SCREENING FOR NEW PRIMARY CANCERS IN CANCER SURVIVORS: SYSTEMATIC REVIEW AND ANALYSIS OF NOVA SCOTIAN COLORECTAL CANCER SURVIVORS

by

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Abstract

Little is known about the receipt of cancer screening for new primary cancers among Canadian cancer survivors. The objectives of this thesis are to i) synthesize evidence comparing receipt cancer screening between cancer survivors and non-cancer controls; and ii) analyze breast and cervical cancer screening receipt among Nova Scotian colorectal cancer (CRC) survivors. This thesis consists of a systematic review and meta-analysis, and a population-based cohort study of Nova Scotian CRC survivors. We found that while cancer survivors were more likely to receive cancer screening than the general population, a significant proportion of cancer survivors were not screened. We observed significant heterogeneity between studies, most of which remained unexplained after subgroup and sensitivity analyses. 30.1% and 47.9% of Nova Scotian CRC survivors never received a breast and cervical cancer screen after their CRC diagnosis. Receipt of pre-CRC diagnosis screening was strongly predictive of receiving screening post-diagnosis.

List of Abbreviations Used

ACCESS – Access to Colorectal Cancer Services in Nova Scotia

CIHI – Canadian Institute for Health Information

CIHR – Canadian Institutes of Health Research

CINAHL – Cumulative Index to Nursing and Allied Health Literature

CRC – Colorectal cancer

DHA – District health authority

MSI – Nova Scotia's Medical Services Insurance

NSCR – Nova Scotia Cancer Registry

OPIS – Oncology Patient Information System

Pap – Papanicolaou

U.S. – United States

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Chapter 1 – Introduction

The 2006 Institute of Medicine report From *Cancer Patient to Cancer Survivor: Lost in Transition* highlights the often overlooked and multiple care needs of cancer survivors, which include: i) surveillance for local, regional, or distant recurrence of the initial cancer; and ii) screening for new primary cancers at other sites[1]. While guidelines for cancer surveillance have been developed for many commonly diagnosed cancers (e.g., breast[2, 3], cervical[4], endometrial[5], colorectal[6, 7], melanoma[8], and prostate[9]), no published guidelines exist for providing preventive screening for new primary cancers among cancer survivors. Previous studies have demonstrated that many cancer survivors at increased risk of developing a second malignancy[10-15], making screening for new primary cancers even more important in these populations.

A current and future challenge for both Canadian and international health care systems is to determine how to best provide long term follow-up care to the growing prevalence of cancer survivors, estimated to number over 28 million worldwide[16]. There is conflicting evidence that suggests those with a previous cancer diagnosis may or may not be as likely to receive cancer screening for new primary cancer sites as the general population. Previous studies point to colorectal cancer survivors either receiving an insufficient amount of follow-up care[17-19], or an abundance of non-recommended follow-up care procedures[20]. One possible explanation is that physicians may focus on and treat the patient as a cancer survivor, failing to recognize and address the general preventive needs of the patient.

Two prior systematic reviews have been published on the uptake of general preventive health care in cancer survivors (including cancer screening)[21, 22]. Despite both of these reviews being published in 2008, the volume of available literature has substantially increased. In addition, these two reviews reached conflicting conclusions, with Wilkins and Woodgate concluding "the prevalence of secondary prevention practices among cancer survivors is generally lower than recommended"[22], but Khan *et al.* concluding "cancer screening is generally well managed through normal channels and is adequate amongst survivors of adult cancer in the United States"[21]. The substantial increase of new literature in this field and conflicting results of previous systematic reviews warrant the conduct of a comprehensive systematic review and meta-analysis.

Cancer screening is an important component of preventive healthcare in defined target populations. In general, women aged 50-69 are recommended to undergo a mammogram every two years for breast cancer screening[23]. The Nova Scotia breast screening program also targets women aged 40-49 for annual mammography. A Papanicolaou (Pap) smear is recommended at least every three years in women aged 21-75 for cervical cancer screening[24]. Breast and cervical cancer screening programs have been shown to decrease mortality from their respective cancers by up to 26%[25] and 50-80%[26, 27] respectively.

The objectives of this thesis are to: i) summarize available evidence to determine whether cancer survivorship is associated with an increased or decreased likelihood of receiving screening for new primary cancers compared to the general population, identifying specific cancer screening procedures which cancer survivors are less (or

more) likely to receive; and ii) examine the practices of cervical and breast cancer screening among a cohort of Nova Scotian colorectal cancer survivors.

This thesis begins by conducting a systematic review and meta-analysis using Cochrane methodology to identify and synthesize evidence which compares receipt of cancer screening for new primary cancers between cancer survivors and the general population. Building upon findings from this systematic review, we investigated receipt of breast and cervical cancer screening in a cohort of Nova Scotian colorectal cancer survivors. The findings from this population-based cohort study will allow us to add local context and results to the dissemination of our systematic review.

This thesis is organized into 4 chapters. Chapters 2 and 3 are stand-alone manuscripts to be submitted to peer-reviewed academic journals. Manuscript one, in Chapter 2, is a systematic review and meta-analysis comparing the receipt of cancer screening for new primary cancers between cancer survivors and non-cancer populations. Manuscript two, in Chapter 3, is a population-based retrospective cohort study descriptively analyzing the receipt of breast and cervical cancer screening among a cohort of Nova Scotian colorectal cancer survivors. Importantly, this local study adds Nova Scotian context to the systematic review in Chapter 2, and will enhance dissemination of our results to local and national audiences. Chapter 4 concludes with a brief summary of the main findings from this thesis, along with recommendations for future researchers.

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Chapter 2 – Manuscript One

2.1 Introduction

A current and future challenge for both Canadian and international health care systems is to determine how to best provide long term follow-up care to the growing prevalence of cancer survivors, estimated to number over 28 million worldwide[1]. An often overlooked but nonetheless important component of follow-up care for cancer survivors is screening for new primary cancers[2]. For most malignancies, a cancer survivor's risk of developing a second primary cancer is at least as great as the general population, even when there are no direct causative links between two cancer sites. However, due to common risk factors, genetic links, and late carcinogenic effects from treatment of the primary cancer, often the risk of developing a second primary cancer at a different anatomical site can be much greater in cancer survivors[3-8].

Conflicting theories suggest that those surviving cancer (or living with other chronic diseases) may be either more or less likely to receive recommended preventive care, of which cancer screening is an important component. One theory[9] and several researchers[10-12] have hypothesized that cancer survivors may receive more frequent screening, as their previous cancer is a comorbid condition which leads to increased contact with the health care system. Studies have concluded that increased contact with the healthcare system and a recommendation from a primary care physician are strongly associated with the uptake of cancer screening in the general population[13-16]. Conversely, the competing demands model[17] and other researchers[18, 19] have hypothesized that despite an increased amount of contact with the health care system, a cancer survivor's previous

cancer diagnosis may shift healthcare workers' attention away from other preventive health services, resulting in less frequent screening.

While two prior systematic reviews have been published on the uptake of general preventive health care in cancer survivors (including cancer screening)[20, 21], the volume of available literature has substantially increased since these reviews were published. In addition, these two reviews reached conflicting conclusions, with Wilkins and Woodgate concluding "the prevalence of secondary prevention practices among cancer survivors is generally lower than recommended" [21], but Khan *et al.* concluding "cancer screening is generally well managed through normal channels and is adequate amongst survivors of adult cancer in the United States"[20].

The substantial increase of new literature in this field and conflicting results of previous systematic reviews warrant the conduct of a comprehensive systematic review and meta-analysis. In particular, such a review is needed to assist with the development of clear evidence-based recommendations for cancer screening in cancer survivor populations and to inform the primary care and specialist communities caring for individuals in the survivorship period.

2.2 Objectives

The objectives of this systematic review are to: i) Summarize available evidence to determine whether cancer survivorship is associated with a decreased likelihood of receiving recommended cancer screening for new primary cancers compared to the

general population; and ii) Identify the specific screening procedures for which cancer survivors are less (or more) likely to receive relative to the general population.

2.3 Methods

To evaluate the above objectives, we conducted a systematic review using methods similar to those advocated by the Cochrane Collaboration[22]. We systematically identified and included observational studies that measured the risk of cancer survivors receiving/not receiving recommended screening for new primary cancers, as compared to a non-cancer control group. Our Population, Exposure, Comparison, and Outcome group definitions were developed in consultation with healthcare professionals, program managers/administrators, and other decision-makers and stakeholders from the cancer care community during interactive workshops. These definitions are described in Table 1.

2.3.1 Data Sources and Search Strategy

We searched three electronic databases (PubMed, EMBASE, and CINAHL; all available years to April 2010) using a combination of MeSH terms and keywords relating to cancer, cancer survivorship, and cancer screening. The PubMed search strategy can be viewed in Appendix A; similar terms were used for the EMBASE and CINAHL databases. No date or language restrictions were used in the search strategy. Reference lists of included studies and previous reviews were screened to identify additional articles.

2.3.2. Study Selection and Data Abstraction

We included studies that measured the receipt of one or more cancer screening tests in both the cancer survivor and non-cancer control groups. Studies which measured the receipt of these screening tests outside of the recommended age ranges were included and explored with subgroup analysis. Any definition of cancer survivorship was eligible for inclusion in this study, regardless of time since diagnosis or cancer site. All cancer screening sites and tests were eligible for inclusion, regardless of whether the screening was opportunistic or programmatic in nature. Unpublished literature was sought through contact with content experts.

A standardized study selection and data abstraction form was used, available in Appendix B. The initial literature screen of titles and abstracts was done by one author [MC] in order to remove citations that were clearly not relevant to the study objectives. Application of the study inclusion criteria to the full-text articles and abstraction of included articles was conducted independently by two individuals [MC, CS] with formal systematic review training. Disagreements were resolved through consensus and consultation with a third reviewer [JH], if necessary.

We abstracted demographic and cancer history information of study subjects (for example, age, sex, ethnicity, initial cancer site), cancer site(s) screened, the screening test(s) used, the length of the screening time period, and the associated odds ratios of cancer survivors receiving the screening test(s) relative to the non-cancer control group. If available, appropriately adjusted odds ratios were favoured over unadjusted estimates. If odds ratio estimates were not available in the primary study, crude odds ratios were calculated from raw data. Data for individual screening tests (for example, fecal occult

blood testing [FOBT] and endoscopy for colorectal cancer screening) were recorded separately whenever possible. Study authors were contacted to retrieve missing data.

2.3.3. Risk of Bias Assessment

Study level risk of bias was assessed using four categories selected from quality assessment tools used to assess prognosis studies and randomized controlled trials of intervention effectiveness [23, 24], and modified to fit the review question and types of observational studies included in this review. These four risk of bias categories were: i) How was the source or study population selected, ii) How were cancer survivors defined: (low: long-term survivors (all ≥5 years); moderate: mostly long-term survivors; high: time since diagnosis not measured or short-term survivors); iii) How was screening measured (low: administrative databases, moderate: self-reported); and iv) Confounding (e.g. did the study match survivors and non-cancer controls, or adjust for important potential confounders?). Further details of the risk of bias categories and coding is available in Appendix C. These risk of bias assessments were used to guide sensitivity analyses.

2.3.4. Analysis Strategy

We conducted meta-analyses of study data investigating the relationship between cancer survivorship and screening for new primary cancers, supplemented with a thoughtful qualitative discussion. For the quantitative synthesis, odds ratio effect estimates by cancer site and screening rate were pooled using a random effect generic

inverse variance model with Review Manager 5.0 (Cochrane Collaboration, Oxford, United Kingdom) software. A meta-analysis was not conducted for skin and testicular cancer screening due to the small number of studies reporting these outcomes (n=1 and n=2, respectively).

An overall summary estimate of the association between cancer survivorship and cancer screening was calculated using data from all included studies and any screening site. We selected and pooled the single odds ratio estimate from each included study that represented the screening site with the lowest standard error. This decision rule was determined *a priori*, and selected to minimize possible selection bias.

Heterogeneity was measured using the I^2 statistic[22]. The qualitative synthesis included studies which could not be quantitatively combined and analyzed, results from the risk of bias assessment, and other potential sources of heterogeneity from the meta-analysis, such as study-level demographic and cancer survivor information.

