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Coronary artery disease surveillance among childhood, adolescent, and young adult cancer survivors: a systematic review and recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group

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ABSTRACT

Background

Coronary artery disease (CAD) is a concerning late outcome for cancer survivors. However, uniform surveillance guidelines are lacking.

Aim

To harmonize international recommendations for CAD surveillance for survivors of childhood, adolescent and young adult (CAYA) cancers.

Methods

A systematic literature review was performed and evidence graded using the Grading of Recommendations, Assessment, Development, and Evaluation criteria. Eligiblity included English language studies, a minimum of 20 off-therapy cancer survivors assessed for CAD, and 75% diagnosed prior to age 35 years. All study designs were included, and a multidisciplinary guideline panel formulated and graded recommendations.

Results

32 of 522 identified articles met eligibility criteria. The prevalence of CAD ranged from 0-72% and was significantly increased compared to control populations. The risk of CAD was increased among survivors who received radiotherapy exposing the heart, especially at doses ≥15 Gy (moderate quality evidence). The guideline panel agreed that healthcare providers and CAYA cancer survivors treated with radiotherapy exposing the heart should be counselled about the increased risk for premature CAD. While the evidence is insufficient to support primary screening, monitoring and early management of modifiable cardiovascular risk factors is recommended. Initiation and

frequency of surveillance should be based on the intensity of treatment exposures, family history, and presence of co-morbidities but at least by age 40 years and at a minimum of every 5 years. All were strong recommendations.

Conclusion

These systematically assessed and harmonized recommendations for CAD surveillance will inform care and guide research concerning this critical outcome for CAYA cancer survivors.

INTRODUCTION

Five-year survival rates for children, adolescent, and young adults (CAYA) diagnosed with cancer now exceed 80% in most high-income countries[1,2]. While the number of life-years saved is high for this population, most experience substantial sequelae related to their prior therapy[3,4]. Cardiovascular disease (CVD), one of the most concerning late outcomes, leads to substantial premature morbidity and mortality.

Guidelines for cardiac surveillance have largely focused on screening for late cardiomyopathy and less on other cardiovascular complications, such as coronary artery disease (CAD). However, several studies have reported an increased risk of premature CAD among CAYA cancer survivors, particularly among survivors of classical Hodgkin lymphoma exposed to chest radiation[5-8].

Screening guidelines have been developed by both North American and European groups[9-12] but vary in definitions for at-risk populations, surveillance modalities, screening frequencies and recommended interventions. With the goal of establishing consensus and improving long-term care, the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) commissioned a review of the evidence and recommendations for CAD surveillance in this population.

MATERIAL AND METHODS

IGHG methods have been previously published[13]. Initially the guideline panel (Appendix A) identified areas of concordance and discordance across the Children's Oncology Group[9], Dutch Childhood Oncology Group[10], United Kingdom Children's Cancer and Leukaemia Group[12], and Scottish Intercollegiate Guidelines Network[11] guidelines. Clinical questions were formulated (Appendix B). MEDLINE (1-1-1990 to 8-26-2020) and reference lists of relevant articles were

searched (Appendix C). Eligibile investigations included English language studies of cancer survivors off treatment, with at least 75% of participants diagnosed before age 35 years, and assessments performed post-completion of therapy. Definitions of CAD were as described in each eligible study. All study designs with at least 20 cancer survivors, except case reports, case series, and narrative reviews were included (Appendix D).

Evidence and summary tables were generated, and the total body of evidence graded according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework. (Appendix E parts 1 and 2).

For surveillance and management of modifiable CVD risk factors, guidelines for the general population and other high-risk populations were identified by experts in the field.

All panel members reviewed the final evidence tables, discussed potential benefits and harms and unanimously agreed on the final recommendations. Recommendations were graded according to IGHG evidence-based methods (Appendix E part 3).

The final draft was critically appraised by two independent experts and two patient representatives for completeness of the evidence and applicability of the recommendations. These reviews were considered in formulating the final recommendations. Research results are regularly disseminated through the IGHG website (www.ighg.org). The guideline panel will continue to review newly available evidence and determine if recommendations need to be refined every 5 years.

