). A summated score of marginalization was also calculated, based on the RPDB data, as described by Matheson and van Ingen 2016.[23] Quintiles for neighbourhood income were also included in analyses, represented on an ordinal scale from 1 (lowest) to 5 (highest). Clinical factors, including age at diagnosis, cancer type, mode of treatment received (chemotherapy, radiation, reproductive related cancer surgery), death within 1 year of diagnosis, and region of oncology care. Cancer diagnoses were defined according to Barr et al[24] and grouped into low, moderate, and high risk for future infertility as follows: low (melanoma, thyroid cancer, other) moderate (brain tumors, bone and soft tissue sarcomas, colorectal cancer), and high risk (cancers of the reproductive tract, Hodgkin and non-Hodgkin lymphoma, leukemias). Treatment information for chemotherapy and radiation therapy were obtained from the ALR database and surgery related to a reproductive cancer was identified from OHIP (excluding biopsies), using billing codes S589, S590, S598. We did not examine parity, a known significant factor associated with the referral of females diagnosed with cancer,[25,26] because information regarding fathers is not collected in any linkable databases in Ontario.

Analysis

Descriptive statistics were calculated for all demographic and clinical variables and the percentage of missing data was assessed. Analyses were completed using univariate logistic regression models with intercepts to assess the relationship between each factor and the outcome event of attending a fertility consultation within 30 days of

diagnosis. Significant factors were entered into a logistic model using a backwards selection approach, with a two way cut-off $p<0.05$ for inclusion into the model. Odds ratios and 95% confidence intervals were calculated for the final model. Model fit was assessed using the Hosmer and Lemeshow Goodness of Fit test, AIC and the c statistic.

RESULTS

Demographic and clinical statistics are shown in Table 1. From the total sample of 13,720 cases, 8.5% had the outcome of interest; attending a fertility consultation within 30 days of diagnosis. The proportion of male cancer patients attending a fertility consultation within 30 days of diagnosis, over the study period, is shown in Figure 1.

Univariate results

The total of 13,720 cases were included in analyses. All factors were significantly associated with attending a fertility consultation within 30 days of diagnosis ($p\leq0.006$) (Appendix 1). Income and material deprivation quintiles were correlated (0.73; $p<0.0001$), and the latter was removed from further modelling because of a greater proportion of missing data. The Ontario Marginalization Summary Score was also calculated, based on ethnicity concentration, dependency, instability and deprivation quintiles, and correlated with the deprivation quintile (0.72; $p<0.0001$). It was decided to retain the individual factors and drop the index score from the model.

Multivariate results

The backwards elimination was completed in three steps with ethnic concentration quintile (step1 $p=0.09$), dependency quintile (step 2 $p=0.06$), and death within 1 year of diagnosis ($p=0.06$) removed from the final model. The Hosmer and Lemeshow Goodness of Fit test indicated the final model fit the data well ($p=0.616$). Living in an urban area

(OR=1.3; 95% CI[1.0, 1.8]), radiation therapy (OR=1.4; 95% CI [1.2,1.6]), chemotherapy (OR=1.9; 95% CI [1.6,2.2]), and reproductive organ-related cancer surgery (OR=1.5;95% CI [1.2,1.7]) were associated with a greater likelihood of attending a fertility consultation within 30 days of diagnosis (Figure 2; Appendix 2). Older age (OR=0.2;95% CI[0.1,0.2]), living in a northern region (OR=0.3; 95% CI [0.2,0.5]), having a cancer with low (OR=0.3; 95% CI [0.2,0.4]) or moderate risk to fertility (OR=0.6; 95% CI [0.5, 0.7]), and living in a neighbourhood with lower income (OR=0.4; 95% CI [0.3,0.5]) and residential instability quintile (OR=0.8; 95% CI [0.6,1.0]) were associated with being less likely to attend a fertility consultation (Figure 2; Appendix 2). The greatest effect (OR=5.5; 95% CI [4.6, 6.6]) was associated with most recent years of diagnosis (2016-2019). Patients in this period were 5 times more likely to attend a fertility consultation within 30 days of diagnosis than those diagnosed in the earliest time period (2006-2010) ($p<0.0001$).

DISCUSSION

This study identified factors associated with males diagnosed with cancer attending a fertility consultation within 30 days of diagnosis, and found low rates of attendance over the study time period (8.5%). Although increases were observed over time, rates remained low in certain groups, based on various clinical and demographic factors. Given the importance of fertility and the association of treatment-induced infertility with both lower physical and mental quality of life,[27-29] it is essential to better understand low referral rates for fertility consultations among males with cancer, as well as disparities based on clinical and demographic factors.

The year of diagnosis had the largest effect, with those diagnosed after 2016 having the greatest likelihood of attending consultations. The rates of men attending fertility consultations have increased steadily, with a low of 2% in 2007 to a high of 19% in 2019. This is consistent with a previous Canadian study which found that sperm banking services were underutilized by cancer patients.[16] The steep rise in consultations for males diagnosed with cancer in later years corresponds to the start of government funding for fertility preservation for cancer patients in December 2015.[30] Another study in Canada found that public funding was an important facilitator for males with cancer undertaking fertility preservation, with cancer patients having an increased number of sperm cryopreservation sessions when charges to the patients for this service were removed.[31]

High risk cancers, such as testicular cancer, had the greatest proportion of fertility referrals (14.2%), and men with these cancers were 40% and 70% more likely to attend a consultation than men with either moderate or low risk to fertility cancers, respectively. A previous study found that 25.7% of males diagnosed with reproductive organ cancers attended a fertility consultation, which was a much greater uptake of these services than was found in females with reproductive organ cancers (9.9%).[22] Another study showed that patients with genitourinary cancers and sarcomas were more likely to undergo fertility counseling than patients with head and neck or gastrointestinal cancers.[21] In this current study, even though men with cancers associated with a greater risk for infertility are more likely to attend visits, rates were still low with only 14% of men with these cancers undertaking fertility consultations. Interventions targeted at particular cancer

types, such as decision aids or specialized programs, along with greater advocacy may help to improve rates. This appears to be an effective strategy as seen in fertility consultation rates for women with breast cancer,[22,32] for whom targeted decision aids and programs have been implemented.[33,34]

Of the different modes of treatment, chemotherapy had the greatest effect size, with men undergoing this treatment 90% more likely to attend a fertility consultation than those who did not have these treatments. Those who had reproductive surgery or radiation therapy were 50% and 36% more likely to undergo a fertility consultation than those who did not receive these treatments, respectively. It is well known chemotherapeutic drugs, such as alkylating agents, and radiotherapy can result in disrupted spermatogenesis, DNA damage, and/or erectile/ejaculator dysfunction,[35-39] while surgery can either remove organs necessary for sperm production or damage nerves leading to erectile dysfunction.[13,35] Depending on a variety of factors, fertility may be regained after the completion of treatment; however, the quality of the sperm produced may still be impaired for months or years.[13] In a comprehensive systematic review of evidence, an international group developed guidelines regarding fertility preservation in males with cancer up to 25 years of age. It is strongly recommended that males undergo fertility preservation if their treatment plan includes chemotherapy using high or low dose alkylating agents or cisplatin; radiotherapy, either cranial or testicular; hematopoetic stem cell transplantation; or orchiectomy.[40] Our results appear to be consistent with the risk to fertility related to treatment described by that review. However, despite this recommendation, the proportion of men undergoing these treatments who attend fertility

consultations is still small, with the highest consultation rate (13.5%) in our study observed in men undergoing reproductive-related surgeries.

Increased age at diagnosis was associated with lower rates, with only 3.5% of men 35-39 years of age attending consultations compared to 15.8% of men 15-19 years of age. This finding is similar to that reported by Grover et al.[21] who observed a relationship between older age and lower fertility counseling rates. A previous Canadian study found that younger men and those without children were more likely to have had a fertility discussion with health care providers.[41] This is consistent with other reports in the literature[41,42] that older males and those with children tend to be less likely to attend fertility consultations. Also likely related to age, those with least residential instability were slightly more likely (10.5%) to attend fertility consultations than those who lived in neighbourhoods with greater residential instability. Residential instability captures neighbourhoods with people living alone, and with a higher proportion of rented dwellings and apartment buildings, which are likely characteristic of younger populations who have not established a family yet.[23]

Wealthier neighbourhood income quintiles were also associated with attending fertility consultation within 30 days of diagnosis. Those in the wealthiest income quintiles had consultation rates of approximately 10% compared to 5.4%-7.9% in the lowest two income quintiles. A Canadian survey in 2011 found that cost was not a factor for males with cancer regarding their decision to use sperm banking services. However, this survey only included men who chose to bank sperm.[43] More recently, a study of Canadian men with cancer at 18 to 55 years of age observed similar trends with income or employment

status not associated with attending a fertility consultation.[41] In the province of Ontario, most costs for sperm banking for cancer patients are publicly funded.[30] However, yearly storage costs of $250-$500 may be a barrier for some lower income patients. Further investigation of barriers for low income patients is warranted to better understand how income influences decisions for fertility consultation.