When a study separately reported two screening tests for a single cancer, we chose the screening test we felt was more likely to be included in a programmatic, population-level screening intervention to include in the overall estimate of screening for that site (for example, in studies that separately reported the receipt of FOBT and endoscopy screening to detect colorectal cancer, we included the FOBT estimate in the colorectal cancer screening overall estimate). When multiple studies presented data from the same cohort, we avoided double counting participants in these studies by only including the single study with the largest sample size in our meta-analysis. Sensitivity analyses were conducted to determine whether this decision rule impacted our overall results.

2.4 Results

We identified 1778 citations using our electronic database search strategy. Of these, we retrieved and screened the abstracts of 218 potentially eligible papers. 33 papers remained after title and abstract screening, and were assessed in full. Two additional papers were identified through contact with content experts. Of these 35 articles, 20 met the criteria for inclusion in our systematic review[10-12, 18, 19, 25-39]. The flow of study selection and reasons for full-text article exclusion is presented in Figure 1.

A summary of the characteristics of the 20 included studies is presented in Table 2. These 20 studies reported 48 different cancer screening site outcomes (14 breast screening, 14 cervical screening, 11 colorectal screening, 6 prostate screening, 1 skin screening, and 2 testicular screening), with many studies reporting multiple screening sites. Only one study was conducted outside North America (United Kingdom, Khan 2010). There were three overlapping study populations observed (Bellizzi 2005 and Trask 2005, Grunfeld (unpublished) and Kwon 2009, and Oeffinger 2009 and Yeazel 2003).

The demographics of the cancer survivors in the included studies varied greatly, and ranged from childhood cancer survivors to elderly populations. The predominant ethnicity in studies where this was reported was white/Caucasian, with only one study focusing on an ethnic minority (Hispanic, Aparicio-Ting 2003). Most studies contained survivor populations with mixed initial cancer diagnosis types (n = 10); the most common single initial cancer diagnosis type reported upon was breast cancer (n = 5).

The screening tests/timeframe, age restrictions, and screening outcomes for each cancer site and study are shown in Table 3. In all studies, mammography was used for

breast cancer screening (Table 3a) except one study which measured a combination of clinical breast examination or mammography. Cervical cancer screening (Table 3b) was defined as receipt of a Pap smear in all studies. Colorectal cancer screening (Table 3c) was defined as the receipt of FOBT, endoscopy procedures (colonoscopy, sigmoidoscopy, or proctoscopy), barium enema, or some combination of these three. Prostate cancer screening (Table 3d) was defined as receipt of a prostate specific antigen (PSA) test in all studies, except one which measured receipt of either a PSA or digital rectal examination (DRE). Skin and testicular cancer screening tests are described in Tables 3e and 3f.

Screening timeframes within each screening site varied greatly between studies, and ranged from within the last 12 months to ever/never being screened. The most common screening timeframes were: breast cancer screening (2 year interval, 7/14 studies), cervical cancer screening (3 year interval, 7/14 studies), colorectal cancer screening (FOBT, 1 year interval, 4/9 studies; endoscopy, 5 or 10 year intervals, 4/11 studies), and prostate cancer screening (1 year interval, 4/6 studies).

Where available, the unadjusted proportions of cancer survivors and controls screened for each cancer site is presented in Table 3. The proportion of cancer survivors and controls screened varied greatly between studies, and appeared to be influenced by the age of the participants in each study, the length of screening timeframe (longer screening timeframes resulted in a greater proportion of both cancer survivors and controls receiving screening), and disease site being screened for (lower screening rates for colorectal cancer than breast or cervical cancer). Across all screening sites, a large proportion of both cancer survivors and non-cancer controls did not receive adequate

screening for new primary cancers, as defined by the screening recommendations used in each primary study.

Cancer survivors were more likely to receive screening for new primary cancers than non-cancer controls across all four cancer sites where a meta-analysis was conducted, as well as for skin and testicular cancer screening. Across all studies, cancer survivors were 27% more likely to receive screening for new primary cancers compared to non-cancer controls (OR: 1.27, 95% CI: 1.19 – 1.36). Cancer survivors were 19% more likely to receive breast cancer screening (OR: 1.19, 95% CI: 1.06 – 1.34, p=0.004) [Figure 2], 22% more likely to receive cervical cancer screening (OR: 1.22, 95% CI: 1.12 – 1.33, p< 0.001) [Figure 3], 19% more likely to receive colorectal cancer screening (OR: 1.19, 95% CI: 1.10 – 1.30, p< 0.001) [Figure 4], and 22% more likely to receive prostate cancer screening (OR: 1.22, 95% CI: 1.10 – 1.36, p< 0.001) [Figure 5].

Two studies were included in the review that were not appropriate to incorporate into our meta-analyses. Duffy *et al.*[18] used different definitions of appropriate cervical cancer screening in their cancer survivor (annual screening) and non-cancer control (biannual screening) groups, which precluded its inclusion into our meta-analysis. Duffy *et al.* [18] reported that cancer survivors were as likely to receive an annual Pap smear as non-cancer survivors were to receive a biannual Pap smear (OR: 0.98, 95% CI: 0.60 – 1.60). Kwon *et al.*[30] was the only study to compare receipt of breast and cervical cancer screening among cancer survivors and a general population screening rate, and found that cancer survivors were about twice as likely to receive breast cancer screening (cancer survivors: 64%, general population: 31%) and colorectal cancer screening (cancer survivors: 30%, general population: 15%) during their study follow-up period. We did not

include Kwon *et al.* [30] into our meta-analyses for two reasons: first, the study population overlapped with the study by Grunfeld *et al.*[28], which was larger; second, this was the only included study that used general population screening rates as a comparison group.

There was significant heterogeneity observed between studies for breast (n = 11), cervical (n = 11), and colorectal (n = 9) screening sites (I^2 = 89%, 75%, and 87% respectively, all $p<0.001$). No single study accounted for the statistically significant heterogeneity for these sites. There was no significant heterogeneity observed between five studies for prostate cancer screening (I^2 = 34%, p=0.19), and therefore we did not conduct subgroup or sensitivity analyses for prostate cancer screening.

Risk of bias varied considerably between studies, ranging from studies using linked administrative databases with low risk of selection and measurement bias, to higher risk of bias studies using responses from self-reported surveys. Most studies using self-reported surveys had low response rates, introducing a further potential source of bias. Included studies also contained variable lengths of cancer survivorship follow-up, with some studies exclusively focusing on long-term survivors, while others contained a wide range of cancer survivorship follow-up time. Study risk of bias is reported in Table 4. Explanations of risk of bias categorization can be found in Appendix D.

To explore potential sources of heterogeneity in the breast, cervical, and colorectal cancer screening meta-analyses, we conducted several sensitivity and subgroup analyses, presented in Table 5. Only two categories were statistically significant: Inadequate controlling for confounding/using a matched cohort (colorectal cancer screening), and the use of a cohort of childhood cancer survivors (colorectal cancer screening). These

significant differences were localized to one study reporting receipt of colorectal cancer screening.

We found no significant effect on our overall meta-analysis results when we conducted a sensitivity analysis on our decision rule for excluding studies with overlapping study populations.

2.5 Discussion

We conducted a systematic review and meta-analysis that included 20 primary studies comparing receipt of cancer screening between cancer survivors and a non-cancer control group. Our meta-analyses indicated that cancer survivors were more likely to receive screening for new primary cancers across all screening sites included in this review (19% more likely to receive breast and colorectal cancer screening, 22% more likely to receive cervical and prostate cancer screening). Taking the effect estimate with the lowest standard error from all studies included in our meta-analysis, cancer survivors overall were 27% more likely to receive screening for new primary cancers.

While cancer survivors were more likely to receive screening for new primary cancers at each of the screening sites reported in this review, this finding must be interpreted in light of the receipt of cancer screening as a whole. Studies in our review reported that many individuals from both the general population and cancer survivor subpopulation did not receive screening tests recommended for the detection of new primary cancers. Previous research has shown that both male and female cancer survivors are at an increased risk of developing a new primary cancer (Standardized Incidence

Ratios, Males: 1.22 (95% CI: 1.20 – 1.24), Females: 1.36 (95% CI: 1.33 – 1.39)[40]. Little is known about the long-term efficacy of cancer screening among cancer survivors, and should be an area of exploration in future research. With presently available data, we know cancer survivors are a high-risk population who should be targeted for risk factor modification, as well as encouraged to meet screening recommendations for the detection of new primary cancers. As no guidelines exist specifically for screening of new primary cancer sites among cancer survivors, survivorship care planning could explicitly address the issue of screening for new primary cancers, and recommend that cancer survivors at minimum follow population-based cancer screening guidelines.

We observed significant heterogeneity in our breast, cervical, and colorectal cancer screening analyses. However, almost all of the potential sources of bias identified in our subgroup and sensitivity analyses had little impact on the observed likelihood of cancer survivors receiving more cancer screening than non-cancer control groups. Where significant differences in our subgroup and sensitivity analyses were observed, this was attributable to one lower quality study. Due to the small number of studies included within each screening site, the statistical tests for detecting heterogeneity were underpowered.

There are likely other sources of heterogeneity hidden within the studies which we could not measure. Key contextual factors that were not reported in primary studies include how local screening programs function (e.g. did local screening programs actively target age groups to increase screening uptake, or depend on GP- or self-referral into screening programs?), and the degree to which follow-up care is integrated with cancer screening programs. As these were not reported in any included study, we could not

assess these factors as potential sources of heterogeneity. The organization of screening programs is a key determinant of screening patterns in both the general population and cancer survivors. Differences in how screening programs operate are very likely a source of unmeasurable heterogeneity in this systematic review, and we would encourage future studies to report how their local screening programs function. As the studies included in our systematic review are predominantly from the United States, it is unclear whether the summary estimates in this study are applicable to other healthcare systems.

Most studies implemented some attempt at focusing their analysis on cancer survivors who were within general consensus population-based screening recommended age groups. We hypothesized that cancer survivors might have higher uptake of cancer screening outside typical age restricted screening recommendations, which might present a source of bias in studies which did not use an upper age restriction. Healthcare providers or cancer survivors may recognize that cancer survivors are at a greater risk, and recommend starting or ending screening at earlier/later ages compared to the general population. However, our subgroup analysis did not find that studies which did not use upper or lower age restrictions to be a significant source of heterogeneity. This finding is mirrored in studies that only contained an exclusively elderly population (≥ age 65), where no significant difference was observed. Future research should compare the receipt of screening within and outside guideline-based age recommendations to further explore whether the differences in screening uptake exclusively occur outside screening guideline age recommendations.

The two studies that we were not included in our meta-analyses appeared to reach similar conclusions as the included literature. Despite using an annual screening

timeframe for cancer survivors, and a biennial screening timeframe for non-cancer controls, Duffy *et al.*[18] found that cancer survivors were as likely to receive annual screening as non-cancer controls were to receive biennial screening. This would likely indicate that if similar screening timeframes were used for these two populations, cancer survivors would be screened more frequently than non-cancer controls. Kwon *et al.*[30] reported absolute screening differences that were much greater than any other study included in our review. This finding may influenced by the researchers not restricting their analysis to guideline-based age recommendations, the inclusion of many survivors outside of screening age recommendations, and their comparison group being age-standardized general population screening rates. The difference in screening receipt reported by Kwon *et al.* lends further strength to our hypothesis that cancer survivors are screened more frequently than the general population outside of guideline-based age recommendations.

In the absence of evidence which directly examines screening efficacy among cancer survivors, several studies have demonstrated that many cancer survivor populations are at an increased risk of developing second primary cancers[3-8]. Long-term cancer survivors, or short-term cancer survivors who are likely to survive long-term based on the clinical characteristics of their disease, should be encouraged to meet population-based screening recommendations. Their risk of developing a second cancer is at least as great as the general population, and often will be higher. Future research should directly measure the efficacy and cost-effectiveness of cancer screening among cancer survivors, and also seek to determine whether the optimal screening frequency for cancer survivors should be different than the general population.

The results of this review should be useful to healthcare providers, policy makers, other administrative decision-makers (e.g. cancer program managers), and future researchers. Healthcare providers may use the results of this research to actively encourage their cancer survivor patients to participate in local cancer screening programs. It is known that recommendation from a healthcare provider is a leading predictor of receipt of cancer screening[13-16], and encouraging cancer survivors would be one of the first steps to further improving the rate at which they are screened for new primary cancers.