RESULTS

Concordance across guidelines was found for the following statements (Table 1): 1) CAYA cancer survivors treated with radiotherapy exposing the heart are at increased risk of CAD, 2) anthracycline and mitoxantrone exposure does not increase the risk, and 3) surveillance of modifiable CVD risk factors should be performed. Guidelines were discordant for: 1) which cancer survivors are at highest risk, 2) use of surveillance electrocardiogram (ECG), 3) frequency of ECG and risk factor screening, and 4) timing of cardiology referrals.

Thirty-two studies[5-8,14-41], including 10 relevant multivariable analyses[14,20,22-24,29,32,34,40,41], were identified (Figure 1). Definitions of CAD (symptomatic and asymptomatic), treatment histories and follow-up durations varied across studies. The conclusions and quality of the evidence are summarized in Table 2, with final recommendations in Table 3.

Evidence

CAD in CAYA cancer survivors

The prevalence of CAD varied widely (0 – 72%), and the risk was significantly increased compared to siblings[14,24,38,40] and the general population[5,32] (Appendix F and G). After adjustment for current age, sex and race/ethnicity, a higher relative risk (RR) for CAD (defined as Common Terminology Criteria for Adverse Events (CTCAE) grades 3 and 4) was noted in survivors compared to a sibling comparison group (RR 10.4; 95% CI 4.1-25.9)[38].

The cumulative incidence of CAD in CAYA cancer survivors increases with longer follow-up[16,20,24,29,32,39], and higher attained age[14, 41]. By age 45 years, the cumulative incidence of CAD was reported to be 5.3% (95% CI 4.4%-6.1%) in survivors compared to 0.9% (95% CI 0.4-1.4%) among siblings[14]; by age 50 years it was 7.7% (95% CI 6.3-9.1%) in survivors compared to 1.2% (95% CI 0.4-2%) among siblings[42]. In a risk prediction model by Chow and colleagues, the

occurrence varied by sex and chest radiation dose, with the highest cumulative incidence (19.9%; 95% CI 15.0-24.7) in males treated with >35Gy[42].

Risk factors

Radiotherapy, chemotherapy, and stem cell transplant

Survivors treated with radiotherapy exposing the heart have an increased risk of CAD (moderate quality evidence[22-24,29,34,40,41]) directly proportional to the prescribed or calculated radiation heart dose (moderate quality evidence[20,22-24,34,40]). A threshold dose could not be identified. However, studies have demonstrated an increased risk at doses ≥15 Gy, while showing no significant associations at lower doses[20,22-24,34,40]. Chemotherapy was not significantly associated with CAD (moderate quality evidence[20,41]). However, an increased risk was suggested at anthracycline doses ≥250 mg/m^2 compared to no anthracycline (low quality evidence[23,24,40]). There was no significant additive effect of chemotherapy (with or without anthracyclines) on the coronary risk incurred by mediastinal radiotherapy alone (low quality evidence[29]). No studies addressed the risk of CAD following stem cell transplant (Appendix H).

Sex and age at treatment

There is low quality evidence[20,23,24,32,40,41] for increased risk of CAD with male sex and moderate quality evidence for increased risk with older age at treatment[20,23,24,32,41] (Appendix H).

Modifiable CVD risk factors

Hypertension (high quality evidence[14,20,40]), dyslipidaemia (moderate quality evidence [14,20,22,29,40]), obesity (low quality evidence[14]), and diabetes mellitus (moderate quality evidence[14,29,40]) increase the risk of CAD. Smoking, defined as current or past tobacco use, was

also associated with an increased risk (very low quality evidence[14,29]). Importantly, moderate quality evidence suggests that having more than one modifiable CVD risk factor increases the risk of CAD[14]. Interactions between chest-directed radiotherapy and hypertension (relative excess risk due to interaction (RERI) 24.2 (95% CI 11.8-39.7), dyslipidaemia (RERI 16.4 (95% CI 7.9-29.8), and obesity (RERI 4.3 (95% CI 0.9-8.7) are more than additive (low quality of evidence[14]). There is no significant additive interaction between chest-directed radiotherapy and diabetes (very low quality evidence[14]) (Appendix H).

Surveillance and treatment

No studies reported the accuracy, sensitivity, specificity, or positive and negative predictive values of CAD surveillance modalities (i.e. imaging, ECG). Additionally, no studies investigated prevention with lipid-lowering agents, anti-hypertensives, or lifestyle modifications.

Recommendations

Survivors and their health care providers should be advised of the increased risk for premature CAD following radiotherapy exposing the heart (strong recommendation based on moderate level evidence and expert opinion) (Table 3).