Access to care was also identified as a factor for males diagnosed with cancer, with those living in northern Ontario (3.6%) and rural areas (6.1%) being less likely to attend fertility consultations. Given the large geographic size of Ontario, it is perhaps not surprising that access to fertility services varies across the Province. Although sperm banking is more accessible than female fertility preservation, which requires more specialized clinics, travel to a private clinic offering sperm banking may be a barrier due to costs and time. A global review of barriers to oncofertility care also identified that a lack of providers is an issue in Canada,[44] which would be especially relevant to the northern region where fewer fertility specialists are located. The creation of formalized oncofertility programs in Northern Ontario may help to improve rates in this area. A study in the United States found that both the rates of males with cancer attending consultations and those undertaking sperm cryopreservation improved with the implementation of a formalized oncofertility program.[44] This initiative could also leverage telemedicine to enable visits with fertility specialists located in central and southern Ontario for initial consultations to help address issues with lack of providers in the other areas.

This study has some limitations, despite its large sample obtained from administrative databases. Firstly, it examined only fertility consultation for males diagnosed with cancer between the ages of 15 and 39 years of age. Given that male fertility can extend well beyond 39 years of age, further work should also consider this older age group. Also in Ontario, only mothers are identified in readily accessible administrative databases such as MOMBABY. This does not allow examination of parity in males. Parity has been identified as an important factor associated with fertility consultation for females with cancer.[25,26] There is some evidence in the literature that this is also a factor for males with cancer. In a retrospective review of fertility consultations at a single site, men with two or more children were less likely than those with no children to undergo fertility preservation consultation.[44] In our study, residential instability may have served as a proxy metric for parity. However, developing data resources related to parity for males is important, and the lack of these data is a major limitation for cancer-related fertility research in this population. Completeness of treatment data is another limitation. It is unknown how many cases may have incomplete records for treatment in ALR. Missing treatment data has been identified previously as a potential issue in a study developing an oncofertility indicator.[22] Also, socio-demographics were only available at aggregate neighbourhood levels, with the potential for statistics not to match individuals residing in those areas. Greater availability of gender, race, ethnicity and income data within cancer administrative databases would greatly facilitate various types of cancer research, and help assess equity issues related to treatment and outcomes.

CONCLUSIONS

Although the proportions of men aged 15 to 39 years of age with cancer attending fertility consultations have increased over time this rate remains low, with important disparities related to both sociodemographic factors and access to care. Funding for fertility preservation has had the greatest impact on improving rates of fertility consultation in this population. Further interventions focusing on improving access across Ontario, and greater awareness and advocacy targeting those groups with the lowest uptake of fertility services could improve attendance at fertility consultations for AYA male cancer patients.

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TABLES AND FIGURES

Table 1. Clinical and demographic statistics, males aged 15-39 years diagnosed with cancer in Ontario, Canada (N=13,720)

Characteristics	Sub-groups	%	n	% attending fertility consult within 30 days
Fertility Consult within 30 days of diagnosis	No	91.5	12556	
	Yes	8.5	1164	
Diagnosis year	2006-2010	33.2	4551	4.2
	2011-2015	37.1	5096	5.6
	2016-2019	29.7	4073	16.8
Age group (years)	15-19	10	1374	15.8
	20-24	15.9	2176	13.0
	25-29	20	2749	10.8
	30-34	24.8	3407	6.8
	35-39	29.3	4014	3.5
Cancer diagnosis	Brain tumour	2.7	373	5.1
	Bone tumours	1.4	188	17.0
	Colorectal cancer	7.5	1030	6.3
	Hodgkin Lymphoma	7.7	1050	16.8
	Leukemias	3.1	430	17.9
	Male reproductive cancers	22.3	3053	14.0
	Melanoma	6.4	879	*combined with other
	Non Hodgkin Lymphoma	9.4	1287	11.1
	Soft tissue sarcoma	4	546	8.1
	Thyroid	9.4	1288	1.0
	Other	26.2	3596	3.7
Cancer risk to fertility	Low	42.0	5763	3.1
	Moderate	15.6	2137	7.5
	High	42.4	5820	14.2
Rural	No	91.3	12507	8.7
	Yes	8.7	1190	6.1

	Missing		23	
Region	Central	41.6	5711	7.9
	North	8.5	1162	3.6
	South East	22.4	3073	9.3
	South West	10.9	1494	8.3
	Southern	16.6	2280	11.3
Death within 1st year after diagnosis	No	93.2	12781	8.8
	Yes	6.8	939	4.7
Chemotherapy	No	39.8	5456	5.1
	Yes	60.2	8264	10.7
Radiation	No	59.8	8206	7.9
	Yes	40.2	5514	9.4
Reproductive surgery	No	73.6	10092	6.7
	Yes	26.4	3628	13.5
Neighbourhood Income Quintile	1 (lowest)	19.4	2650	5.4
	2	20.5	2794	7.9
	3	19.7	2685	8.4
	4	21	2874	10.0
	5 (highest)	19.4	2655	10.6
	Missing		62	
Residential Instability Quintile	1 (least)	20.4	2686	10.5
	2	17.9	2352	8.8
	3	16.6	2185	8.6
	4	18.7	2455	8.4
	5 (most)	26.5	3487	7.3
	Missing		555	
Ethnic Concentration Quintile	1 (least)	13.8	1814	7.1
	2	15.5	2043	9.2
	3	18.3	2408	10.4
	4	24.2	3188	9.1
	5 (most)	28.2	3712	7.5
	Missing		555	
Material Deprivation Quintile	1 (least)	21.7	2861	12.2
	2	20.7	2728	9.1
	3	19.2	2526	9.7

	4	18.3	2407	6.3
	5 (most)	20.1	2643	5.5
	Missing		555	
Dependency Quintile	1 (least)	28.1	3699	9.8
	2	22.3	2935	9.2
	3	17.8	2343	7.6
	4	16.4	2159	7.5
	5 (most)	15.4	2029	8.2
	Missing		555	
Ontario Marginalization Summary Score	1 (least)	0.2	22	11.2*
	2	22.5	2957	
	3	42.3	5567	9.0
	4	31.6	4162	6.7
	5 (most)	3.5	457	5.0
	Missing		555	

*Value suppressed cell size <6

Figure 1. Percentage of AYA males with cancer attending a fertility consultation within 30 days of diagnosis, by year of diagnosis