Policy makers and other decision-makers in cancer control, in conjunction with researchers, may use this review to create and implement interventions to further increase the receipt of screening for new primary cancers among cancer survivors. No studies in this review reported attempts to implement such interventions, but as cancer survivors represent a high-risk population, such interventions could have an impact on reducing the likelihood of cancer survivors being diagnosed with late-stage new primary cancers. Interventions that have been shown to increase screening uptake in the general population include: providing reminders, small media (e.g. videos and printed materials), one-on-one education, and reducing structural barriers[41]. Providing health care providers with assessment and feedback has also been shown to increase screening rates[41]. It is likely that these same interventions would increase the uptake of cancer screening among cancer survivors as well.

The emergence and development of survivorship care plans could potentially provide a medium for cancer care providers to correspond with both cancer survivors and their healthcare practitioners on the importance of screening for new primary cancers

during the survivorship period, and to communicate screening recommendations specifically for the detection of new primary cancers in cancer survivors. While our review found that cancer survivors were more likely to be screened for new primary cancers, we also noted that a large proportion of cancer survivors are still not receiving screening consistent with general population screening guidelines. We recommend further research into whether increased screening for new primary cancers actually leads to better health outcomes in cancer survivors. If increased screening leads to better health outcomes, evidence-based recommendations for screening for new primary cancers should be included in survivorship care plans. However, even in the absence of such studies, the inclusion of general population screening recommendations into survivorship care plans may still be warranted to serve as a reminder for cancer survivors to discuss cancer screening with their healthcare provider.

Our study has several strengths. We used a rigorous search strategy which identified a yet-to-be published primary study. We were able to use two authors to abstract data in an effort to minimize data abstraction errors. Our meta-analysis and sensitivity/subgroup analyses were planned a priori. Finally, we tailored our review question and reporting of results to meet the needs of healthcare professionals, program managers/administrators, and other decision-makers by holding interactive workshops with key stakeholders throughout the review process.

Our study limitations largely mirror the limitations of the included literature. As only 20 studies were identified, subgroup and sensitivity analyses were likely underpowered to detect potential differences. Important contextual factors were not available for analysis in our systematic review, such as how screening programs local to

each study operate, and could be a potential source the observed heterogeneity in our study. Many studies contained incomplete information, which we were mostly able to overcome through contact with study authors. Few studies reported results separately for short- or long-term cancer survivors. Some studies did not use upper or lower age limits to compare receipt of cancer screening between cancer survivors and non-cancer controls. There were inconsistencies between studies' use of screening timeframes, which often did not reflect national recommendations for population-based cancer screening. Our review could have been strengthened through use of an individual patient data meta-analysis, which may have overcome several of the limitations in the identified literature.

2.6 Conclusion

Our results demonstrate that cancer survivors are more likely to receive screening for new primary cancers than non-cancer controls. These results should be interpreted in light of suboptimal cancer screening rates in both cancer survivors and the general population. While cancer survivors receive more frequent screening, previous research has demonstrated that some survivor populations are at a greater risk of developing a new primary cancer than the general population. Future research should differentiate between screening within and outside of general population screening recommendations, as it appears that within guideline-recommended screening ages, fewer differences in screening receipt may exist between cancer survivors and non-cancer controls. Future research should also report context-specific factors, such as how local screening programs recruit participants, as this may be an unexplained source of heterogeneity in our meta-analyses.

2.7 Tables and Figures

Table 1 – Definition of the systematic Review's Population, Exposure, Comparison, and Outcome groups	
Population	General population recommended to receive cancer screening: Studies which used age- and sex-specific population-based cancer screening guidelines appropriate for the general population were included.
Exposure	Cancer survivorship: An individual with any previous cancer diagnosis, irrespective of any other factors (i.e. type, stage, time since diagnosis, current treatment status).
Comparison	Non-cancer control group: We only included studies which utilized a non-cancer comparison group(s). Even if there is no direct causative link between subsequent cancer diagnoses, the risk of a cancer survivor to develop any new primary cancer will be at least as great as the general population, making the general population a valid benchmark against which the receipt of screening among cancer survivors can be measured against.
Outcome	Receipt of recommended cancer screening: Screening for any cancer site will be analyzed. Our systematic review found six screening sites reported upon in the literature: Breast, Cervical, Colorectal, Prostate, Skin, and Testicular. Receipt of these screening procedures must have been to identify new primary cancers, not as surveillance related to a previously diagnosed cancer.

Table 2 – Characteristics of Included Studies

First Author	Year	Country	Number of Participants	Survivor Characteristics	Initial Cancer Diagnosis Type	Control Group Source	Study Design/Exposure Measurement/Outcome Measurement			Cancer Sites Screened For					
										Breast	Cervical	Colorectal	Prostate	Skin	Testicular
Aparicio-Ting[25]	2003	USA	112 survivors, 2062 controls	34% between age 50-64, 100% female, 100% hispanic	Mixed	Non-matched, non-cancer cohort	CS	SR	SR	■	■				
Bellizzi[26]	2005	USA	7,384 survivors, 121,347 controls	52.7% ≥ age 65, 60.6% female, 88.5% white ethnicity	Mixed	Non-matched, non-cancer cohort	CS	SR	SR	■	■		■		
Bishop[10]	2010	North America	662 survivors, 158 controls	Median age: 49.1, 62% female, 92% caucasian ethnicity	Mixed	Matched, non-cancer cohort	CS	AD	SR	■	■	■	■		
Breslau[11]	2010	USA	1,502 survivors, 31,911 controls	Mean age: 66.8, 100% female, 76.3% white ethnicity	Breast Cancer	Non-matched, non-cancer cohort	CS	SR	SR		■	■			
Duffy[18]	2006	USA	85 survivors, 340 controls	Mean age: 61.7, 100% female, 85.9% caucasian/other ethnicity	Breast Cancer	Matched, non-cancer cohort	CS	SR	SR		■				
Earle[27]	2003	USA	5,965 survivors, 6,062 controls	Mean age: 78.7, 100% female, 89% white ethnicity	Breast Cancer	Matched, non-cancer cohort	RC	AD	AD		■	■			
Earle[19]	2004	USA	14,884 survivors, 16,659 controls	Mean age: 79.9, 57.6% female, 86.4% white ethnicity	Colorectal Cancer	Matched, non-cancer cohort	RC	AD	AD	■	■				
Grunfeld[28]	n/a	Canada	21,111 survivors, 105,340 controls	Mean age: 58.6, 86% female, no ethnic information	Mixed	Marched, non-cancer cohort	RC	AD	AD	■	■	■			
Hudson[39]	2009	USA	109 survivors, 641 controls	Mean age: 68.7, 59% female, 80% white ethnicity	Mixed	Non-matched, non-cancer cohort	CS	SR	SR + CR	■		■	■		
Khan[29]	2010	United Kingdom	29,244 survivors, 116,418 controls	Mean age: 70.7, 73.4% female, no ethnic information	Mixed	Matched, non-cancer cohort	RC	AD	AD	■	■		■		
Kwon[30]	2009	Canada	3,473 survivors	Mean age: 63, 100% female, no ethnic information	Endometrial Cancer	Population based screening rates	RC	AD	AD	■		■			
Mayer[31]	2007	USA	619 survivors, 2,141 controls	Mean age: 58, 65.5% female, 81.5% white ethnicity	Mixed	Non-matched, non-cancer cohort	CS	SR	SR	■	■	■	■		
McBean[33]	2008	USA	14,575 survivors, 14,575 controls	31.9% between ages 67-74, 100% female, 94.3% white ethnicity	Uterine Cancer	Matched, non-cancer cohort	RC	AD	AD	■		■			
McBean[32]	2009	USA	7,666 survivors, 36,433 controls	Mean age: 73.6, 100% female, 85% white ethnicity	Colorectal Cancer	Matched, non-cancer cohort	RC	AD	AD	■					
Ng[34]	2008	USA	511 survivors, 224 controls	Median age: 44, 51% female, no ethnic information available	Hodgkin's Lymphoma	Non-matched, non-cancer cohort (sibling cohort)	CS	AD	SR		■				■
Oeffinger[35]	2009	North America	551 chest RT survivors, 561 no chest RT survivors, 622 controls	Chest RT: 46.3% between ages 40-50, 100% female, 92.4% white No Chest RT: 45.8% between ages 40-50, 100% female, 93.2% white	Mixed	Non-matched, non-cancer cohort (sibling cohort)	CS	AD	SR	■	■				
Snyder *(a)*[37]	2009	USA	1961 survivors, 1961 controls	Mean age: 75, 100% female, 90% white ethnicity	Breast Cancer	Matched, non-cancer cohort	RC	AD	AD			■			
Snyder *(b)*[36]	2009	USA	23,731 survivors, 47,127 controls†	Mean age: 75.7, 100% female, 90% white ethnicity	Breast Cancer	Matched, non-cancer cohort	RC	AD	AD			■			
Trask[12]	2005	USA	2,151 survivors, 30,195 controls	Mean age: 61.9, 59.7% female, 90% white ethnicity	Mixed	Non-matched, non-cancer cohort	CS	SR	SR	■	■	■	■	■	
Yeazel[38]	2004	North America	9,434 survivors, 2,667 controls	No age information, 46.8% female, no ethnic information	Mixed	Non-matched, non-cancer cohort (sibling cohort)	CS	AD	SR	■	■				■

Legend: CS: Cross-Sectional Survey, RC: Retrospective Cohort Study, SR: Self-Reported exposure/outcome, AD: Administratively determined exposure/outcome, CR: Chart Review, † Study contained two controls groups: 23,731 controls with mammogram in same year as survivor's dx., 23,396 controls with the same comorbidity score

Table 3 – Summary of included studies by cancer site screened

Table 3a - Breast Cancer Screening						
First Author	**Year**	**Screening Test**	**Screening Timeframe**	**Age Restriction Inherent or Applied?**	**Unadjusted Breast Cancer Screening Proportions**	**Meta-Analysis?**
Aparicio-Ting	2003	Mammogram	Within last 2 years	No	Cancer Survivors: 80.0% Controls: 85.0%	Yes
Bellizzi	2005	Mammogram	Within last 2 years	≥ 40, no upper age	Cancer Survivors: 88.2% Controls: 81.9%	Yes
Bishop	2010	CBE and/or Mammogram	Within last 12 months	Age 50-65 only	Cancer Survivors: 76.7% Controls: 84.1%	Yes
Earle	2004	Mammogram	Within 2 year window (1997-1998)	Age 70-75 only	Cancer Survivors: 54.0% Controls: 51.5%	Yes
Grunfeld	Unpub.	Mammogram	Ever/Never within 2nd-5th year after diagnosis	Age 50 – 79 only	Cancer Survivors: 62.6% Controls: 58.0%	Yes
Hudson	2009	Mammogram	Within last 12 months	≥ 50, no upper limit	Chart Review Cancer Survivors: 42.2% Controls: 34.5%	No
					Self Report Cancer Survivors: 71.9% Controls: 69.3%	Yes
Khan	2010	Mammogram	Within 3 year window (2003-2006)	Age 50 - 69 only	Cancer Survivors: 60.5% Controls: 58.5%	Yes
Kwon	2009	Mammogram	Within 5 years after diagnosis	No	Cancer Survivors: 64% Controls: 31%	No
Mayer	2007	Mammogram	Ever/Never	≥ 40, no upper limit	Cancer Survivors: 91.8% Controls: 84.9%	Yes
McBean	2008	Mammogram	Within 2 year window (1999-2000)	≥ 67, no upper limit	Cancer Survivors: 56.1% Controls: 49.9%	Yes
McBean	2009	Mammogram	1st & 2nd, 3rd & 4th year after diagnosis	Age 67-84 only	1st and 2nd year Cancer Survivors: 49.7% Controls: 47.6%	No
					3rd and 4th year Cancer Survivors: 54.5% Controls: 50.4%	Yes
Oeffinger	2009	Mammogram	Within last 2 years	Age 40-50	Chest RT vs. Controls Cancer Survivors: 76.5% Controls: 67.0%	No
					No Chest RT vs. Controls Cancer Survivors: 70.0% Controls: 67.0%	No
Trask	2005	Mammogram	Within last 2 years	≥ 40, no upper limit	Raw data not available	No
Yeazel	2004	Mammogram	Ever/Never	No (≥ 18)	Raw data not available	Yes