Who needs surveillance and what modality should be used?

Given that there were no studies assessing the diagnostic value of CAD surveillance modalities in cancer survivors, the panel reviewed guidelines for other high-risk populations (i.e. diabetes[43] and familial hypercholesterolemia[44]) and the general population[45,46]. Imaging and ECG surveillance is not routinely recommended for any of these populations if asymptomatic. It is unclear if early detection of coronary artery stenosis reduces morbidity and mortality in CAYA cancer survivors. Currently, no recommendation can be formulated for routine primary CAD surveillance of CAYA

cancer survivors treated with radiotherapy exposing the heart (Table 3). Evaluation should be based on the presence of signs and symptoms of cardiac dysfunction.

Who needs surveillance regarding modifiable CVD risk factors?

Potential benefits and harms of modifiable CVD risk factor surveillance and management should be considered for survivors at high risk. Hypertension, dyslipidaemia, diabetes, obesity, and tobacco use significantly increase the risk of CAD, and outcomes are likely improved if these risks are identified early and medically managed. Changes in metabolic profiles may alter the trajectory of the CAD risk (existing guideline[45]). The potential for false-positive findings, emotional stress, anxiety, costs of further testing, and a self-perception of illness versus health should be considered (expert opinion). While relatively non-invasive, results of surveillance may lead to life-long treatment, possible side effects, and increased cost (existing guideline[45], expert opinion). The guideline panel felt that CAYA cancer survivors treated with radiotherapy exposing the heart, irrespective of dose, would benefit from surveillance and management of modifiable CVD risk factors at an early age.

When should surveillance for modifiable CVD risk factors be initiated and with what frequency?

The increased risk for CVD in CAYA cancer survivors early in life limits the applicability of traditional CVD risk scores that are weighted on age (Appendix I). While the initiation of surveillance varies across countries and healthcare systems, general population surveillance before age 40 years is not commonly recommended in the absence of other CVD risk factors[45,46]. Screening at least every 5 years has been reported when no risk factors are identified; more frequently if CVD risks are found[46] (Appendix J).

The panel agreed that surveillance for modifiable CVD risk factors, per local or national standards, is recommended for CAYA cancer survivors treated with radiotherapy exposing the heart. In some

countries this may involve referral to a cardiovascular specialist. Past cardiotoxic exposures increase the risk for CAD among survivors compared to the general population. Therefore, we recommend CVD risk factor surveillance be performed at least every 5 years and at a minimum by age 40 years (very low to high level evidence, existing guidelines, and expert opinion, strong recommendation).

What can be done when modifiable CVD risk factors are identified?

Timely management of CVD risk factors (i.e. hypertension, dyslipidaemia, diabetes, obesity, tobacco use) is recommended (existing guidelines and expert opinion, strong recommendation).

DISCUSSION

The cardiovascular sequelae of curative childhood cancer therapy can be substantial. The risks increase with time from diagnosis with clinical events only presenting later in life. While the risk for premature CAD is significant, surveillance modalities, screening frequencies, and intervention methods have yet to be rigorously investigated. We systematically reviewed the literature and international guidelines for CAD monitoring in this population and present harmonized surveillance recommendations. Our recommendations are based on a critical analysis of the literature, using strict standards to grade evidence, supplemented by expert consensus where little or no evidence is available. While limited evidence suggests detection of asymptomatic CAD may reduce morbidity and mortality[47,48], data in cancer survivors are lacking; therefore, no recommendation can be formulated for or against routine surveillance. Nevertheless, cancer survivors treated with radiotherapy exposing the heart, irrespective of dose, would likely benefit from early identification and management of modifiable CVD risk factors.

Reports of CAD in childhood cancer survivors are heterogeneous contributing to the wide prevalence estimates (0%-72%). Differences in definitions, patient characteristics, treatment exposures, and

follow-up time need to be considered, as well as potential surveillance bias from preferential screening of those with higher cardiotoxic exposures. We included all CAD definitions reported by the studies reviewed and confirmed that CAYA cancer survivors are at a higher risk of developing premature CAD compared to their siblings and the general population. While early reports suggested a possible plateau in the cumulative incidence of myocardial infarction following cancer therapy[24], more recent analyses do not confirm this and suggest a continued increase with time from diagnosis[40], Importantly, Fidler et al. reported a consistently higher mortality from CAD among childhood cancer survivors with over a two-fold risk (SMR 2.3 95% CI 1.3 – 3.8) beyond age 60 years[32]. Our review confirmed that the most significant therapeutic exposure is radiation therapy exposing the heart. Added risks from chemotherapy were not identified, and interactions have not been investigated. However, evidence suggests that traditional CVD risk factors such as hypertension, dyslipidaemia, diabetes and obesity significantly increase the risk for CAD in CAYA cancer survivors. These potential targets for intervention require additional study to determine if modifications can change the trajectory of cardiac injury in cancer survivors.