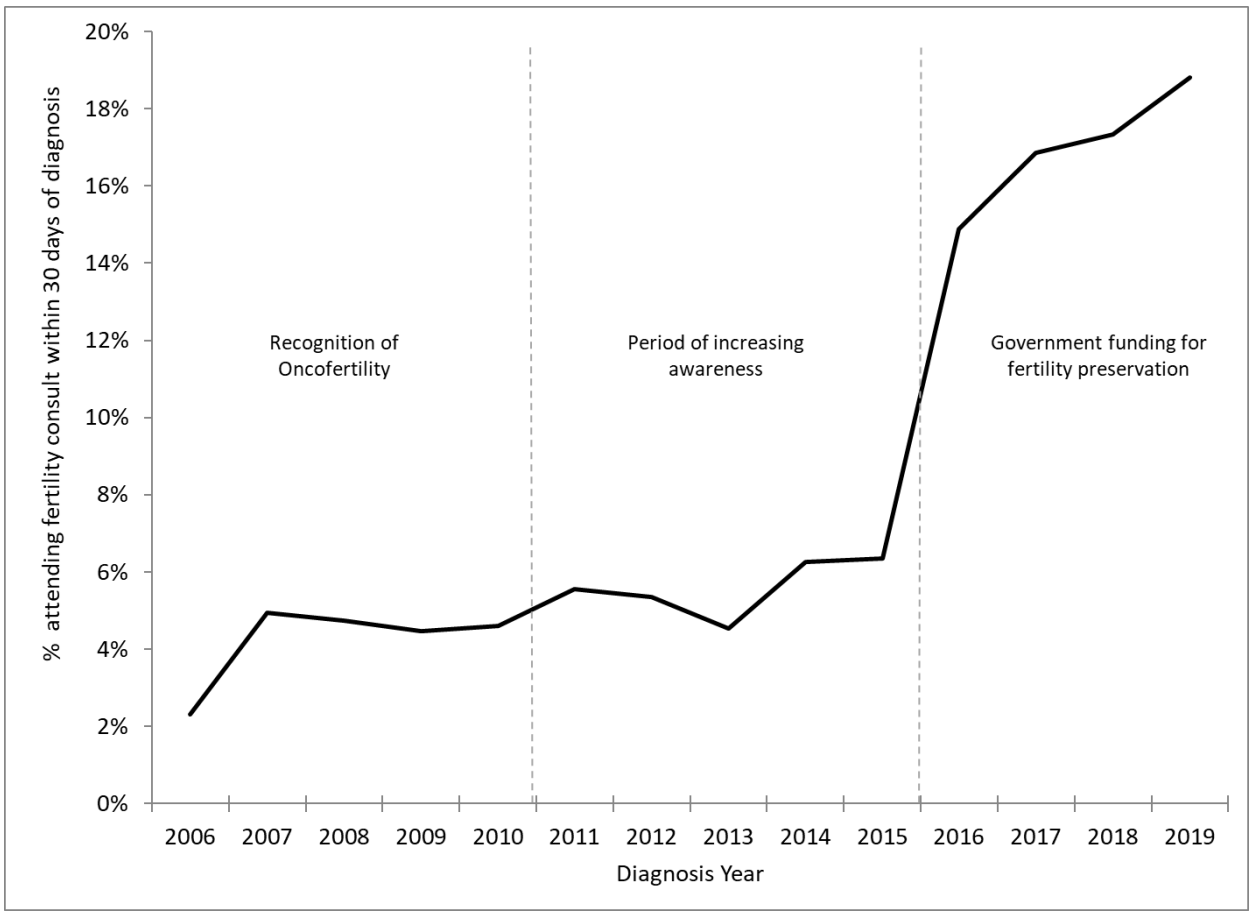
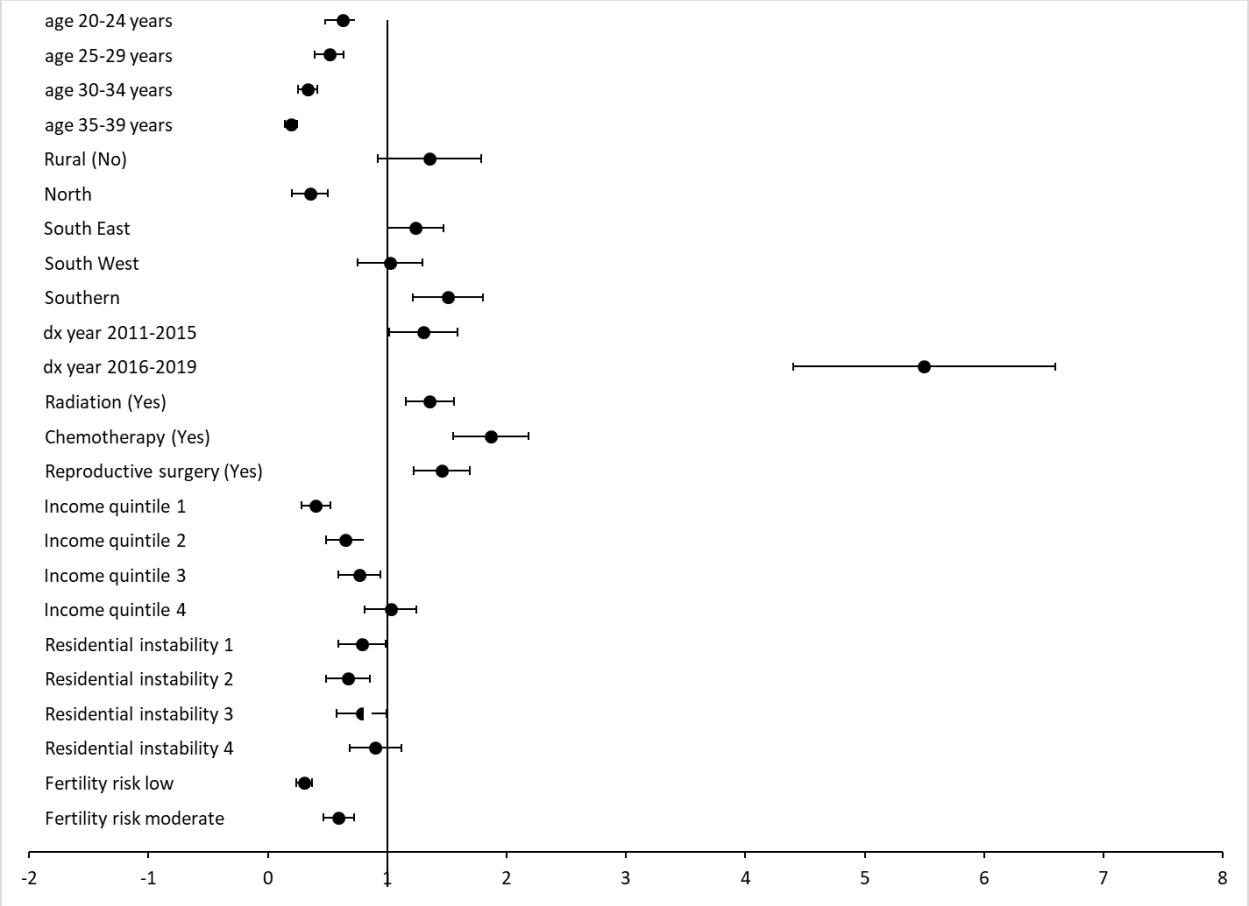


Figure 2. Odds ratios and 95% confidence intervals for multivariate logistic regression with factors regressed on attending a fertility consult within 30 days of diagnosis for males 15-39 years of age at diagnosis



dx - diagnosis

*Reference categories: Age at dx 15-19 years; Region Central; dx year 2006-2010; Income quintile 5 wealthiest; Residential instability 5 most marginalized; Risk to fertility high

Appendix 1. Odds ratios and 95% confidence intervals for univariate logistic regression with factors regressed on attending a fertility consult within 30 days of diagnosis for males 15-39 years of age at diagnosis

			Odds ratio				N	c
		% attending fertility consult within 30 days	Point estimate	Lower Bound	Upper Bound	p-value		
Cancer risk to fertility	**Low**	3.1	0.2	0.2	0.2	<.0001		
	Moderate	7.5	0.5	0.4	0.6	<.0001		
	High(ref)	14.2					13720	0.67
Diagnosis year	**2006-2010 (ref)**	4.2						
	2011-2015	5.6	1.4	1.1	1.6	0.001		
	2016-2019	16.8	4.6	3.9	5.4	<.0001	13720	0.67
Age at diagnosis (years)	**15-19 (ref)**	15.8						
	20-24	13.0	0.8	0.7	1.0	0.0181		
	25-29	10.8	0.6	0.5	0.8	<.0001		
	30-34	6.8	0.4	0.3	0.5	<.0001		
	35-39	3.5	0.2	0.2	0.2	<.0001	13720	0.65
Chemotherapy	**No (ref)**	5.1						
	Yes	10.7	2.2	1.9	2.6	<.0001	13720	0.59
Reproductive related surgery	**No (ref)**	6.7						
	Yes	13.5	2.2	1.9	2.4	<.0001	13720	0.59
Material Deprivation Quintile	**1**	12.2	2.4	1.9	2.9	<.0001		
	2	9.1	1.7	1.4	2.1	<.0001		
	3	9.7	1.8	1.5	2.3	<.0001		
	4	6.3	1.2	0.9	1.5	0.234		
	5 (ref)	5.5					13165	0.59
Income Quintile	**1**	5.4	0.5	0.4	0.6	<.0001		
	2	7.9	0.7	0.6	0.9	0.001		
	3	8.4	0.8	0.6	0.9	0.005		
	4	10.0	0.9	0.8	1.1	0.463		
	5 (ref)	10.6					13720	0.56
Ontario Marginalization Summary score	**1**	11.2	0.9	0.1	7.0	0.919		
	2		2.4	1.5	3.7	<.0001		
	3	9.0	1.9	1.2	2.9	0.004		
	4	6.7	1.4	0.9	2.1	0.166	13165	0.56

	5 (ref)	5.0						
Region	**North**	3.6	0.4	0.3	0.6	<.0001		
	South East	9.3	1.2	1.0	1.4	0.657		
	South West	8.3	1.0	0.9	1.3	0.657		
	Southern	11.3	1.5	1.3	1.7	<.0001		
	Central	7.9					13720	0.56
Ethnic Concentration Quintile	**1**	7.1	0.9	0.8	1.2	0.565		
	2	9.2	1.2	1.0	1.5	0.027		
	3	10.4	1.4	1.2	1.7	<.0001		
	4	9.1	1.2	1.0	1.5	0.020		
	5 (ref)	7.5					13165	0.54
Residential Instability Quintile	**1**	10.5	1.5	1.2	1.8	<.0001		
	2	8.8	1.2	1.0	1.5	0.043		
	3	8.6	1.2	1.0	1.4	0.097		
	4	8.4	1.2	1.0	1.4	0.137		
	5 (ref)	7.3					13165	0.54
Dependency Quintile	**1**	9.8	1.2	1.0	1.5	0.045		
	2	9.2	1.1	0.9	1.4	0.228		
	3	7.6	0.9	0.7	1.2	0.508		
	4	7.5	0.9	0.7	1.1	0.415		
	5 (ref)	8.2					13165	0.53
Radiation Therapy	**No (ref)**	7.9	1.2	1.1	1.4	0.002		
	Yes	9.4					13720	0.52
Death Within 1st Year of Diagnosis	**No (ref)**	8.8	0.5	0.4	0.7	<.0001		
	Yes	4.7					13720	0.52
Rural	**No**	8.7	1.5	1.1	1.9	0.002		
	Yes (ref)	6.1					13697	0.51

Appendix 2. Odds ratios and 95% confidence intervals for multivariate logistic regression with factors regressed on attending a fertility consult within 30 days of diagnosis for males 15-39 years of age at diagnosis

		95% Confidence Intervals	
	Odds Ratio	**Lower bound**	**Upper bound**
age 20-24 years	0.63	0.51	0.77
age 25-29 years	0.51	0.42	0.64
age 30-34 years	0.33	0.27	0.41
age 35-39 years	0.20	0.15	0.25
Rural (No)	1.35	1.03	1.79
North	0.35	0.25	0.51
South East	1.23	1.04	1.47
South West	1.02	0.81	1.29
Southern	1.51	1.26	1.80
dx year 2011-2015	1.30	1.07	1.59
dx year 2016-2019	5.50	4.58	6.59
Radiation (Yes)	1.36	1.18	1.56
Chemotherapy (Yes)	1.87	1.60	2.18
Reproductive surgery (Yes)	1.46	1.25	1.70
Income quintile 1	0.40	0.31	0.53
Income quintile 2	0.65	0.52	0.81
Income quintile 3	0.77	0.63	0.95
Income quintile 4	1.03	0.85	1.25
Residential instability 1	0.79	0.63	0.99
Residential instability 2	0.67	0.53	0.85
Residential instability 3	0.79	0.62	0.99
Residential instability 4	0.90	0.73	1.12
Fertility risk low	0.30	0.25	0.37
Fertility risk moderate	0.59	0.49	0.72

PART B. REFERRAL PATTERNS IN WOMEN WITH CANCER

ABSTRACT

Objective: To examine the factors associated with women attending a fertility consultation within 30 days of cancer diagnosis.