Table 3b - Cervical Cancer Screening						
First Author	**Year**	**Screening Test**	**Screening Timeframe**	**Age Restriction Inherent or Applied?**	**Unadjusted Cervical Cancer Screening Proportions**	**Meta-Analysis?**
Aparicio-Ting	2003	Pap Smear	Within last 3 years	No	Cancer Survivors: 86.0% Controls: 80.0%	Yes
Bellizzi	2005	Pap Smear	Within last 3 years	≥ 18, no upper age	Cancer Survivors: 77.9% Controls: 86.8%	Yes
Bishop	2010	Pap Smear	Within last 12 months	No	Cancer Survivors: 72.6% Controls: 82.6%	Yes
Breslau	2010	Pap Smear	Within last 3 years	≥ 40, no upper age	Cancer Survivors: 80.4% Controls: 82.5%	Yes
Duffy	2006	Pap Smear	Within last year (survivors), last 2 years (controls)	≥ 40, no upper limit	Cancer Survivors: 60.2% Controls: 60.7%	No
Earle	2003	Pap Smear	Within 2 year window (1997-1998)	≥ 70, no upper limit	Cancer Survivors: 31% Controls: 27%	Yes
Earle	2004	Pap Smear	Within 2 year window (1997-1998)	≥ 70, no upper limit	Cancer Survivors: 17.8% Controls: 21.9%	Yes
Grunfeld	Unpub.	Pap Smear	Ever/Never within 2^{nd}-5^{th} year after diagnosis	Age 20 – 69 only	Cancer Survivors: 59.0% Controls: 52.1%	Yes
Khan	2010	Pap Smear	Within 3 year window (age 30-49, 2003-2006), 5 year window (age 50-64, 2001-2006)	Age 30-64 only	Cancer Survivors: 34.2% Controls: 35.6%	Yes
Mayer	2007	Pap Smear	Ever/Never	≥ 18, no upper age	Cancer Survivors: 98.7% Controls: 91.6%	Yes
Ng	2008	Pap Smear	Within last 3 years	Age of entire cohort within appropriate screening ages	Cancer Survivors: 94% Controls: 91%	Yes
Oeffinger	2009	Pap Smear	Within last 2 years	Age of entire cohort within appropriate screening ages	Chest RT vs. Controls Cancer Survivors: 88.2% Controls: 86.9%	No
					No Chest RT vs. Controls Cancer Survivors: 85.3% Controls: 86.9%	No
Trask	2005	Pap Smear	Within last year (age 21-29), 3 years (age ≥ 30)	≥ 21, no upper limit	Raw data not available	No
Yeazel	2004	Pap Smear	Within last 3 years	Age of entire cohort within appropriate screening ages	Raw data not available	No

Table 3c - Colorectal Cancer Screening						
First Author	**Year**	**Screening Test**	**Screening Timeframe**	**Age Restriction Inherent or Applied?**	**Unadjusted Colorectal Cancer Screening Proportions**	**Meta-Analysis?**
Bishop	2010	FOBT and/or Endoscopy	Within last 12 months	≥ 50, no upper limit	Cancer Survivors: 47.0% Controls: 57.3%	Yes
Breslau	2010	FOBT	Within last 12 months	≥ 50, no upper limit	Cancer Survivors: 24.6% Controls: 19.1%	Yes
		Endoscopy	Within last 10 years		Cancer Survivors: 57.2% Controls: 42.9%	No
Earle	2003	FOBT, BE, and/or Endoscopy	Within 2 year window (1997-1998)	≥ 70, no upper limit	Cancer Survivors: 17.0% Controls: 14.0%	Yes
Grunfeld	Unpub.	FOBT, BE, and/or Endoscopy	Ever/Never within 2nd-5th year after diagnosis	Age 50 – 74 only	Cancer Survivors: 34.2% Controls: 31.9%	Yes
Hudson	2009	FOBT and/or Endoscopy	Within last: FOBT (1 yr), sigmoidoscopy (5 yr), colonoscopy (10 yr)	≥ 50, no upper limit	Chart Review Cancer Survivors: 56.0% Controls: 49.1%	No
					Self Report Cancer Survivors: 80.7% Controls: 67.7%	Yes
Kwon	2009	FOBT, BE, and/or Endoscopy	Within 5 years after diagnosis	No	Cancer Survivors: 30%, General Population: 15%	No
Mayer	2007	FOBT and/or Endoscopy	Ever/Never	≥ 50, no upper limit	Cancer Survivors: 84.6% Controls: 69.0%	Yes
McBean	2008	BE and/or Endoscopy	Within 4 year window (1999-2002)	≥ 67, no upper limit	Cancer Survivors: 21.3% Controls: 19.8%	Yes
Snyder *(a)*	2009	FOBT and/or Endoscopy	Within each year of follow-up	≥ 67, no upper limit	Cancer survivors less likely to receive screening during each of the 5 years of survivorship ($p < 0.05$ for all years)	No
Snyder *(b)*	2009	FOBT, Endoscopy, and/or DRE	Within 366-730 days after dx. or matched dx.	≥ 67, no upper limit	Cancer Survivors vs. Comorbidity Controls Cancer Survivors: 39.6% Controls: 29.7%	Yes
					Cancer Survivors vs. Screening Controls Cancer Survivors: 39.6% Controls:45.2%	No
Trask	2005	FOBT	Within last 12 months	≥ 50, no upper limit	Raw data not available	Yes
		Endoscopy	Within last 5 years			No

Table 3d - Prostate Cancer Screening						
First Author	**Year**	**Screening Test**	**Screening Timeframe**	**Age Restriction Inherent or Applied?**	**Unadjusted Prostate Cancer Screening Proportions**	**Meta-Analysis?**
Bellizzi	2005	PSA	Within last 12 months	≥ 50, no upper limit	Cancer Survivors: 74.6% Controls: 70.1%	Yes
Bishop	2010	DRE and/or PSA	Within last 12 months	≥ 50, no upper limit	Cancer Survivors: 62.6% Controls: 80.0%	Yes
Hudson	2009	PSA	Within last 12 months	Age 50-75	Chart Review Cancer Survivors: 48.4% Controls: 48.1%	No
					Self Report Cancer Survivors: 77.4% Controls: 53.4%	Yes
Khan	2010	PSA	Within 3 year window (2003-2006)	≥ 50, no upper limit	Cancer Survivors: 22.1% Controls: 19.0%	Yes
Mayer	2007	PSA	Ever/Never	≥ 50, no upper limit	Cancer Survivors: 76.0% Controls: 58.7%	Yes
Trask	2005	PSA	Within last 12 months	≥ 50, no upper limit	Raw data not available	No

Table 3e - Skin Cancer Screening						
First Author	**Year**	**Screening Test**	**Screening Timeframe**	**Age Restriction Inherent or Applied?**	**Unadjusted Skin Cancer Screening Proportions**	**Meta-Analysis?**
Trask	2005	Total Skin Exam	Within last 3 years (age 20-39), last year (age ≥ 40)	≥ 20, no upper limit	Raw data not available	No

Table 3f - Testicular Cancer Screening						
First Author	**Year**	**Screening Test**	**Screening Timeframe**	**Age Restriction Inherent or Applied?**	**Unadjusted Testicular Cancer Screening Proportions**	**Meta-Analysis?**
Ng	2008	TSE	Monthly	No	Cancer Survivors: 19.0% Controls: 9.0%	No
Yeazel	2004	TSE	Monthly	No	Raw data not available	No

Legend
CBE: Clinical Breast Examination, FOBT: Fecal Occult Blood Test, BE: Barium Enema DRE: Digital Rectal Exam, PSA: Prostate Specific Antigen, TSE: Testicular Self Exam
Endoscopy: one or more of: Colonoscopy, Sigmoidoscopy,or Proctoscopy

Table 4 – Study Risk of Bias Results					
First Author	**Year**	**Selection Bias**	**Cancer Survivor Selection**	**Screening rate measurement**	**Comparable cancer survivors and controls, adjustment for confounding**
Aparicio-Ting	2003	M	H	M	H
Bellizzi	2005	M	M	M	L
Bishop	2010	H	M	M	H
Breslau	2010	H	M	M	L
Duffy	2006	M	M	M	L
Earle	2003	L	L	L	L
Earle	2004	L	L	L	L
Grunfeld	Unpub.	L	L	L	L
Hudson	2009	H	H	M	L
Khan	2010	L	L	L	L
Kwon	2009	L	M	L	M
Mayer	2007	H	M	M	L
McBean	2008	L	L	L	L
McBean	2009	L	M	L	L
Ng	2008	H	L	M	M
Oeffinger	2009	H	L	M	M
Snyder *(a)*	2009	L	M	L	L
Snyder *(b)*	2009	L	H	L	L
Trask	2005	M	M	M	L
Yeazel	2004	H	L	M	M

Table 5– Sensitivity and Subgroup Analyses for Breast, Cervical, and Colorectal Cancer Screening			
	Breast Cancer Screening	**Cervical Cancer Screening**	**Colorectal Cancer Screening**
	Summary odds ratio estimate, 95% C.I.		
All Studies	**1.19, 95% CI: 1.06 – 1.34** n = 11	**1.22, 95% CI: 1.12 – 1.33** n = 11	**1.19, 95% CI: 1.10 – 1.30** n = 9
Risk of Bias Categories **1) Selection Bias**			
Low/Moderate risk	1.16, 95% CI: 1.02 – 1.30 n = 7	1.27, 95% CI: 1.21 – 1.33 n = 6	1.22, 95% CI: 1.11 – 1.34 n = 5
High risk	1.25, 95% CI: 0.78 – 2.02 n = 4	1.08, 95% CI: 0.70 – 1.65 n = 5	1.14, 95% CI: 0.92 – 1.42 n = 4
2) Adequate Cancer Survivor Selection			
Low/Moderate risk	1.23, 95% CI: 1.09 – 1.40 n = 9	1.22, 95% CI: 1.12 – 1.33 n = 10	1.18, 95% CI: 1.09 – 1.29 n = 7
High risk	0.96, 95% CI: 0.78 – 1.17 n = 2	1.50, 95% CI: 0.67 – 3.37 n = 1	1.21, 95% CI: 0.99 – 1.47 n = 2
3) Screening Measurement			
Administratively collected	1.14, 95% CI: 0.99 – 1.30 n = 5	1.26, 95% CI: 1.19 – 1.33 n = 4	1.20, 95% CI: 1.08 – 1.33 n = 4
Self-reported	1.22, 95% CI: 0.93 – 1.61 n = 6	1.16, 95% CI: 0.87 – 1.54 n = 7	1.19, 95% CI: 1.00 – 1.43 n = 5
4) Controlling for Confounding/Using a Matched Cohort			
Low/Moderate risk	1.22, 95% CI: 1.02 – 1.38 n = 9	1.24, 95% CI: 1.15 – 1.34 n = 9	1.21, 95% CI: 1.11 – 1.31 n = 8
Unadjusted studies (high risk)	0.65, 95% CI: 0.37 – 1.15 n = 2	0.87, 95% CI: 0.33 – 2.29 n = 2	0.66, 95% CI: 0.40 – 1.10 n = 1
Study Characteristics			
Elderly population (65+)	1.12, 95% CI: 0.91 – 1.37 n = 3	1.26, 95% CI: 1.18 – 1.34 n = 2	1.23, 95% CI: 1.08 – 1.40 n = 3
Non-elderly population	1.24, 95% CI: 1.05 – 1.46 n = 8	1.19, 95% CI: 1.04 – 1.36 n = 9	1.16, 95% CI: 1.05 – 1.29 n = 6
Childhood cancer survivors	1.17, 95% CI: 0.41 – 3.28 n = 2	0.87, 95% CI: 0.53 – 1.43 n = 3	0.66, 95% CI: 0.40 – 1.10 n = 1
Non-childhood cancer survivors	1.15, 95% CI: 1.02-1.28 n = 9	1.28, 95% CI: 1.22 – 1.34 n = 8	1.21, 95% CI: 1.11 – 1.31 n = 8
Ages of Cancer Survivors/Controls within Screening Guidelines			
Adequate lower and upper age limits	1.06, 95% CI: 0.95 – 1.19 n = 5	1.14, 95% CI: 0.95 – 1.37 n = 4	1.11, 95% CI: 1.06 – 1.17 n = 1
No lower and upper age limits	1.34, 95% CI: 1.13 – 1.59 n = 6	1.28, 95% CI: 1.16 – 1.41 n = 7	1.21, 95% CI: 1.10 – 1.33 n = 8
Adequate lower age, with or without upper age limit	1.15, 95% CI: 1.02 – 1.28 n = 9	1.22, 95% CI: 1.12 – 1.33 n = 11	1.19, 95% CI: 1.10 – 1.30 n = 9
No lower age limit, with or without upper age limit	1.18, 95% CI: 0.45 – 3.13 n = 2	n/a n = 0	n/a n = 0