While many studies, utilizing a variety of assessment measures, have reported elevated risks for CAD among cancer survivors, the current evidence is insufficient to support routine surveillance, beyond risk-stratification assessments. This is not unlike the general population where risk-stratification is the norm. However, debate has frequently centred on the various cardiovascular risk calculators (Framingham, Pooled Cohort Equation, QRISK2, ASSIGN, etc.)[49]. Models include commonly accepted factors (age, blood pressure, smoking, lipid status, diabetes) but differ on the inclusion of factors, such as family history, biomarkers, and vascular imaging. Discrepancies exist across more than 360 prognostic models[50], and worldwide consensus has yet to be reached. Importantly, no models include the additive risk of cancer therapy. Using the well-characterized Childhood Cancer Survivor Study cohort, only Chow and colleagues have addressed this gap[42]. Models including the

presence or absence of cardiotoxic exposures had fair predictive capability (AUC 0.68, C-statistic 0.69) through age 50 years and only moderate improvement when detailed heart radiation dose was added (AUC 0.70, C-statistic 0.70).

Traditional cardiovascular risk factors, modifiable (weight, tobacco use, diet, hypertension, dyslipidemia, physical inactivity, etc.) and non-modifiable (family history, age, gender, race/ethnicity, etc.), significantly influence the risk of heart disease in the general population. Our review identified a high prevalence of modifiable risk factors that significantly augment the risks in cancer survivors. Given the young age of this population and variation across health systems, the guideline panel felt that survivors, particularly those treated with radiotherapy exposing the heart, would benefit from early surveillance and management of modifiable CVD risk factors. Guidelines exist for lifestyle modification and meta-analyses from population studies have shown a reduction in lifetime risk of CAD and total cardiovascular disease among those with optimal risk profiles in middle age[51,52]. Whether similar results occur in adult survivors of childhood cancer have not been studied. While most survivors report having established primary care, a recent study suggested as many as 20% may have uncontrolled or undertreated hypertension[53]. The IGHG has convened a guideline panel to specifically review the evidence related to the metabolic syndrome – obesity, hypertension, insulin resistance, and dyslipidemia – that further exacerbates CAD in this population.

Despite a multidisciplinary review and systematic grading of the evidence, some limitations should be considered when interpreting our recommendations. Across studies, a variety of CAD definitions and diagnostic assessments were used. We chose to use the definitions as reported in each analysis, thus, potentially limiting comparisons across studies. Notably, no studies reported the sensitivity, specificity, or positive/negative predictive values of the diagnostic tests applied. For some clinical questions data were scarce, limiting multivariable analyses and our ability to formulate definitive

recommendations. Given the latency of the development of CAD, current investigations have relied upon historical treatment exposures and few have accounted for changing trends in treatment strategies over time. No studies included contemporary radiation techniques and delivery modalities. Adding long-term health objectives to current therapeutic protocols will improve the understanding of cardiovascular disease in future cancer survivors[54].

We identified several knowledge gaps regarding CAD in CAYA cancer survivors (Table 4). Research to address these will require multi-disciplinary, multi-centre, and multi-national collaborations to acquire and follow a sufficient number of patients across the life spectrum. Our guideline is the first effort to methodically review the literature and formulate recommendations for CAD surveillance in this high-risk population, with the goal of improving long-term health.

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DECLARATION OF INTEREST STATEMENT

None declared.