Design: A retrospective cohort study using administrative data from the Institute of Clinical and Evaluative Sciences (ICES).

Patients: Females, 15 to 39 years of age, diagnosed with cancer in Ontario, Canada between 2006 and 2019.

Intervention (s): Not applicable.

Main Outcome Measure(s): Odds ratios for attendance at a fertility consultation within 30 days of a cancer diagnosis.

Results: A total of 20,556 women were included in the study, with 7% having attended a fertility visit within 30 days of diagnosis. Factors including not currently having children (OR=4.3; 95% CI (3.6,5.1)), later years of diagnosis (OR=3.2; 95% CI (2.8,3.8)), and having undergone chemotherapy (OR=3.6; 95% CI (3.0, 4.3)) or radiation (OR=1.9; 95% CI (1.6,2.2)) were associated with being more likely to attend a consultation within 30 days. Having a cancer with lower risk to fertility (OR=0.3; 95% CI (0.2,0.3)), death within a year of diagnosis (OR=0.4; 95% CI (0.3,0.6)), and residing in a northern region of Ontario (OR=0.3; 95% CI (0.2,0.4)) were associated with being less likely to attend. For socio-demographic factors, lower levels of income (OR=0.5; 95% CI (0.4,0.6)) and residential instability marginalization (OR=0.6; 95% CI (0.5,0.8)) and less marginalization within dependency quintiles (OR 1.4; 95% CI (1.1, 1.7)) were also associated with being more likely to attend a fertility consultation.

Conclusions: Rates for female fertility consultations after a cancer diagnosis remain low, with disparities by both clinical and demographic factors.

INTRODUCTION

Adolescents and young adults (AYAs), 15 to 39 years of age, with cancer are recognized to have unique challenges.[1,2] Fertility is one of the most important issues for women diagnosed with cancer which can impact both quality of life and psychosocial well-being.[3-9] Females with cancer have reported to be frustrated regarding both a lack of information about fertility risks as well as an inability to undertake fertility preservation before treatment.[6] Providing patients with information before treatment regarding fertility is important considering the results of a recent study which showed that female cancer survivors had a 30% greater overall risk of an infertility diagnosis than a matched cohort of females who had never had cancer .[10] Research has also shown that fertility consultations before treatment can reduce regret related to decisions around fertility preservation.[9] Better understanding of factors affecting uptake of fertility consultations in this population is important to help improve oncofertility care in women with cancer.

There are many factors related to cancer and its treatment which may lead to lower fertility rates in female survivors, with the risk to fertility highly dependent upon both the specific treatment and the particular disease.[11] There are several potential options for women to preserve fertility after a cancer diagnosis including fertility sparing procedures, embryo or oocyte cryopreservation. However, the availability of these vary according to age at diagnosis, cancer type and access to specialized fertility clinics. Discussion regarding fertility preservation before cancer treatment is recommended for all young cancer patients, to discuss these options and help patients better understand fertility risks before undergoing therapy.[12-14] Pre-treatment fertility consultations have been found to lead to greater uptake of fertility preservation in women diagnosed with cancer.[7]

Also, those women who underwent fertility preservation had less regret after cancer treatment than those who did not pursue this option.[7]

Some work has been done examining factors associated with referral of cancer patients for fertility consultation. Investigators in the Netherlands, which also has a publicly funded healthcare system, conducted a study of female cancer patients, finding that 9.8% were referred for fertility preservation counselling, with breast cancer and lymphoma and being aged 20-29 years at diagnosis as important factors associated with acceptance of fertility counselling.[15] In Ontario, Canada two studies have examined fertility consultation referrals, finding low rates for female AYAs with breast cancer[16] and lymphoma.[17] However, these studies were disease specific, not covering all females diagnosed with cancer.

In order to ensure effective planning it is important to understand the current state of fertility referrals which occur within the optimal window before commencement of treatment. The objective of this study was to determine factors associated with attending a fertility consultation for AYA women with cancer in Ontario within the first 30 days of cancer diagnosis. Thirty days after diagnosis was chosen as a proxy for the start of treatment, based on results from the development of an indicator to monitor oncofertility care.[18]

METHODS

A retrospective cohort study, approved by Hamilton Integrated Research Ethics Board (HiREB), was performed on data obtained from the Institute of Clinical Evaluative Sciences (ICES) in Toronto, Ontario. All analyses were completed in iDAVE, a remote access server using SAS.

Population

We included all females, 15 to 39 years of age, diagnosed with cancer in Ontario between January 1, 2006 and September 30, 2019. Exclusion criteria were a secondary cancer diagnosis; fertility consultation preceding 30 days prior to cancer diagnosis; non-Ontario resident status; and prior sterilization procedure (hysterectomy, oophorectomy, tubal ligation). Sterilization procedures were identified using the following diagnostics codes in the Ontario Health Insurance Plan (OHIP): S816, S781, S776, S763, S762, S759, S758, S757, S727, S710, P042, E090, S799, S782, S750, S747, S745, S738, S727, S714, E853, S741, P041, S783.

Data

Data were extracted between April 1, 1988 and November 30, 2020 from the following administrative databases housed at ICES: Ontario Cancer Registry (OCR), OHIP Claims Database, Registered Persons Database (RPDB), MOMBABY and Cancer Activity Level Reporting (ALR).

A service visit for a female fertility consultation was identified using the diagnostic billing code ICD-9 628 in the OHIP database. The male infertility ICD-9 606 billing code was also included because misclassification by sex has been identified for this code.[18] Treatment information for chemotherapy and radiation were obtained from ALR. Reproductive related cancer surgeries (excluding biopsies) were identified from OHIP using billing codes which have been identified previously by ICES (R912, R913, S213, S312, S704, S705, S710, S714, S738, S744, S745, S750, S754, S757, S758, S759,

S762, S763, S764, S765, S766, S767, S776, S781, S782, S810, Z553, Z563, Z583, Z720, Z723, Z729, Z730, Z731, Z735, Z766, Z769). [19]

Factors included in analyses were informed by those identified previously by Korkidakis et al 2019 and Coleman et al 2020.[16,17] Data for patient characteristics were obtained from RPDB, including rurality, as well as quintiles for residential instability, material deprivation, economic dependency and ethnic concentration. Quintiles are interpreted as marginalization on an ordinal scale from one (least) to five (most). A summated score of marginalization was also calculated as described by Matheson and van Ingen.[20] Neighbourhood income quintiles were also considered and represented on an ordinal scale from one (poorest) to five (wealthiest). Clinical factors, including age at diagnosis, year of diagnosis (2006-2010, 2011-2015, 2016-2019), cancer diagnosis, type of treatment received (chemotherapy, radiation, reproductive related cancer surgery), death within one year of diagnosis, and geographical region of oncology care were also examined. Years of diagnoses were grouped according to time periods of changes which occurred in oncofertility care as follows: 2006-2010, oncofertility field newly formed; 2011-2015, a period of greater awareness, and the addition of oocyte cryopreservation; 2016-2019, government funding became available for cancer patients in Ontario. Cancer diagnoses were defined according to Barr et al[21] and grouped into low (melanoma, thyroid cancer, other), moderate (brain tumors, bone and soft tissue sarcomas, breast cancer, colorectal cancer), and high risk (cancers of the reproductive tract, Hodgkin and non-Hodgkin lymphoma, leukemias) of future infertility. Parity of cases was obtained from MOMBABY.

Analysis

Descriptive statistics were calculated for all demographic and clinical variables and occurrences of missing data were assessed.

Univariate analyses were completed using one factor logistic regression models with intercepts to assess the relationship of each factor to the outcome event of attending a fertility consulttion within 30 days of diagnosis. Correlations between continuous variables were assessed; if variables had a correlation coefficient >0.70 one variable was excluded from multi-variate modelling. Significant factors from the univariate analyses were entered into a logistic model using a backward approach, with a two way cut-off $p<0.05$ for inclusion in the model. Odds ratios and 95% confidence intervals were calculated for the final model. Model fit was assessed using the Hosmer and Lemeshow Goodness of Fit test, AIC and the concordance statistic. Cases with missing data were excluded from the logistic model.