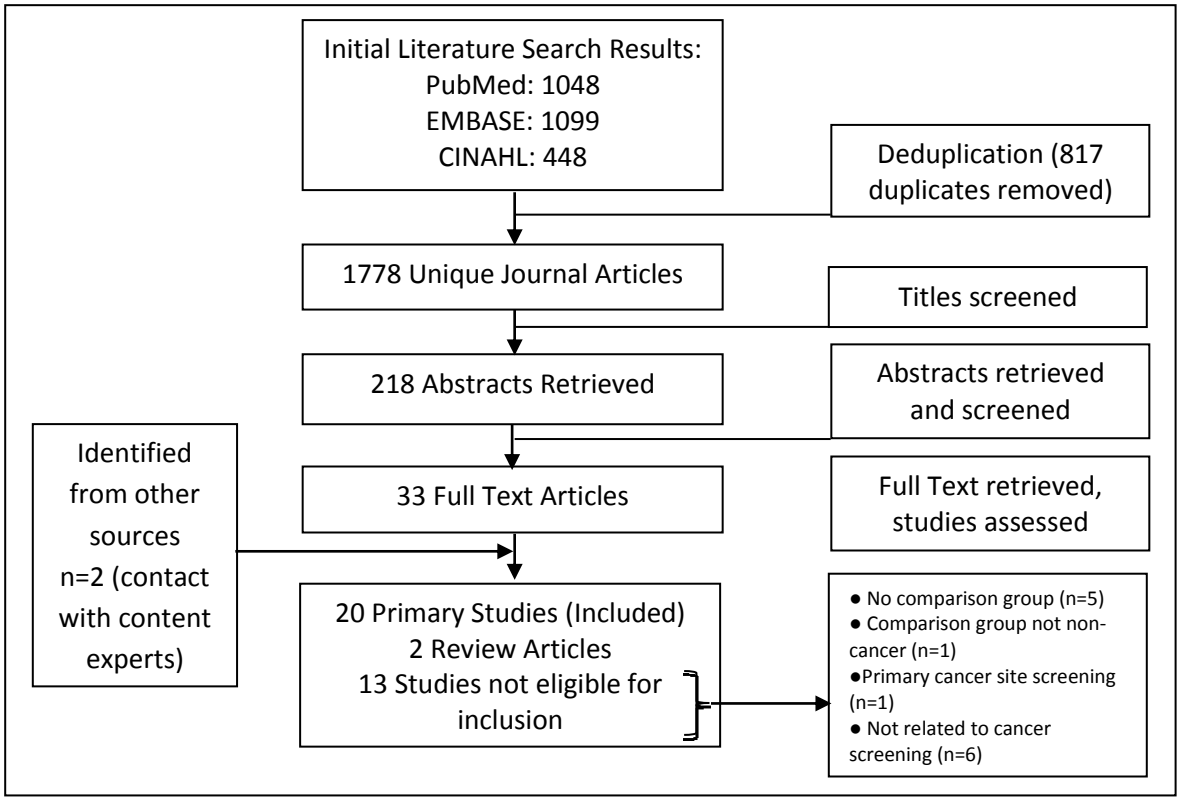

Figure 1 – Flowchart showing selection of articles for inclusion in the systematic review

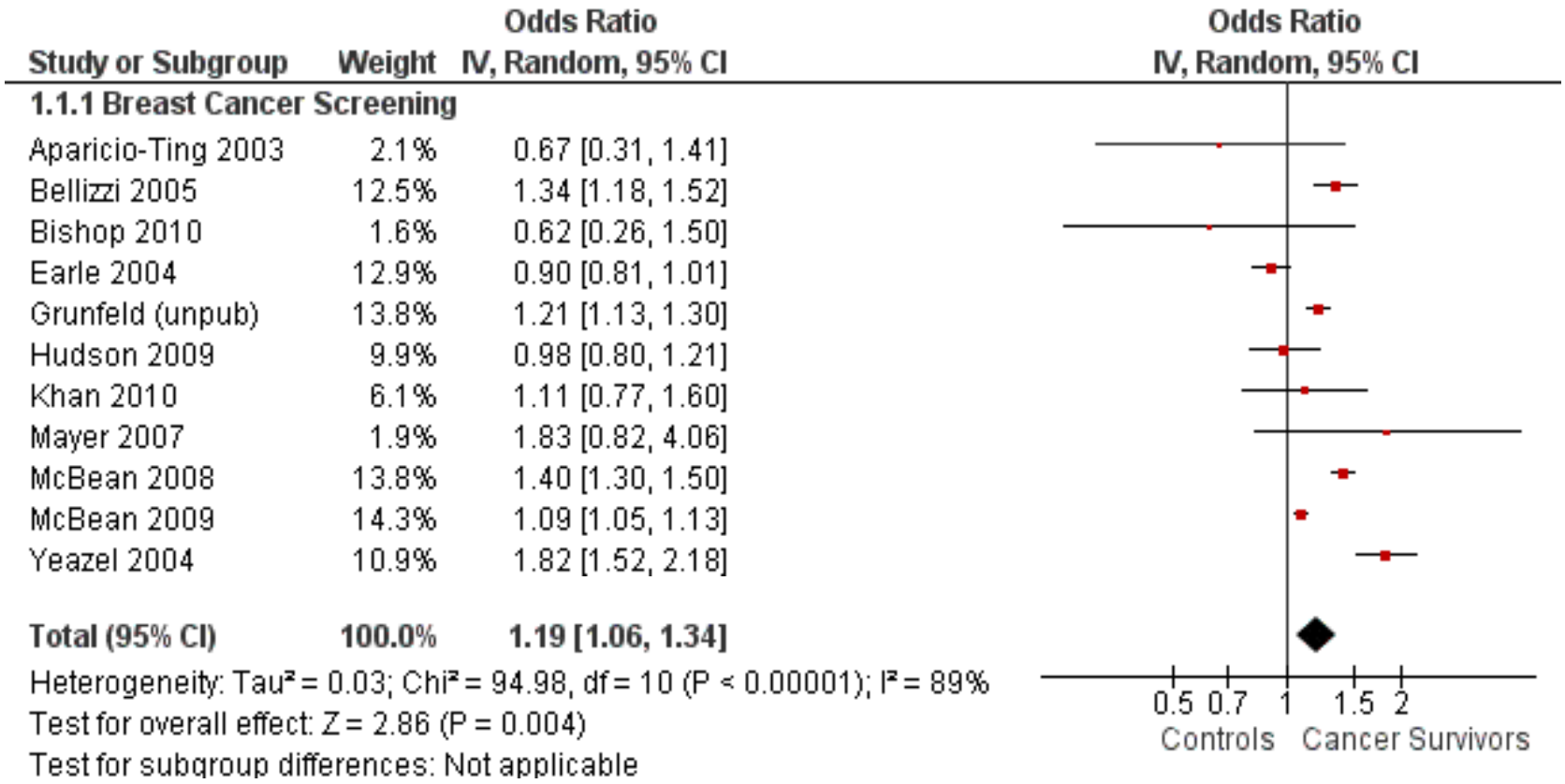

Figure 2 – **Breast Cancer Screening Meta Analysis, Generic Inverse Variance Random Effects Model**

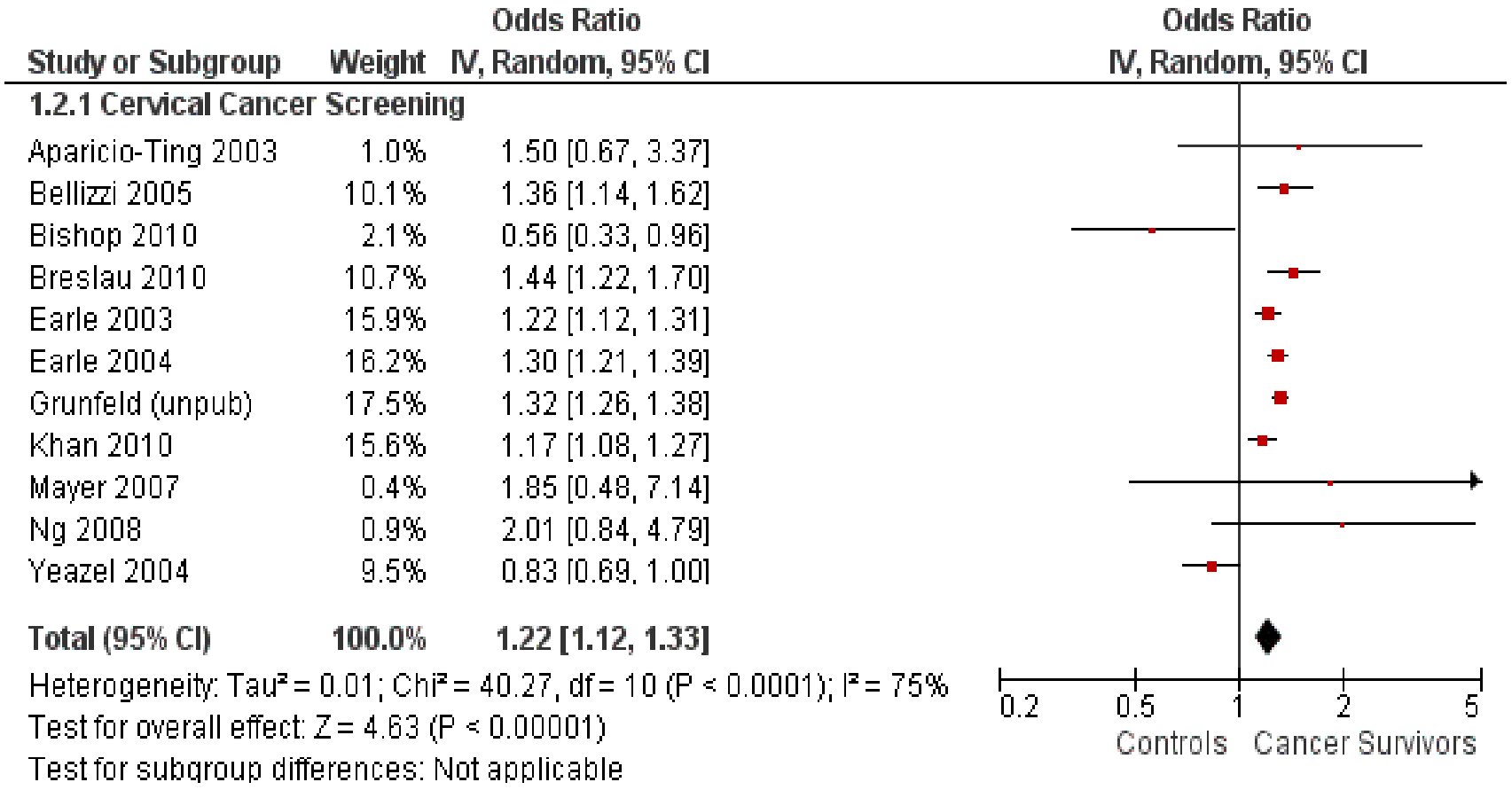

Figure 3 – **Cervical Cancer Screening Meta Analysis, Generic Inverse Variance Random Effects Model**