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	North American Children's Oncology Group [9]	Dutch Childhood Oncology Group [10]	Scottish Intercollegiate Guidelines Network [11]	UK Children's Cancer and Leukaemia Group [12]	Concordant /discordant
			Who needs surveillance?		
Anthracyclines	No	No	No	No	Concordant
Mitoxantrone	No	No	No	No	Concordant
Radiotherapy exposing the heart	Yes	Yes	Yes	Yes	Concordant
Higher risk	Radiation dose ≥20 Gy to chest; TBI; combined with radiomimetic chemotherapy (e.g. doxorubicin, dactinomycin); combined with other cardiotoxic chemotherapy (anthracyclines, cyclophosphamide conditioning for HCT, amsacrine)	Not specified	≥30 Gy radiotherapy exposing the heart; minimal protective cardiac blocking and younger age at irradiation	Not specified	Discordant
Highest Risk Factors	Anteriorly weighted radiation fields; lack of subcarinal shielding; doses ≥30 Gy in patients who have received anthracyclines; doses ≥40 Gy in patients who have not received anthracyclines; longer time since treatment	Not specified	Not specified	Not specified	Discordant
			What surveillance modality should be used?		
ECG	Yes	Yes	No	No	Discordant

Modifiable risk factors	Yes	Yes	Yes	Yes	Concordant
		At what frequency should surveillance be performed?			
ECG	Baseline at entry LTFU, repeat as clinically indicated	Baseline at 5 years following diagnosis, repeat if clinical concerns	-	-	Discordant
Modifiable risk factors	Not mentioned for all modifiable risk factors, but if mentioned: dependent on specific risk factor	Not mentioned	Not mentioned	Not mentioned for all modifiable risk factors, but if mentioned: regularly all survivors	Discordant
		What should be done when abnormalities are identified?			
Refer to cardiologist	Yes for patients with subclinical abnormalities on screening evaluations; consider cardiology consultation (5-10 years after radiation) to evaluate risk for CAD in patients who received ≥40 Gy chest radiation alone or ≥30 Gy chest radiation plus anthracycline.	Yes	Not specified	Yes	Discordant

*Most cardiac guidelines did not focus on CAD, but only on cardiomyopathy; LTFU = long term follow-up; ECG = electrocardiogram

Table 1 Concordances and discordances among existing guidelines for CAYA cancer survivors*

Who needs surveillance?	
Risk of coronary artery disease in childhood, adolescent and young adult cancer survivors	**Quality of evidence**
Increased risk after radiotherapy exposing the heart	⊕⊕⊕⊖ MODERATE [22-24, 29, 34, 40, 41]
Increased risk after higher doses of radiotherapy exposing the heart, especially after ≥15Gy	⊕⊕⊕⊖ MODERATE [20, 22-24, 34, 40]
The interaction between chest-directed radiotherapy and hypertension is more than additive with regard to the increased risk	⊕⊕⊖⊖ LOW [14]
The interaction between chest-directed radiotherapy and dyslipidaemia is more than additive with regard to the increased risk	⊕⊕⊖⊖ LOW [14]
No significant additive interaction between chest-directed radiotherapy and diabetes	⊕⊕⊖⊖ LOW [14]
The interaction between chest-directed radiotherapy and obesity is more than additive with regard to the increased risk	⊕⊕⊖⊖ LOW [14]
No significant effect of chemotherapy (as a group)	⊕⊕⊕⊖ MODERATE [20, 41]
No significant effect of vincristine	⊕⊕⊖⊖ LOW [24]
No significant effect of anthracycline containing chemotherapy as compared to no anthracycline containing chemotherapy when cumulative anthracycline dose is not taken into account	⊕⊕⊖⊖ LOW [23, 24, 29, 40]
No significant effect of anthracycline dose <250 mg/m^2 as compared to no anthracyclines	⊕⊕⊖⊖ LOW [23, 24, 40]
Increased risk after anthracycline dose ≥250 mg/m^2 as compared to no anthracyclines	⊕⊕⊖⊖ LOW [23, 24, 40]
No significant effect of mediastinal radiotherapy and chemotherapy (without anthracyclines) as compared to mediastinal radiotherapy only (i.e. added risk of chemotherapy)	⊕⊖⊖⊖ VERY LOW [29]
No significant effect of mediastinal radiotherapy and chemotherapy (including anthracyclines) as compared to mediastinal radiotherapy only (i.e. added risk of chemotherapy)	⊕⊖⊖⊖ VERY LOW [29]
Increased risk with male gender	⊕⊕⊖⊖ LOW [20, 23, 24, 32, 40, 41]
Increased risk of older age at treatment	⊕⊕⊕⊖ MODERATE [20, 23, 24, 32, 41]
Increased risk with dyslipidaemia	⊕⊕⊕⊖ MODERATE [14, 20, 22, 29, 40]
Increased risk with hypertension	⊕⊕⊕⊕ HIGH [14, 20, 40]
Increased risk with diabetes mellitus	⊕⊕⊕⊖ MODERATE [14, 29, 40]
Increased risk with (recent) smoking	⊕⊖⊖⊖ VERY LOW [14, 29]
Increased risk with obesity	⊕⊕⊖⊖ LOW [14]
Increased risk with an increase in the number of cardiovascular risk factors (hypertension, dyslipidaemia, diabetes, obesity)	⊕⊕⊕⊖ MODERATE [14]
What surveillance modality should be used?	