RESULTS

Demographic and clinical statistics are shown in Table 1. There were 20,556 AYA females diagnosed with cancer during the time period included in analyses. A considerable (84%) majority of cases did not attend a fertility consultation within 30 days of diagnosis. The proportion over time in this study is shown in Figure 1.

Univariate results

These are shown in Appendix 1. All factors were associated significantly with attending a fertility consultation ($p\leq0.006$), with a concordance statistic >0.50. The material deprivation and income quintile were correlated ($r=0.73$; $p<0.0001$), therefore the material deprivation quintile was dropped from modelling and the income quintile was

retained because of a lower percentage of missing data. Also, because the Ontario Marginalization Summary Score is an index of the ethnicity concentration, economic dependency, residential instability and material deprivation quintiles it was dropped from further modelling as it had the lowest concordance value of the associated variables and small cell sizes.

Multivariate results

The backwards elimination was completed in three steps, with the Ontario rurality index (step1 p=0.72) reproductive-related surgery (step 2 p=0.39), and ethnic concentration quintile (p=0.13) removed from the final model. The Hosmer and Lemeshow Goodness of Fit test indicated that the final model fit the data well (p=0.979). Point estimates for odds ratios and 95% confidence intervals for final model parameters are shown Figure 2 (Appendix 2). Effect sizes with increased odds of attending a fertility consultation within 30 days of diagnosis were greatest for not currently having children (OR=4.3; 95% CI (3.6,5.1)), later years of diagnosis (OR=3.2; 95% CI (2.8,3.8)), and having undergone chemotherapy (OR=3.6; 95% CI (3.0, 4.3)) or radiation (OR=1.9; 95% CI (1.6,2.2)). Having a cancer with lower risk to fertility (OR=0.3; 95% CI (0.2,0.3)), death within a year of diagnosis (OR=0.4; 95% CI (0.3,0.6)), and residing in a northern region of Ontario (OR=0.3; 95% CI (0.2,0.4)) were associated with being less likely to attend a fertility consultation within 30 days of diagnosis . Lower income (OR=0.5; 95% CI (0.4,0.6)) and marginalization in residential instability (OR=0.6; 95% CI (0.5,0.8)) were also associated with being less likely to attend a fertility consultation within 30 days.

Being less marginalized within the dependency quintiles (OR 1.4; 95% CI (1.1, 1.7)) was associated with an increased likelihood of attending a fertility consultation.

DISCUSSION

The results of this study identified factors associated with attendance at a fertility consultation within 30 days of diagnosis by female AYAs (women 15-39 years of age) with cancer. The findings are consistent with previous work in women with breast cancer and lymphoma.[16,17] Overall, the proportion of women attending fertility consultations was 7% (10.2% in the most recent period, 2016-2019), similar to previously reported rates for breast cancer (8.0%) [16] and lymphoma (10.7%).[17] Increasing attendance at consultations over time was also consistent with previous reports.[16,17] Despite improvements over time, rates remain low with important disparities related to clinical and socio-demographic factors.

As described previously by both Korkidakis et al[16] and Coleman et al,[17] parity was one of the most important factors associated with attending a fertility consultation appointment, with women who did not have children being 4 times more likely to attend the visit. Parity has also been described as an important factor influencing referral for fertility preservation in women diagnosed with cancer in the United States.[22] It is important to determine the mechanism underlying this finding and whether women with children decide not to pursue fertility preservation because of completion of their family or whether clinicians are less likely to discuss fertility risk with women who already have children. Previously, Adam et al[23] found that a patient already having children was considered a barrier for oncologists initiating discussion about fertility preservation. Also,

in a national American survey, 10% of oncologists identified already having children as a reason for not discussing fertility.[24] Further understanding of patient and clinician attitudes and beliefs surrounding parity and fertility preservation is needed to ensure that women with children are being informed of the risks to fertility and offered services.

Parity may also partly explain the low rates of referral for those 35-39 years of age (4.1%) compared to younger age groups (20 to 34 year of age), range 8.1-9.6%, with increasing age likely associated with completion of child bearing. However, the 20-34 year age group was approximately two times more likely to attend a fertility consultation than the youngest age group 15-19 years of age. A study examining barriers to fertility preservation for pediatric patients from the perspective of oncologists found that, although most physicians were comfortable with discussing sperm banking, only half of physicians in the study stated that they discussed fertility preservation with females, with most reporting that they were unfamiliar with the options.[25] The lack of knowledge of preservation options for young female patients was also highlighted in a single site study of health care professionals in a pediatric hematology/oncology service.[26] This also fits with findings from an indicator development study which found a notable disparity between female and male adolescent cancer patients within the 15-19 years age group, with 31% of males attending a fertility consultation compared to only 8.5% of females.[18] This difference may be attributable to the complexity of fertility preservation procedures for females, lack of provider knowledge of female fertility preservation options, or access to specialized services.[25-27] Mature oocyte cryopreservation requires the administration of gonadotropins for 8 to 14 days followed by surgical retrieval of oocytes guided by

transvaginal ultrasound. [28] This may be a barrier for some females given their young age, because of the invasiveness of the procedure and worries about delaying treatment. The development of a Pediatric Fertility Preservation Program, similar to the one discussed by Moravek et al,[28] to support young adolescent cancer patients may help facilitate increased use of fertility preservation in this group.

Year of diagnosis was an important factor with women diagnosed in 2016-2019 three times more likely to attend a consultation than those diagnosed in the earliest time period. Funding for fertility preservation was implemented in Ontario in December 2015, reducing financial barriers. However, increases in uptake of consultations after funding was not as distinct as an increase reported in men,[29] with trends for women having increased more steadily over time. Another factor likely associated with improving rates maybe the approval of oocyte cryopreservation for non-experimental use in 2013.[30] Since this method does not require a sperm donor this option may reduce barriers for younger patients who are not yet in long-term relationships.[30] Policy changes did not lead to a substantial increase in consultations suggesting that advocacy and research targeted at women with cancer in Ontario[31,32] have also played an important role in the steady upwards trend oberved in this study.

There were many clinical factors associated with attending a fertility consultation, including death within the first year after diagnosis, cancer risk to fertility, and the type of treatment received. Death within in the first year after diagnosis was used as a proxy for the severity of the cancer. Cancer staging was found previously to be associated significantly with attendance at a fertility consultation in univariate analyses, but not in a

multi-variate analysis, for women with breast cancer, with lower stages having higher consultation rates.[16] In this current study, women who did not survive beyond a year of diagnosis were 60% less likely to attend a fertility consultation, suggesting that the severity of the cancer could impact the views of both patients and clinicians on fertility preservation prior to treatment.

Risk to fertility was also an important factor. It has been suggested that detailed treatment information should be used to determine the risk to fertility, given that there are only a few cancers for which the disease impacts fertility directly.[33] However, this approach was infeasible for this study because administrative data in Ontario are not detailed enough to allow this classification. This lack of detail is a barrier to more in depth exploration of treatment risks to fertility in cancer patients. However, despite the broad nature of the classification, 'risk to fertility' was still an important factor. Women with cancers having moderate risk (13.1%) to fertility were more likely to attend fertility consultations than those with cancers having a higher risk to fertility (9.2%). This unexpected difference may be attributable to a focus on fertility in women with breast cancer, a cancer classified with a moderate risk to fertility. Much research has focused on this sub-group of patients in relation to fertility, including the development of breast cancer specific decision aids for fertility preservation.[31,34,35]Also Srikanthan et al,[32] found that a dedicated program for breast cancer patients helped improve fertility referrals of these women, suggesting that cancer-specific approaches may be effective methods for improving uptake of fertility consultations. Two institutions in which a set of decision aids were developed (Women's College Hospital) [31] and the fertility program dedicated

to breast cancer was implemented (The Odette Cancer Centre)[32] are both located in Toronto, Ontario, and are therefore included in this study's analysis. These institutions treat a large proportion of AYA aged breast cancer patients in Ontario. This likely had substantial influence on the results of our Ontario-based study, and this disease-related finding may not be generalizable to other provinces or countries, but warrants further investigation.

Receiving chemotherapy or radiation were also important factors associated with women attending fertility consultations. The effects of chemotherapy and radiation on female fertility are well documented, mainly affecting oocyte and gonadal function.[36,37] There is a dose relationship with higher doses increasing the risk to fertility.[11] Age and ovarian reserve are important factors influencing the risk that radiation and chemotherapy pose to fertility.[36] In the multivariate model, receiving chemotherapy and/or radiation resulted in an increased likelihood of attending a fertility consultation by a factor of 3 and 2, respectively.