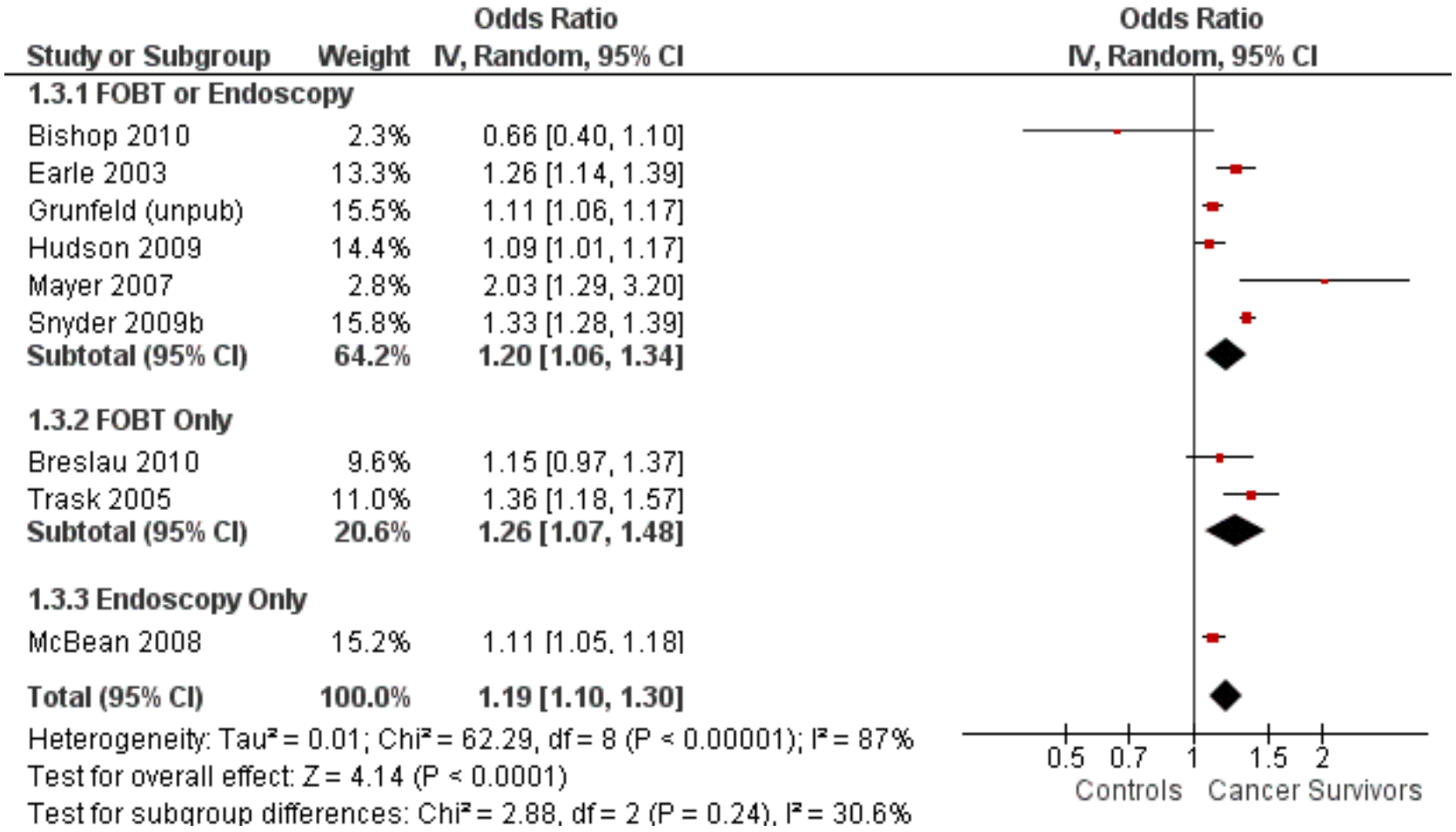

Figure 4 – Colorectal Cancer Screening Meta Analysis, Generic Inverse Variance Random Effects Model

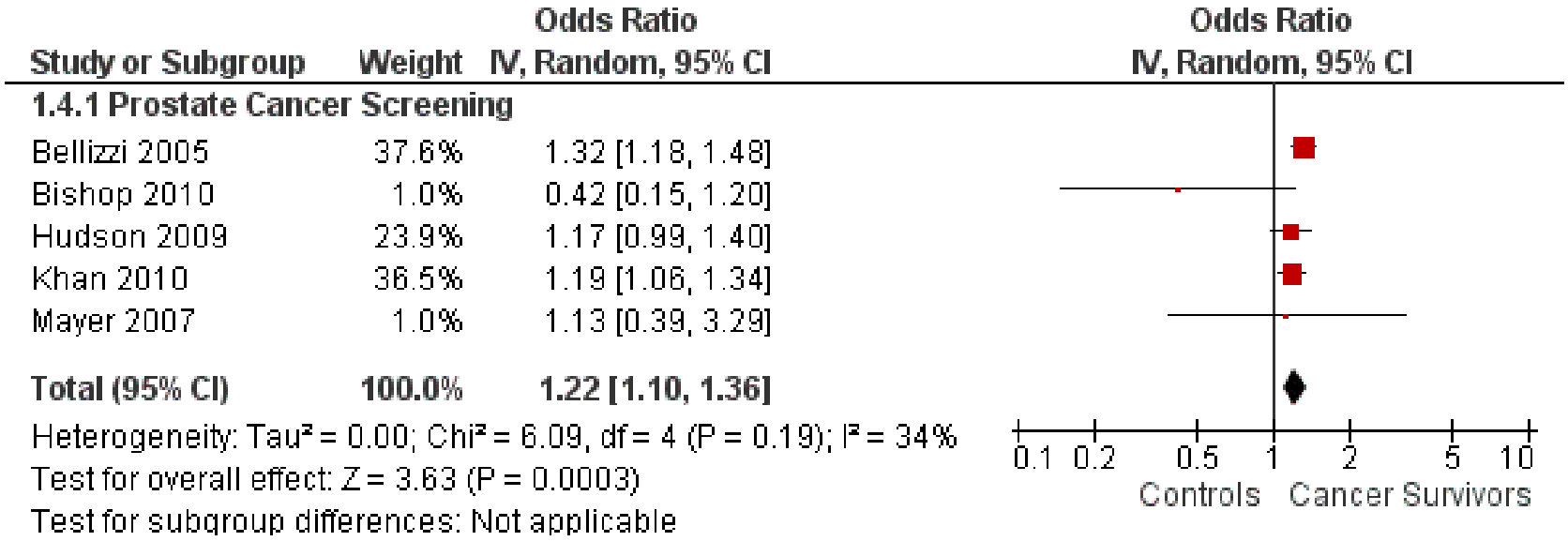

Figure 5 – **Prostate Cancer Screening Meta Analysis, Generic Inverse Variance Random Effects Model**

2.8 References

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Chapter 3 – Manuscript Two

3.1 Introduction

Approximately 750,000 Canadians have been diagnosed with at least one primary invasive cancer in the past 10 years[1]. Among Canadian cancer survivors, colorectal cancer is the third most common cancer survivorship site, with approximately 100,000 survivors. This high number is a result of high incidence (colorectal cancer is the third most frequently diagnosed cancer in both men and women, with 22,200 incident cases per year) and 63% 5-year relative survival[1].

With a growing and aging population, the number of incident cancer cases in Canada is expected to continue rising[2]. Those diagnosed with cancer are now surviving longer than ever[3], which combined with the growing incidence of cancer means that we can expect to see an increased burden on the healthcare system due to a growing number of cancer survivors. Nova Scotia is of particular interest, as the province has the second highest incidence of colorectal cancer in Canada[1].

The 2006 Institute of Medicine report *From Cancer Patient to Cancer Survivor: Lost in Transition* highlights the often overlooked and multiple care needs of cancer survivors, which include: i) surveillance for local, regional, or distant recurrence of the initial cancer; and ii) screening for new primary cancers at other sites[4]. While guidelines for cancer surveillance have been created for many commonly diagnosed cancers (e.g., breast[5, 6], cervical[7], endometrial[8], colorectal[9, 10], melanoma[11], and prostate[12]), no published guidelines exist for providing preventive screening for new primary cancers among

cancer survivors, despite previous studies demonstrating that many cancer survivors are at increased risk of developing a second malignancy[13-18].

Cancer screening is an important component of preventive healthcare in defined target populations. These target populations vary by screening site as well as location. In general, women aged 50-69 are recommended to undergo a mammogram every two years for breast cancer screening[19]; some programs (including the Nova Scotia Breast Screening Program) also target women aged 40-49 for annual mammography. A Papanicolaou (Pap) smear is recommended at least every three years in women aged 21-75 for cervical cancer screening[20]. Breast and cervical cancer screening programs have been shown to decrease mortality from their respective cancers by up to 26%[21] and 50-80%[22, 23] respectively.

Our recent systematic review concluded that although cancer survivors were more likely than the general population to receive screening for new primary cancers, a significant proportion of the cancer survivor population did not receive screening for new primary cancers[24]. However, the majority of the studies included in this review were from the United States (U.S.), and little is known about cancer screening practices among Canadian cancer survivors. One Canadian study[25] reported that colorectal cancer survivors from Ontario were less likely to receive breast cancer screening than a matched, non-cancer control population, and no more likely to receive cervical cancer screening; these results contrast with the predominantly U.S.-based meta-analysis. In addition, through the systematic review, we identified the need to analyze receipt of cancer screening among cancer survivors within recommended ages in general population screening guidelines.

3.2 Objective

The objective of this study was to describe the receipt of breast and cervical cancer screening among colorectal cancer survivors in Nova Scotia.

3.3 Methods

3.3.1 Data and Subjects

We conducted a retrospective population-based cohort study using the CIHR/CCNS Team ACCESS: Access to Colorectal Cancer Services in Nova Scotia database[26]. The ACCESS database is comprised of 15 linked administrative databases, and includes all individuals diagnosed with colorectal cancer in Nova Scotia between January 1st, 2001 and December 31st, 2005.

For this study, we included all patients diagnosed with stage I, II, or III colorectal cancer in Nova Scotia between January 1st, 2001 and December 31st, 2005. Stage IV diagnoses were not included as a stage IV diagnosis is associated with extremely poor 5-year survival rates, and at diagnosis, their disease had already spread outside the primary cancer site. Those diagnosed with an unknown stage disease have similar survival patterns to those with stage IV disease, and were not included. We only included females in our cohort, as our objective was to examine receipt of breast and cervical cancer screening. We only included those who underwent resection surgery, as this is indicative of curative intent in colorectal cancer treatment.

We excluded those who displayed evidence of recurrence or advanced disease within the first year after diagnosis using the Oncology Patient Information System

(OPIS) database. The Canadian Institute for Health Information (CIHI) Discharge Abstract Database and Nova Scotia's Medical Services Insurance (MSI) physician billings data were used to identify and exclude patients who underwent surgical resections at common colorectal cancer metastasis sites (liver and lung) within the first year after diagnosis. Through linkage with the Nova Scotia Cancer Registry (NSCR), those with a cancer diagnosis prior to their colorectal cancer were excluded, as their healthcare utilization and cancer screening behavior could be influenced by their previous cancer diagnosis. We excluded those residing within Cumberland District Health Authority, as these individuals may receive some of their healthcare in New Brunswick, which would not be adequately captured in our data. The inclusion and exclusion criteria for the cancer survivor cohort are summarized in Table 6.

We considered the cancer survivorship period to begin immediately after an individual's colorectal cancer diagnosis, as the purpose of our study was to describe receipt of screening, not adherence to guidelines. This is in contrast with some, but not all, studies in the cancer survivorship literature, where some analyses begin one year after an individual's cancer diagnosis. While healthcare utilization during the first year after diagnosis may be focused on primary cancer treatment and not representative of 'usual' general preventive care, we observed a large proportion of our cancer survivor cohort received both breast and cervical cancer screening in the first year after diagnosis.

The cancer survivorship period continued until censorship or the end of available data/study end date (March 31st 2008, 62.8% of our cohort). Date of censorship was calculated using the earliest criterion of the list presented in Table 7. We censored individuals 90 days prior to either the diagnosis of new primary cancers (from the NSCR)

or evidence of colorectal cancer recurrence which occurred after the one year exclusion period. Evidence included initiation of chemotherapy or radiotherapy greater than 365 days after diagnosis (as this would indicate either recurrence or palliative treatment); surgical resection of distant recurrence sites (liver and lung); enrolment in a palliative care program; date of death; or a cancer recurrence diagnosis in OPIS.