Surveillance options for asymptomatic coronary artery disease in childhood, adolescent and young adult cancer survivors	
Unknown diagnostic value of possible surveillance modalities	No studies
What should be done when abnormalities are identified?	
Treatment of asymptomatic coronary artery disease in childhood, adolescent and young adult cancer survivors	
Unknown effect of treatment with lipid-lowering agents	No studies
Unknown effect of treatment with anti-hypertensive agents	No studies
Unknown effect of lifestyle modification	No studies

Table 2 Conclusions and quality of evidence from the systematic literature search for CAD surveillance in CAYA cancer survivors

1. **Coronary artery disease**

General recommendation
Health care providers and childhood, adolescent and young adult cancer survivors treated with radiotherapy exposing the heart should be aware of the increased risk of coronary artery disease (moderate level evidence and expert opinion, strong recommendation).

2. **Surveillance for coronary artery disease**

Who needs coronary artery disease surveillance and what modality should be used?
Due to insufficient evidence, currently no recommendation can be formulated for routine primary CAD surveillance of childhood, adolescent and young adult cancer survivors treated with radiotherapy involving the heart*.

** Insufficient evidence to determine the diagnostic value of surveillance options for asymptomatic abnormalities of the coronary arteries and whether early detection reduces morbidity and mortality (no studies/expert opinion).*

3. **Modifiable cardiovascular disease risk factors**

Who needs surveillance of modifiable cardiovascular disease risk factors?
Surveillance for modifiable cardiovascular disease risk factors according to national or local guidelines, which may involve referral to a cardiovascular specialist, is recommended for childhood, adolescent and young adult cancer survivors treated with radiotherapy exposing the heart
When should surveillance for modifiable cardiovascular risk factors be initiated and at what frequency?
Timing of initiation and frequency should be based on the intensity of cardiotoxic treatment exposure(s), family history and presence of co-morbid conditions associated with cardiovascular disease risk, but at least by age 40 years and at a minimum of every 5 years (very low to high level evidence, existing guidelines and expert opinion, strong recommendation).
What can be done when modifiable cardiovascular disease risk factors have been identified?
Timely management of all modifiable cardiovascular disease risk factors (such as hypertension, dyslipidaemia, diabetes, overweight/obesity and smoking) is recommended due to the increased risk of coronary artery disease in childhood, adolescent and young adult cancer survivors treated with radiotherapy exposing the heart (existing guidelines and expert opinion, strong recommendation).

Table 3. Harmonized recommendations for surveillance of asymptomatic coronary artery disease and modifiable cardiovascular disease risk factors in childhood, adolescent and young adult cancer survivors

Therapeutic Exposure
Radiation dose thresholds for CAD, particularly doses <15 Gy Effect of age at radiation exposure Risk of CAD in CAYA cancer survivors exposed to chemotherapy only Risk from traditionally non-cardiotoxic chemotherapeutic agents (alkylating agents, heavy metals, vinca alkaloids) Risk of CAD in CAYA cancer survivors exposed to radiotherapy only Risk from radiation dose-volume relationships to the heart Risk from radiation dose to the coronary arteries Risk of CAD in CAYA cancer survivors exposed to both chemotherapy and radiotherapy Risk from hematopoietic cell transplant
Prevention/reduction of CAD risk
Utility of adding cancer treatment exposures to atherosclerotic cardiovascular disease (ASCVD) risk prediction models Efficacy of primary prevention, impact of interventions to reduce modifiable risk factors Genetic contributions to CAD in cancer survivors Efficacy of cardiac imaging, serum biomarkers of atherosclerotic disease Impact of chronological aging on CAD in cancer survivors
Future survivors
Risk from changes in radiation delivery (involved field, intensity modulated therapy, proton beam) Risk from new cancer therapies (tyrosine kinase inhibitors, immune checkpoint inhibitors, chimeric antigen receptor (CAR) T-cell therapy, etc.)