Surprisingly, women who underwent reproductive related surgeries were not more likely to attend a fertility consultation, and this was not a significant factor in the final model. Surgery to reproductive organs and radiation to either the pelvic area or the hypothalamic-pituitary-gonadal axis can lower fertility rates in female cancer survivors.[11,38] Although fertility sparing surgery is possible for most germ cell tumors regardless of stage,[39] it would be expected that this group with gynecological cancer would have some of the highest rates of referral for fertility consultation given the nature of their cancer. In a recent review of the literature, examining quality of life and fertility

preservation counseling for women with gynecological cancers, it was noted that fertility preservation has an important impact on both quality of life and psychological well-being in survivors.[8] It is important to better understand the lower consultation rates in women undergoing reproductive-related cancer surgeries (7.7%) compared to the other treatment modalities, chemotherapy (11.7%) and radiation therapy (11.6%). Women with gynecological cancers were also found to have a lower fertility consultation rate (9.9%) within 30 days of diagnosis than other cancers, such as breast cancer (25.1%),[18] suggesting that women with these cancers are less likely to attend a consultation regardless of treatment received.

Another important factor in attending a fertility consultation was geographical region of care, for women with cancer in northern Ontario were 70% less likely to attend a consultation than women being treated in central and southern Ontario. Fertility preservation for women requires specialized IVF clinics, none of which is located in northern Ontario.[27] Results in this study were consistent with those found in women with breast cancer, with fewer than 1% of women attending fertility consultations who were treated in northern regions of the Province.[16] Rashedi et al[40] examined fertility preservation options for patients with cancer globally, noting that lack of providers was a specific barrier to fertility preservation in Canada. Given the large geographic area of the province of Ontario, travel distance and costs may present a major challenge for women living in northern regions to access fertility preservation before the start of treatment.

Socio-demographic factors also contributed to the likelihood a woman attended a fertility consultation. Residential instability relates to neighbourhood areas with high

levels of housing or family instability.[20] In our study we found that living in the most marginalized neighbourhoods for this indicator was related to slightly higher rates of fertility consultations than those with more residential stability. Areas with high levels of instability are considered areas with large populations of people living alone, unowned dwellings, apartment buildings, and a high proportion of residents who have moved in the last five years.[20] All these factors are generally associated with younger age groups and individuals who have not yet begun their family; both factors associated with attending a fertility consultation.

This study also found that higher income and lower levels of marginalization in the dependency quintile (high proportion of population in uncompensated work or receiving a disability pension) were associated with a greater likelihood of attendance at a fertility consultation. Previous studies did not find any association between income quintile and attendance at a fertility consultation for women diagnosed with breast cancer or lymphoma.[16,17]However, material deprivation was a significant factors for women with lymphoma.[17] Three other studies also noted no association between income and fertility preservation access in women with cancer.[41-43] However, it has been reported that there is a significant association between level of education and referral for fertility consultations, with women who held a bachelor's degree more likely to be referred.[42]Given that the cost of the initial fertility consultation visit is covered by the Ontario government, and further funding is available for cancer patients to undergo fertility preservation,[44,45] it is possible that income and material deprivation are more reflective of a person's educational

attainment rather than a financial barrier to care. Woman with higher education may be better able to obtain information and better advocate for fertility preservation services.

Although this study had many strengths and represented a large population of AYA aged women with cancer, it does have some limitations. Firstly, the accuracy and completeness of treatment data are unknown. A previous report regarding the development of an oncofertility care indicator identified potentially missing treatment information within the ALR database, and given the nature of the data the percent missing for chemotherapy or radiation cannot be calculated. A previous report on the quality of ALR treatment data using chart abstraction for women with breast cancer found that only 4.5% of chemotherapy data and 1.2% of radiotherapy data were incomplete.[46] Sociodemographic information was also not available at the individual case level but was representative of the neighbourhood in which the individual resided. Demographic data at the individual level could provide more accurate results as well as further insight into differences in fertility consultation rates by race, gender and educational attainment. Also, this study only examined consultations for fertility and may not account for those women who go on to receive fertility preservation. Capturing further information about fertility services in administrative databases could greatly inform the field of oncofertility in Ontario, as well as ensure equitable distribution of services.

CONCLUSIONS

Although improvements are being made in oncofertility care for women shown by increasing uptake of fertility consultations over time, rates remain low. This study also highlighted disparities in clinical and demographic factors influencing the attendance at

fertility consultations within 30 days of diagnosis. The factors identified in this study can be used to inform implementation of various strategies such as targeted decision aids, specialized programs and oncofertility models of care, to help improve consultation rates for fertility preservation prior to treatment in women with cancer.

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TABLES AND FIGURES

Table 1. Clinical and demographic statistics, females aged 15-39 years diagnosed with cancer in Ontario, Canada (N=**20,556)**

Characteristic	Subgroup	%	N	% attendance fertility consult
Fertility Consult within 30 Days dx	**No**	93.2	19154	
	Yes	6.8	1402	
Year of Cancer Diagnosis	**2006-2010**	34.2	7019	4.1
	2011-2015	36.2	7441	6.6
	2016-2019	29.7	6096	10.2
Age at Diagnosis (years)	**15-19**	5.9	1218	4.4
	20-24	10.6	2175	8.1
	25-29	17.7	3645	9.8
	30-34	27.6	5672	8.6
	35-39	38.2	7846	4.1
Cancer Diagnosis	**Brain tumour**	1.3	271	2.2
	Bone tumours	0.7	139	4.3
	Breast cancer	20.6	4234	16.2
	Colorectal cancer	4.6	950	8.0
	Reproductive tract	13.7	2821	5.7
	Hodgkin lymphoma	5.1	1045	19.6
	Leukemia	1.6	332	*combined with 'other'
	Melanoma	6.9	1418	1.0
	Non Hodgkin lymphoma	4.4	906	10.9
	Soft tissue sarcoma	2.0	413	3.1
	Thyroid	25.0	5132	0.6
	Other	14.1	2895	3.4
Fertility Risk Associated with Cancer Diagnosis	**Low**	46.0	9445	1.5
	Moderate	29.2	6007	13.1
	High	24.8	5104	9.2
Region	**Central**	9014	43.9%	8.5
	North	1633	7.9%	2.6
	South East	4648	22.6%	7.5
	South West	2198	10.7%	4.6

	Southern	3063	14.9%	4.6
Rural	**No**	91.9	18880	7.1
	Yes	8.1	1660	3.9
	Missing		16	
Parity	**No**	64.2	13205	9.2
	Yes	35.8	7351	2.6
Death 1st year	**No**	96.4	19823	6.9
	Yes	3.6	733	3.5
Chemotherapy	**No**	49.1	10086	1.8
	Yes	50.9	10470	11.7
Radiation	**No**	56.9	11701	3.2
	Yes	43.1	8855	11.6
Reproductive Surgery	**No**	74.7	15360	6.5
	Yes	25.3	5196	7.7
Nearest Neighbourhood Income Quintile	**1 - Lowest**	19.4	3981	5.7
	2	20.3	4156	6.3
	3	20.4	4177	6.2
	4	21.1	4321	7.6
	5 - Highest	18.9	3864	8.3
	Missing		57	
Residential Instability Quintile	**1 -Least**	21.2	4187	6.2
	2	17.4	3444	6.6
	3	16.8	3318	5.8
	4	18.0	3551	6.2
	5 -Most	26.6	5247	8.9
	Missing		809	
Ethnic Concentration Quintile	**1 -Least**	12.1	2388	4.1
	2	14.3	2822	5.4
	3	18.3	3603	7.6
	4	23.6	4656	8.4
	5 -Most	31.8	6278	7.2
	Missing		809	
Material Deprivation Quintile	**1 -Least**	22.1	4366	9.6
	2	20.9	4129	7.7
	3	18.9	3734	6.2
	4	18.2	3590	5.7
	5 -Most	19.9	3928	4.9

	Missing		809	
Dependency Quintile	**1 -Least**	30.8	6078	8.2
	2	22.4	4417	6.7
	3	17.7	3487	6.7
	4	15.6	3074	5.9
	5 -Most	13.6	2691	5.7
	Missing		809	
Ontario Marginalization Summary Score	**1 -Least**	0.1	25	6.3*
	2	23.1	4552	
	3	42.0	8283	7.8
	4	31.3	6172	6.3
	5 -Most	3.6	715	5.6
	Missing		809	

*Values merged cell size < 6

Figure 1. Percentage of AYA females with cancer attending a fertility consultation within 30 days of diagnosis, by year of diagnosis