We excluded those with a hysterectomy prior to their colorectal cancer diagnosis from the cervical cancer screening analysis, and also used hysterectomy dates as a censoring criterion in our cervical cancer screening analysis. This removed 14 patients from the cervical cancer screening analysis. Hysterectomy procedures were identified using MSI physician billings and the CIHI Discharge Abstract Database, and only those that included removal of the cervix were used

Receipt of breast and cervical cancer screening was obtained through the ACCESS database, which is linked to the Nova Scotia Breast Screening Program and Cervical Cancer Prevention Program databases. Only mammograms booked through the central mammography booking system are included in the Nova Scotia Breast Screening Program database, and did not capture all mammograms during our study period. Mammograms conducted outside of the screening program were not able to be included in our study. To examine the potential for ascertainment bias, we conducted a sensitivity analysis of screening receipt in cancer survivors who were part of the Capital District Health Authority, which used the central mammography booking throughout the study period. Screening tests captured by the Nova Scotia Breast Screening Program differentiate between mammograms conducted with screening and diagnostic intent. We

only included screening mammograms in our study. The Cervical Cancer Prevention Program database records the receipt of all Pap smears conducted in Nova Scotia.

3.3.2 Analysis

We used Kaplan Meier time to event curves and Cox Proportional Hazards models to assess the time to first breast and cervical cancer screen. This analysis technique allowed us to account for the variable lengths of follow-up in our data, due to cancer survivor's staggered entry and censorship throughout the study period. For these analyses, time zero was the date of colorectal cancer diagnosis.

We stratified our cohort into age groups representative of general population breast and cervical cancer screening guidelines, focusing our analyses on survivors within guideline recommended age groups per Nova Scotia screening guidelines[27, 28] (breast cancer screening: ages 40-69, cervical cancer screening: 21-75). In those above the cancer screening guideline's upper age limit, we reported results separately for those who were less than and greater than ten years above the recommended upper age limit. Age groups were defined based on survivors' age at time of colorectal cancer diagnosis, and treated as fixed. Subjects did not switch age groups as they aged in our analysis. We chose not to treat our age groups as a time varying covariate as this would have precluded age-stratified Kaplan Meier curves. Also, we found that only a very small proportion of survivors were inaccurately captured as receiving screening outside our age groups as a result of treating age groups as fixed (across all age groups, breast cancer screening: 2.2%; cervical cancer screening: 0.9%).

As breast cancer screening recommendations in Nova Scotia differ for those aged 40-49 and 50-69, we first examined time to first screen separately for these two groups. As no significant difference was observed between these two groups, we combined these age groups to increase study power in subsequent analyses, and only reported breast cancer screening results for the age group 40-69. Breast cancer screening results were not presented for those under the age of 40 at diagnosis, as there were only a small number of survivors (n = 6) and general population screening guidelines do not apply to this age group.

We conducted univariate analyses using Cox proportional hazards models to identify factors that affect time to first breast or cervical cancer screen during the survivorship period. These univariate comparisons were planned *a priori*. Cox proportional hazards models were used instead of logistic regression as our cohort had variable follow-up lengths due to staggered entry and censoring. The following variables were considered: five-year age at diagnosis groups, cancer site (colon vs. rectal), stage (I, II, or III), comorbidity (modified Elixhauser scale[29], coded 0, 1, ≥2 comorbid conditions, excluding cancer-related comorbid categories), urban or rural residency (coded using the SACtype system used by Statistics Canada{{}}, see Appendix E for further explanation), receipt of breast or cervical cancer screening prior to colorectal cancer diagnosis (within last 3 years for breast cancer screening, last 4 years for cervical cancer screening), primary care physician utilization (annualized rate, excluding visits within the first year after diagnosis, grouped into quartiles) and oncology specialist utilization (annualized rate, excluding visits within the first year after diagnosis, and rounded into one the following categories: 0, 1, ≥2 visits per year). Physician utilization within the first year

after diagnosis was likely to have been heavily focused on primary colorectal cancer treatment, and therefore was not examined. All proportional hazards models satisfied the proportionality assumption ($p > 0.05$), with one exception: urban/rural residency in the breast cancer screening cohort ($p = 0.02$). This exception was analyzed using a stratified Kaplan Meier curve and Log-Rank test.

Our time to second screen analysis included those who had received a breast or cervical cancer screening event during the survivorship period. We then observed the time to a survivor's second screening event, with 'time zero' being the date of the first screening event.

All analyses were conducted using Statistical Analysis System (SAS) version 8. Statistical significance was considered to be $\alpha = 0.05$. Our Cox proportional hazards models had 80% power to detect a significant hazard ratio of 1.53 and 1.43 for our breast and cervical cancer age restricted cohorts, respectively. Data access was approved by the Capital District Health Authority and Dalhousie University Research Ethics Boards.

3.4 Results

The characteristics of both the age-restricted and entire colorectal cancer survivor cohorts are displayed in Table 8. The cohort contained 318 and 443 survivors who were diagnosed with colorectal cancer between the ages of 40-69 and 21-75, respectively.

The time to first breast and cervical screens for the entire colorectal cancer survivor cohort, stratified by age at diagnosis groups, are displayed in Figures 6 and 7. No significant difference in time to first breast screen was observed between the 40-49 and

50-69 age groups ($p = 0.99$). Colorectal cancer survivors above guideline recommended age groups were less likely to receive both breast and cervical cancer screening than those within guideline recommended age groups ($p < 0.001$ for all comparisons)

A significant proportion of colorectal cancer survivors never received breast and cervical cancer screening after their colorectal cancer diagnosis. 30.1% (95% CI: 21.2% - 39.0%) of survivors between ages 40-69 never received a screening mammogram during our study period (after their colorectal cancer diagnosis), and 47.9% (95% CI: 37.8% - 58.0%) of survivors between ages 21-75 never received cervical cancer screening during our study period.

Table 9 presents factors associated with receiving or not receiving breast and cervical cancer screening in our age restricted cohorts. An older age at diagnosis (per five year age increase in age at diagnosis) was associated with not receiving a cervical cancer screen, but not significantly associated with not receiving a breast cancer screen (Cervical cancer screening, HR: 0.76, 95% C.I. 0.71 – 0.86; Breast cancer screening, HR: 0.92, 95% CI: 0.83 – 1.01).

Receipt of pre-diagnosis breast and cervical cancer screening was highly predictive of receiving the same screening test during the survivorship period (Breast cancer screening, HR: 4.71, 95% C.I. 3.42 – 6.51; Cervical cancer screening, HR: 6.83, 95% C.I. 4.58 – 10.16).

Survivors who had an average of one oncology specialist visit per year (excluding the first year after diagnosis) were more likely to receive a screening mammogram and borderline significantly more likely to receive a Pap smear ($p = 0.051$) than those who

received fewer follow-up visits from an oncology specialist. However, no dose-response effect was observed; those who visited their oncology specialists more frequently (two or more times annually) did not receive more frequent screening. No other factors were statistically significant in our analysis.

Figures 8 and 9 present the time to second breast and cervical screen respectively. 89.6% (95% C.I. 82.6% - 96.7%) of those who received a screening mammogram during the survivorship period received a second mammogram during the survivorship period. 82.2% (95% C.I. 74.3% - 90.2%) of those who received a Pap smear during the survivorship period received a second Pap smear during the survivorship period.

3.5 Discussion

In our population-based study of Nova Scotian colorectal cancer survivors, we found 30.1% and 47.9% of colorectal cancer survivors who were within general population screening age recommendations never received a screening mammogram or Pap smear, respectively, during the survivorship period.

While no known studies have examined differential benefits of cancer screening between cancer survivors and the general population, previous literature has shown that colorectal cancer survivors are, at best, as likely as the general population to develop secondary breast and cervical cancers, and often been shown to be at a greater risk to develop these second primary cancers than the general population[16-18]. Future research should seek to compare the survival benefit of screening for new primary cancers among cancer survivors to cancer screening among the general population.

We conducted a recent systematic review and meta-analysis[24] comparing receipt of screening for new primary cancers among cancer survivors and non-cancer controls. In that review, we found that across all cancer screening sites and primary cancer diagnosis sites, cancer survivors were more likely to receive screening for new primary cancers than non-cancer control groups. Compared to the Nova Scotian general population, our results suggest that colorectal cancer survivors appear to be as likely to receive breast cancer screening compared to the general population. 46.4% (95% C.I. 40.3% – 52.5%) of colorectal cancer survivors diagnosed between ages 50-69 received a screening mammogram in the two years following their colorectal cancer diagnosis, compared to 48.03% in the general population aged 50-69 between 2006-2007[30] (the latest two full years which were also examined during our study). As these screening rates have not been age standardized, it is plausible that after age adjustment our colorectal cancer survivor cohort could be more likely to receive breast cancer screening, as our cohort between ages 50-69 is skewed towards slightly older ages.

To check for ascertainment bias, we calculated the proportion of cancer survivors living within the Capital District Health Authority who received a screening mammography within two years after their colorectal cancer diagnosis. 52.9% (95% C.I. 44.1% – 61.6%) of colorectal cancer survivors received a screening mammogram within the first two years after diagnosis, compared with 46.4% (95% C.I. 40.3% – 52.5%) of the entire cohort, which indicates a small but detectable difference in screening rates due to ascertainment bias.

The strongest predictive factor of receiving breast and cervical cancer screening was receipt of the same screening test prior to diagnosis. Prior screening has been shown

to be a predictive utilization measure of repeat mammography in the general population[31], and repeat mammography screening rates are much higher than the overall Nova Scotia general population screening rate (80.8% vs. 57.6%, 2008-2009 data)[32]. We also observed a similar result in our time to second screen analysis, where 89.6% and 82.2% of survivors who received one screening event during the survivorship period received a second breast and cervical cancer screen during the study period, respectively.

The Nova Scotia Breast Screening Program sends reminder cards to those aged 40-69 who are enrolled in the screening program, which is likely responsible for the very high proportion of survivors receiving a second breast screen. After age 70, women are no longer sent reminder cards, but may still receive screening mammograms. The organization of screening programs can be a key determinant of screening patterns among cancer survivors. Previous literature has shown these reminders to be an effective method of increasing adherence to cancer screening in the general population[33], which is consistent with our findings in a colorectal cancer survivor cohort.

Despite the Cervical Cancer Prevention Program not utilizing a reminder card system, we observed similar pre-diagnostic screening and time to second screen results as in breast cancer screening. However, one of the top self-reported reasons women undergo cervical cancer screening is the reminder cards sent by the Nova Scotia Breast Screening Program[32]. Outside of these reminders, the responsibility for repeat cervical cancer screening would fall on both the patient and primary care provider, though primary care physicians may also have their own reminder systems for implementing preventive care.

Our time to second screen analyses indicate that receipt of breast and cervical cancer screening in the colorectal cancer population tends to occur at discrete time points (breast screening: one and two years after first screen; cervical screening: six months and one year after first screen). It should not be surprising that no screening mammograms were observed within the first year of our time to second screen analysis, as any mammograms performed during this time would be performed with diagnostic intent, and not included in our analysis. No distinction is made between screening and diagnostic Pap smears in the Cervical Cancer Prevention Program, and some of the early Pap smears observed in our time to second screen analysis were likely performed for diagnostic purposes.

A younger age at diagnosis was predictive of receiving a cervical cancer screen in our age restricted analysis. However, age at diagnosis had no significant effect in our age restricted breast cancer screening analysis. In previously published literature among cancer survivors, older age was found to be predictive of not receiving cancer screening[34-36]. However, these studies contained older cancer survivors than those in our age restricted analyses. A likely explanation of why we did not see decreased screening receipt in our breast cancer screening analysis was the use of an upper age limit of 69 in our analysis. As we found significantly decreased breast cancer screening receipt in those 70 and older, if we removed our upper age limit we likely would have observed a similar trend to previously published literature.