Table 4. Gaps in knowledge and future directions for research

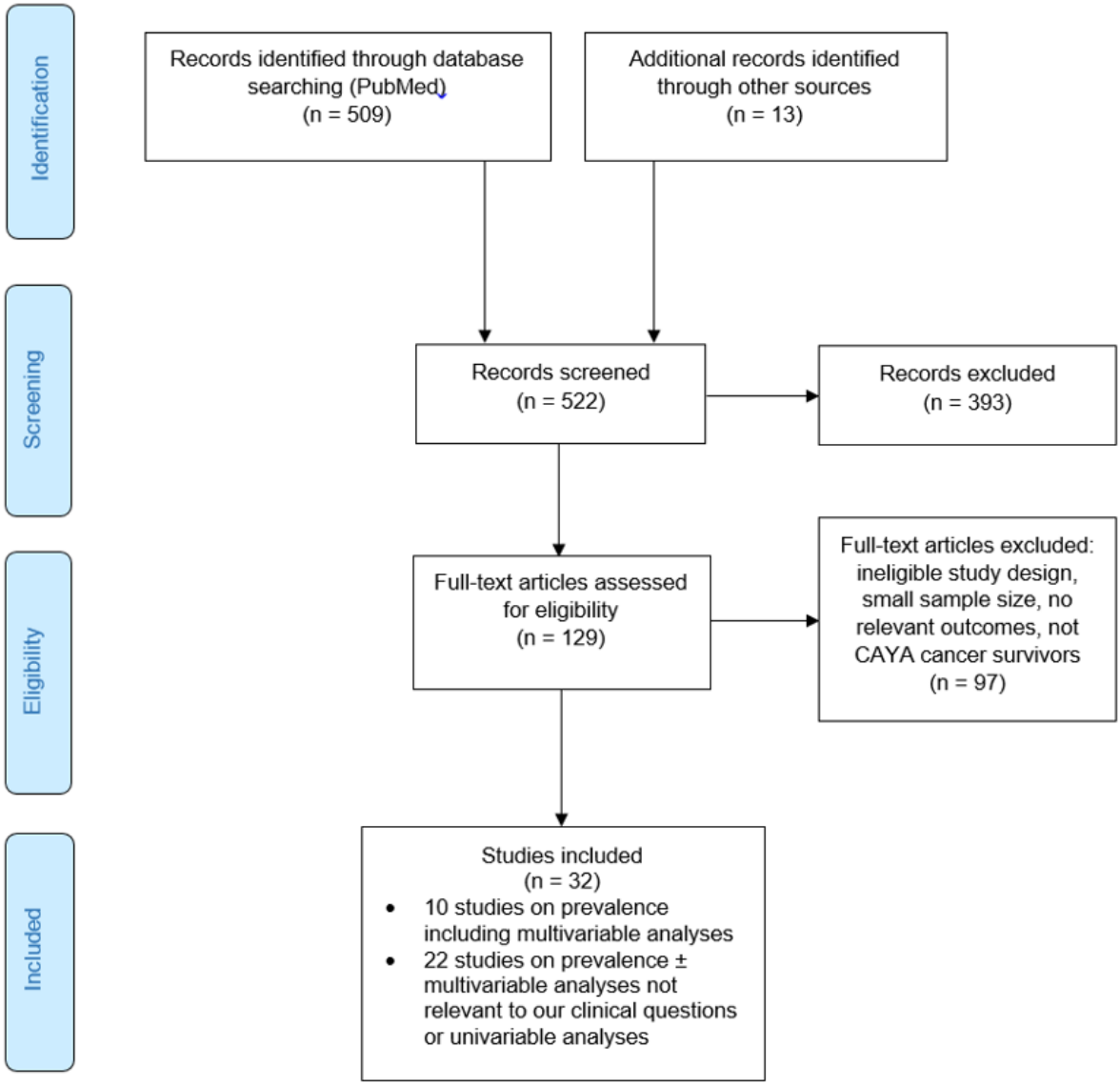

Figure 1: Flow diagram of study selection