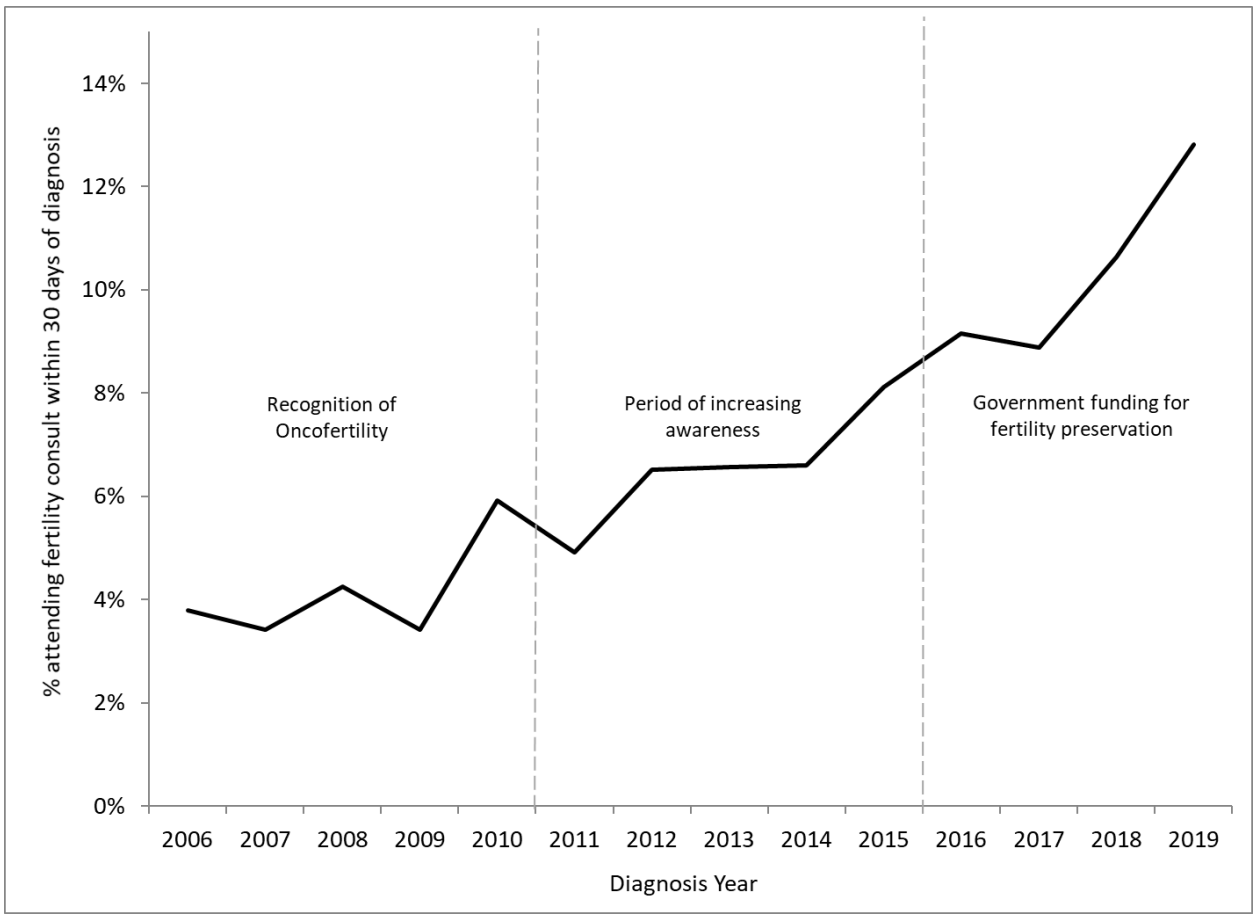
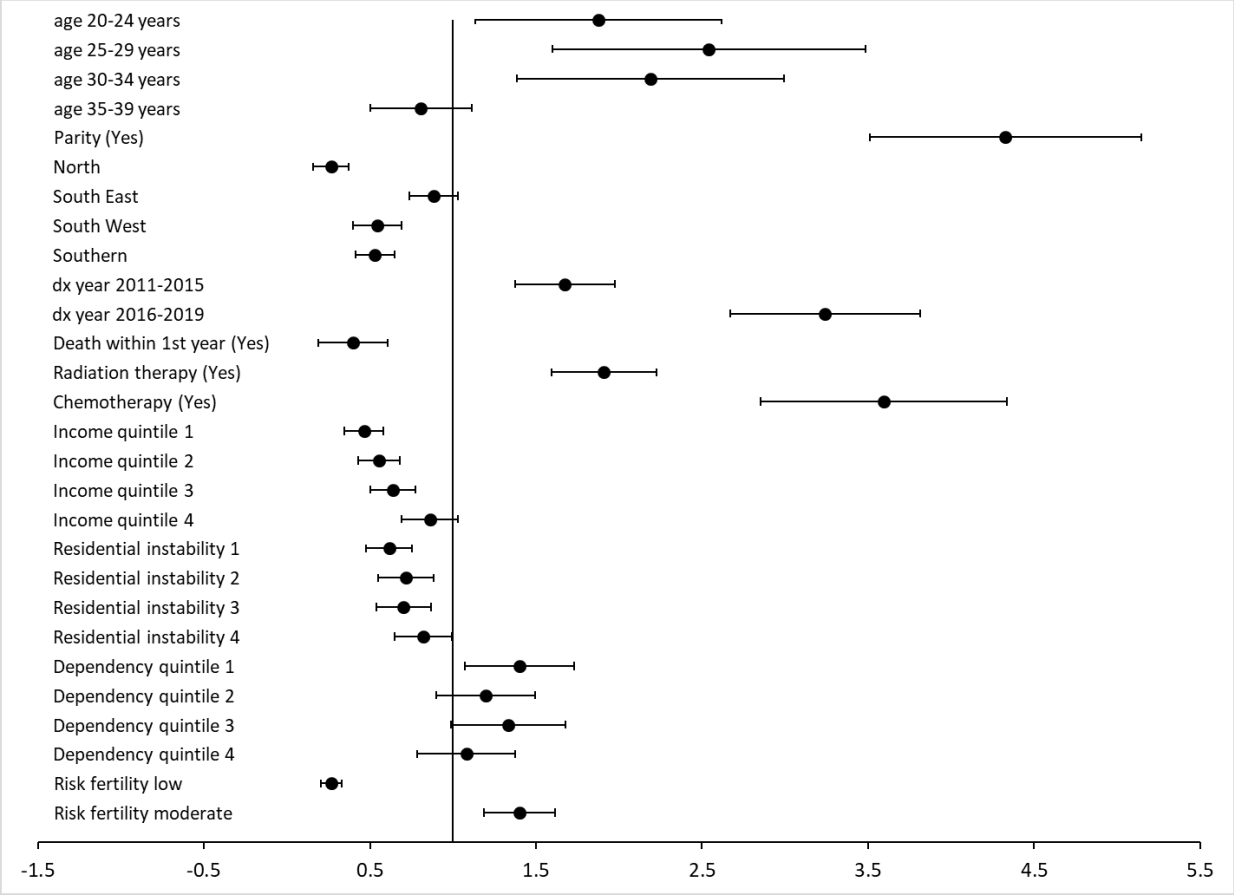


Figure 2. Odds ratios and 95% confidence intervals for multivariate logistic regression with factors regressed on attending a fertility consult within 30 days of diagnosis for females 15-39 years of age at diagnosis



dx - diagnosis

*Reference categories: Age at dx 15-19 years; Region Central; dx year 2006-2010; Income quintile 5 wealthiest; Residential instability 5 most marginalized; Dependency quintile 5 most marginalized; Risk to fertility high

Appendix 1. Odds ratios and 95% confidence intervals for Univariate logistic regression with factors regressed on attending a fertility consult within 30 days of diagnosis for females 15-39 years of age at diagnosis

			Odds ratio				N	c
		% fertility consult	Point estimate	Lower Bound	Upper Bound	p-value		
Fertility risk of cancer dx	**Low**	1.5	0.15	0.13	0.18	<.0001	20556	0.71
	Moderate	13.1	1.49	1.32	1.68	<.0001		
	High(ref)	9.2						
Chemotherapy	**No (ref)**	1.8					20556	0.69
	Yes	11.7	7.27	6.20	8.53	<.0001		
Radiation therapy	**No (ref)**	3.2					20556	0.66
	Yes	11.6	3.95	3.50	4.46	<.0001		
Parity	**No**	9.2	3.81	3.26	4.45	<.0001	20556	0.62
	Yes (ref)	2.6						
Year of Diagnosis	**2006-2010 (ref)**	4.1					20556	0.60
	2011-2015	6.6	1.63	1.40	1.89	<.0001		
	2016-2019	10.2	2.63	2.28	3.03	<.0001		
Age at Diagnosis	**15-19 (ref)**	4.4					20556	0.60
	20-24	8.1	1.94	1.41	2.65	<.0001		
	25-29	9.8	2.40	1.79	3.23	<.0001		
	30-34	8.6	2.08	1.56	2.78	<.0001		
	35-39	4.1	0.95	0.70	1.27	0.718		
Region	**North**	2.6	0.29	0.21	0.40	<.0001	20556	0.58
	South East	7.5	0.87	0.76	0.99	0.033		
	South West	4.6	0.52	0.42	0.64	<.0001		
	Southern	4.6	0.51	0.43	0.62	<.0001		
	Central	8.5						
Material Deprivation Quintile	**1 -Least**	9.6	2.09	1.75	2.49	<.0001	19747	0.57
	2	7.7	1.63	1.35	1.96	<.0001		
	3	6.2	1.30	1.06	1.58	0.010		
	4	5.7	1.19	0.97	1.45	0.101		
	5 (ref) - Most	4.9						
Ethnic Concentration Quintile	**1 -Least**	4.1	0.56	0.45	0.70	<.0001	19747	0.56
	2	5.4	0.73	0.60	0.88	0.001		
	3	7.6	1.05	0.90	1.23	0.508		
	4	8.4	1.18	1.02	1.35	0.025		
	5 (ref) - Most	7.2						
Residential Instability	**1 -Least**	6.2	0.68	0.58	0.79	<.0001	19747	0.56
	2	6.6	0.73	0.62	0.86	0.0002		

Quintile	**3**	5.8	0.64	0.53	0.76	<.0001		
	4	6.2	0.68	0.58	0.81	<.0001		
	5 (ref) - Most	8.9						
Dependency Quintile	**1 -Least**	8.2	1.48	1.23	1.78	<.0001	19747	0.54
	2	6.7	1.19	0.97	1.45	0.094		
	3	6.7	1.19	0.96	1.46	0.113		
	4	5.9	1.03	0.83	1.29	0.789		
	5 (ref) - Most	5.7						
Income Quintile	**1 - Lowest**	5.7	0.68	0.57	0.81	<.0001	20499	0.54
	2	6.3	0.75	0.63	0.89	0.001		
	3	6.2	0.74	0.62	0.87	0.0004		
	4	7.6	0.92	0.78	1.08	0.300		
	5 (ref) - Highest	8.3						
Ontario Marginalization Summary Score	**1 -Least**	6.3*	0.71	0.09	5.33	0.737	19747	0.53
	2		1.14	0.81	1.61	0.439		
	3	7.8	1.43	1.03	1.98	0.035		
	4	6.3	1.14	0.82	1.60	0.440		
	5 (ref) -Most	5.6						
Rurality Index of Ontario	**No**	7.1	1.87	1.45	2.41	<.0001	20540	0.52
	Yes (ref)	3.9						
Reproductive elated surgery	**No (ref)**	6.5					20556	0.52
	Yes	7.7	1.19	1.05	1.34	0.005		
Death within 1st year of diagnosis	**No (ref)**	6.9					20556	0.51
	Yes	3.5	0.49	0.33	0.73	0.001		

*values merged cell size <5

Appendix 2. Odds ratios and 95% confidence intervals for multivariate logistic regression with factors regressed on attending a fertility consult within 30 days of diagnosis for females 15-39 years of age at diagnosis

		95% Confidence interval	
Characteristic	**Point Estimate**	**Lower**	**Upper**
age 15-29 years (ref)			
age 20-24 years	1.9	1.3	2.6
age 25-29 years	2.5	1.9	3.5
age 30-34 years	2.2	1.6	3.0
age 35-39 years	0.8	0.6	1.1
Parity (Yes)	4.3	3.6	5.1
Central (ref)			
North	0.3	0.2	0.4
South East	0.9	0.8	1.0
South West	0.5	0.4	0.7
Southern	0.5	0.4	0.7
dx year 2006-2010 (ref)			
dx year 2011-2015	1.7	1.4	2.0
dx year 2016-2019	3.2	2.8	3.8
Death within 1st year (Yes)	0.4	0.3	0.6
Radiation therapy (Yes)	1.9	1.6	2.2
Chemotherapy (Yes)	3.6	3.0	4.3
Income quintile 1	0.5	0.4	0.6
Income quintile 2	0.6	0.5	0.7
Income quintile 3	0.6	0.5	0.8
Income quintile 4	0.9	0.7	1.0
Income quintile 5 (ref)			
Residential instability 1	0.6	0.5	0.8
Residential instability 2	0.7	0.6	0.9
Residential instability 3	0.7	0.6	0.9
Residential instability 4	0.8	0.7	1.0
Residential instability 5 (ref)			
Dependency quintile 1	1.4	1.1	1.7
Dependency quintile 2	1.2	1.0	1.5
Dependency quintile 3	1.3	1.1	1.7
Dependency quintile 4	1.1	0.8	1.4
Dependency quintile 5 (ref)			
Risk fertility low	0.3	0.2	0.3
Risk fertility moderate	1.4	1.2	1.6
Risk fertility high (ref)			

CHAPTER 8: CONCLUSIONS

This thesis worked to build knowledge in the area of system performance metrics. Each paper included in this work has provided an important contribution to the development and implementation of metrics for use in AYA cancer care and control.

Scoping Review

Gaps in the availability of indicators specific for the AYA cancer population were identified through a scoping review. Specifically, important availability gaps were observed for fertility, psychosocial care, and prevention. The results of the scoping review are useful to help guide other indicator processes being undertaken by organizations in other countries. Initial results of this scoping review informed the brainstorming portion of the subsequent indicator development paper.

Indicator Development

In order to address the gaps identified in the scoping review a consensus-based process was undertaken identifying 14 indicators agreed upon by relevant stakeholders. The purpose of the indicators was to report on processes and outcomes in AYA cancer care and control in Canada. The assembled stakeholder group assessed both the importance and feasibility of each indicator, and related the indicator to the principles and recommendations framework that was created by Fernandez et al.[8] Work to implement these indicators into practice has involved sharing the publication with CPAC's national AYA cancer network as well as the Pediatric Oncology Group of Ontario's (POGO) AYA working group. It is recommended that indicators be implemented in stages starting

with the most feasible to help build buy-in from provinces for AYA-specific indicators. Much work in Canada is required to expand administrative databases and data collection to facilitate the reporting of indicators specific to the AYA population. In order to improve outcomes in this population, efforts should also be made to collaborate with partners in other countries to report and collect on a common set of core indicators. This will allow comparisons between various national strategies to address the needs of the AYA cancer population, as well as allowing examination of outcomes for AYAs with rarer cancers. Work also needs to be undertaken to further develop the identified indicators, including creation of data definitions and identification of benchmarks. The subsequent projects explored two indicators identified by stakeholders: "*Proportion of AYA patients screened for distress with standardized AYA specific tools*" and "*Proportion of AYA patients who had fertility preservation discussion before treatment*".

Psychosocial Care: Distress screening

In order to implement a distress screening indicator for AYA cancer care, it is important to assess available measures for suitability in this population. This thesis examined criteria for selecting a patient report outcome measure (PROM) for use in performance measurement developed by the National Quality Forum (Cella et al[17]) to assess four measures for distress screening in AYA cancer patients and survivors. Measures included PROMS commonly used to assess distress in cancer patients: Hospital Anxiety and Depression Scale (HADS), Edmonton Symptom Assessment Scale – revised (ESAS-r), and the National Cancer Comprehensive Cancer Network - Distress Thermometer (NCCN-DT). This study also assessed the newly developed Cancer Distress Scales –

Adolescent and Young Adults (CDS-AYA). In order to include the CDS-AYA in this assessment it was necessary to first develop cut-points to help interpret scale scores to identify distress. Although cut-points for distress were determined for all five of the CDS-AYA cancers, only the cut-points for the Emotional and Impact of Cancer scales had suitable sensitivity and specificity for inclusion in the comparison study. Using the NQF criteria for selection of a PROM for use in performance measurement showed that, overall, the measures: had good reliability and construct validity; were not burdensome; and were interpretable. The most important difference between the measures was content validity for the AYA population. Content validity assesses how understandable, relevant, and comprehensive the items contained in a measure are to the target population. Of the measures and sub-scales examined, only the CDS-AYA Impact of Cancer scale had content that was considered highly relevant to AYAs with cancer. This paper further highlighted the importance of measure selection by showing the variance between PROMs in the proportion of patients screening positive for distress. Variations likely were related to the differences in the construct of distress which was measured. This work has helped improve the utility of the CDS-AYA by addressing the interpretability of the scales through identification of distress cut-points. The work comparing PROMs is important to help guide the selection of measures for use in both distress screening and performance measurement.

Oncofertility

In order to implement programs to help improve Oncofertility care, it is important to have metrics to monitor for changes in both outcomes and processes. This thesis

evaluated and recommended the indicator "*proportion of cases attending a fertility consult visit ≤ 30 days from diagnosis of cancer*" according to development guidelines provided by the NQF. This presented indicator met the five development criteria of: 'importance to measure and report', 'scientific acceptability of measure properties (validity and reliability)', 'feasibility', 'usability and use', and 'related and competing measures'. There is potential for this indicator to be applied at various system levels, including internationally, which would enable comparisons across countries and models of cares. Incorporating this indicator into national system performance reports such as those produced by CPAC would allow monitor of this indicator over time. This would help to ensure improvements are occurring with various changes in practice and increased awareness of fertility issues in cancer patients. This thesis also identified disparities by both clinical and demographic factors within fertility referral patterns for both men and women diagnosed with cancer. This information can help to inform policies and interventions to improve uptake of fertility consultations within those patient sub-groups that are least likely to attend this service. Enhancement of administrative databases for cancer to enable them to capture greater treatment detail, individual level socio-demographic information, and use of fertility services would greatly facilitate research and advancements in the field of Oncofertility.

Summary

The work presented in this thesis helps to build upon the foundational work of the Canadian Task Force on AYAs with Cancer in which the candidate was a central participant. It has identified and developed indicators based on the principles and

recommendation for AYA cancer care presented in the framework which was developed through stakeholder engagement and collaboration at two international multi-stakeholder workshops.[8,9] The metrics identified in this thesis when implemented will help to monitor and evaluate AYA cancer care in Canada, as well as inform efforts in other countries. It is essential to develop minimum datasets for AYA cancer to support the reporting of system performance metrics in this population. As efforts continue to grow internationally to help support and improve outcomes and care in the AYA cancer population, the metrics identified in this thesis will provide a means to monitor and evaluate the resources, programs and treatments being used to care for this population.

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