Increasing number of total physician visits[36] and primary care visits[37] have been shown to be correlated with increased cancer screening uptake among cancer survivors. However, increasing annualized primary care and oncology specialist visit rates did not

appear to have much influence in our cohort, except for one oncology specialist visit in breast and cervical cancer screening (with borderline statistical significance). This discrepancy could be a result of our analysis technique in a cohort with variable lengths of follow-up. Previous research has shown in a population of breast cancer survivors that physician utilization changes over the course of the survivorship period, with an increasing number of primary care physician and decreasing number of oncology specialist visits over time[38]. We measured physician utilization in an annualized rate measure that would not have captured these changes. This could have biased our results towards the null if those with shorter follow-up lengths were less likely to be screened, and had artificially inflated annualized physician visit rates. The Nova Scotia Breast Screening Program reports that the most frequently self-reported reason for participating in the screening program is recommendation by a family physician, and this likely also holds true for the cancer survivor population as well.

In a study of colorectal cancer survivors identified in the SEER-Medicare database, stage at diagnosis and comorbidity were seen as predictors of not receiving breast cancer screening[39]. Similar results have been shown for breast cancer survivors[40]. In our cohort, we found these predictors not to be significantly predictive of cancer screening receipt. It is possible we did not observe an effect of comorbid conditions because our cohort was restricted to much younger ages than in these other studies (Age 40-69 vs. 67-79), where the influence of comorbidity might be lessened. It is less clear why stage at diagnosis did not have an effect on screening receipt in our cohort.

We focused our analyses on survivors within general population recommended age limits for breast and cervical cancer screening. When we stratified receipt of

screening by those who were within and outside the age recommendations for cancer screening, we found lower, but still existent, screening receipt in those just above the age recommendations. This could present a potential bias in comparative studies between cancer survivors and the general population, as cancer survivors might be preferentially encouraged to receive screening above general population age recommendations due to their higher risk of developing secondary cancers. Because of this, we recommend future research be conducted on age-restricted cohorts until cancer screening guidelines specifically for cancer survivors are developed.

Our study has numerous strengths. We were able to use data from numerous administrative databases to create explicit inclusion/exclusion and censorship criteria. Our censorship criteria allowed us to identify colorectal cancer survivors with variables lengths of follow-up, and we used survival-analysis techniques to appropriately analyze our data. Our source population contained all incident cases of colorectal cancer in Nova Scotia diagnosed between 2001-2005, eliminating potential response bias inherent in many self-reported surveys. We were also able to differentiate between breast cancer screening that was for screening and diagnostic purposes, and only included screening mammograms in our analyses.

Limitations of our study largely reflect limitations in our data set. One limitation was that we could not include all mammograms conducted within Nova Scotia into our study cohort, as mammograms conducted outside the screening program were not captured. This indicates that the screening rates reported in this study likely underrepresent the true screening rates of the entire province. This was further confirmed by observing that proportion of cancer survivors screened within two years after diagnosis

screening rates were higher in the Capital District Health Authority than the screening rate of the entire cohort. Another limitation in our study was data availability. 62.8% of our cohort was censored at our study end date/end of available data, March 31st, 2008. As we included incident colorectal cancer cases until December 31st, 2005, some survivors analyzed in our cohort had less than two and a half years of follow-up on our study. As we did not have access to test results or family history, we could not examine possible overutilization of cancer screening in our cohort. We could not measure clinical or prognostic factors such as frailty, post-operative complications, or treatment side effects which could have influenced receipt of cancer screening due to poor prognosis. Another limitation within our study was power. While our study population included all diagnosed cases of colorectal cancer in Nova Scotia over a five year period, we were only able to obtain an 80% power to detect hazard ratios of 1.53 and 1.43 for our breast and cervical cancer screening Cox proportional hazards models, respectively. We cannot firmly conclude that factors which were not statistically significant truly have no effect on receipt of cancer screening in out cohort due to the limited power of our study.

3.6 Conclusion

In our population-based study of colorectal cancer survivors in Nova Scotia, we found that a significant proportion of cancer survivors within general population screening age recommendations did not receive breast and cervical cancer screening. This finding is concerning, as previous research has shown colorectal cancer survivors are at least as likely as the general population to develop new primary breast and cervical cancers, and often have been shown to be at greater risk than the general population.

Repeat breast and cervical cancer screening among colorectal cancer survivors appeared to be positively influenced by the reminder system implemented by the Nova Scotia Breast Screening Program. Receipt of breast and cervical cancer screening varied substantially between those within and outside age recommendations for population-based screening, which could pose as a source of bias in comparative studies if cancer survivors are more likely to be screened only outside of these age categories. Future research in this area should focus on those who meet age recommendations for population-based cancer screening.

3.7 Tables and Figures

Table 6 – Inclusion and exclusion criteria for cancer survivors

	Cancer Survivors
Inclusion Criteria	• Females diagnosed with stage I, II, or III colorectal cancer in Nova Scotia between 1Jan2001 and 31Dec2005 • Underwent resection surgery
Exclusion Criteria	• Evidence of recurrence or advanced disease within the first year of diagnosis using OPIS Recurrence data, MSI physician billings, or CIHI Discharge Abstract Database • Patients with a previous cancer diagnosis • Patients residing in the Cumberland DHA

Table 7 – Censorship criteria for our cancer survivor cohort

	Cancer Survivors
90 days prior to:	• Diagnosis of new primary cancer (from the Nova Scotia Cancer Registry) • Diagnosis of recurrence (from the Oncology Patient Information System – this is limited to those that are seen in one of two cancer centres in Nova Scotia, located in Halifax or Sydney) • Initiation of any chemotherapy or radiotherapy which occurred greater than one year following date of diagnosis (Chemotherapy from the physician billings database, OPIS for radiotherapy) • Enrollment in a palliative care program (only available in Halifax or Sydney) • Date of Death
On the date of:	• End of MSI eligibility • End of follow-up data (March 31st, 2008) • For cervical cancer screening only: Date of Hysterectomy with removal of cervix

Table 8 – Characteristics of Included Colorectal Cancer Survivors

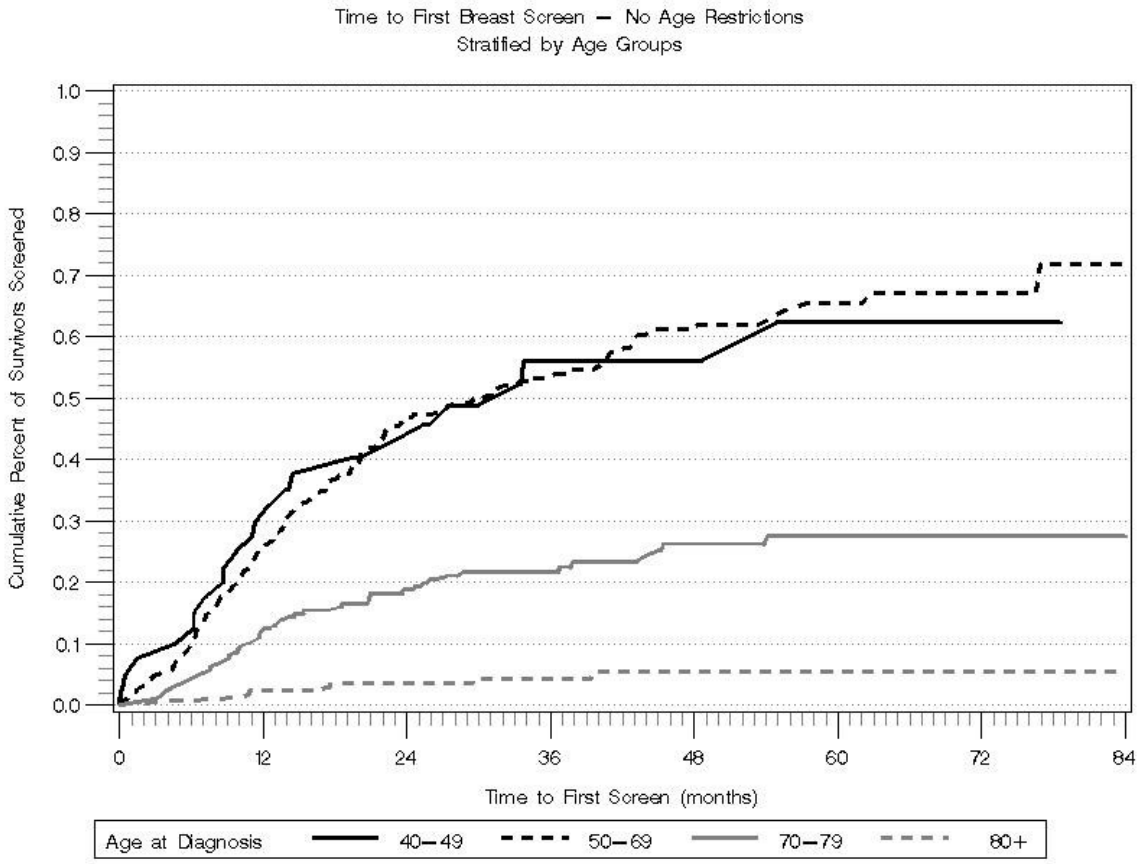
	No Age Restrictions n = 705	Age Restrictions	
		Breast Screening (40-69) n = 318	Cervical Screening (21-75) n = 443
Time on Study (days)			
Median	931	990	1013
Range	366 – 2270	366 – 2256	366 – 2270
Age at Diagnosis (Median)	72	60	64
< 50	6.5% (46)	12.6% (40)	10.4% (46)
50 - 69	39.4% (278)	87.4% (278)	62.7% (278)
70-79	29.7% (209)	0	26.9% (119)
80+	24.4% (172)	0	0
Cancer Diagnosis Site			
Colon	71.5% (504)	66.7% (212)	68.6% (304)
Rectal	28.5% (201)	33.3% (106)	31.4% (139)
Comorbidity			
0	60.4% (426)	71.0% (226)	68.9% (305)
1	22.4% (158)	18.6% (59)	18.5% (82)
≥ 2	17.2% (121)	10.4% (33)	12.6% (56)
Location			
Urban	67.8% (473)	74.0% (233)	70.4% (309)
Rural	32.2% (225)	26.0% (82)	29.6% (130)
Stage at Diagnosis			
I	22.1% (156)	24.2% (77)	24.8% (110)
II	44.0% (310)	39.0% (124)	38.8% (172)
III	33.9% (239)	36.8% (117)	36.3% (161)
Primary Care Physician Visits			
Median Annualized Rate	7	7	7
Oncology Specialist Visits			
Median Annualized Rate	1	1	1
Other Physician Visits			
Median Annualized Rate	1	1	1
Total Physician Visits			
Median Annualized Rate	11	10	10

Table 9 – Factors associated with screening receipt in age restricted groups		
	Breast Cancer Screening (Restricted to ages 40-69)	Cervical Cancer Screening (Restricted to ages 21-75)
Age at Diagnosis (five year increase in age)	0.98 (0.96 – 1.00)	**0.95 (0.94 – 0.96)**
Cancer Diagnosis Site		
Colon	ref	ref
Rectal	1.20 (0.88 – 1.63)	1.03 (0.76 – 1.41)
Stage at Diagnosis		
I	ref	ref
II	0.71 (0.49 – 1.03)	0.96 (0.68 – 1.36)
III	0.86 (0.60 – 1.25)	0.73 (0.50 – 1.06)
Comorbidity		
0	ref	ref
1	0.86 (0.57 – 1.27)	0.83 (0.57 – 1.21)
≥ 2	0.96 (0.60 – 1.56)	0.65 (0.40 – 1.07)
Location		
Urban	ref	ref
Rural	p = 0.10[Ω]	0.75 (0.54 – 1.04)
Pre-diagnosis Screening[*]		
No	ref	ref
Yes	**4.71 (3.42 – 6.51)**	**6.83 (4.58 – 10.16)**
Annualized Primary Care Physician Visit Quartiles (Lowest = 1, Highest = 4)		
1	ref	ref
2	1.04 (0.70 – 1.55)	1.14 (0.78 – 1.67)
3	1.46 (0.96 – 2.28)	0.86 (0.56 – 1.33)
4	1.10 (0.72 – 1.68)	1.08 (0.72 – 1.64)
Annualized Oncology Specialist Visits		
0	ref	ref
1	**1.57 (1.05 – 2.36)**	1.46 (1.00– 2.12)
≥ 2	1.37 (0.92 – 2.03)	1.25 (0.86 – 1.82)

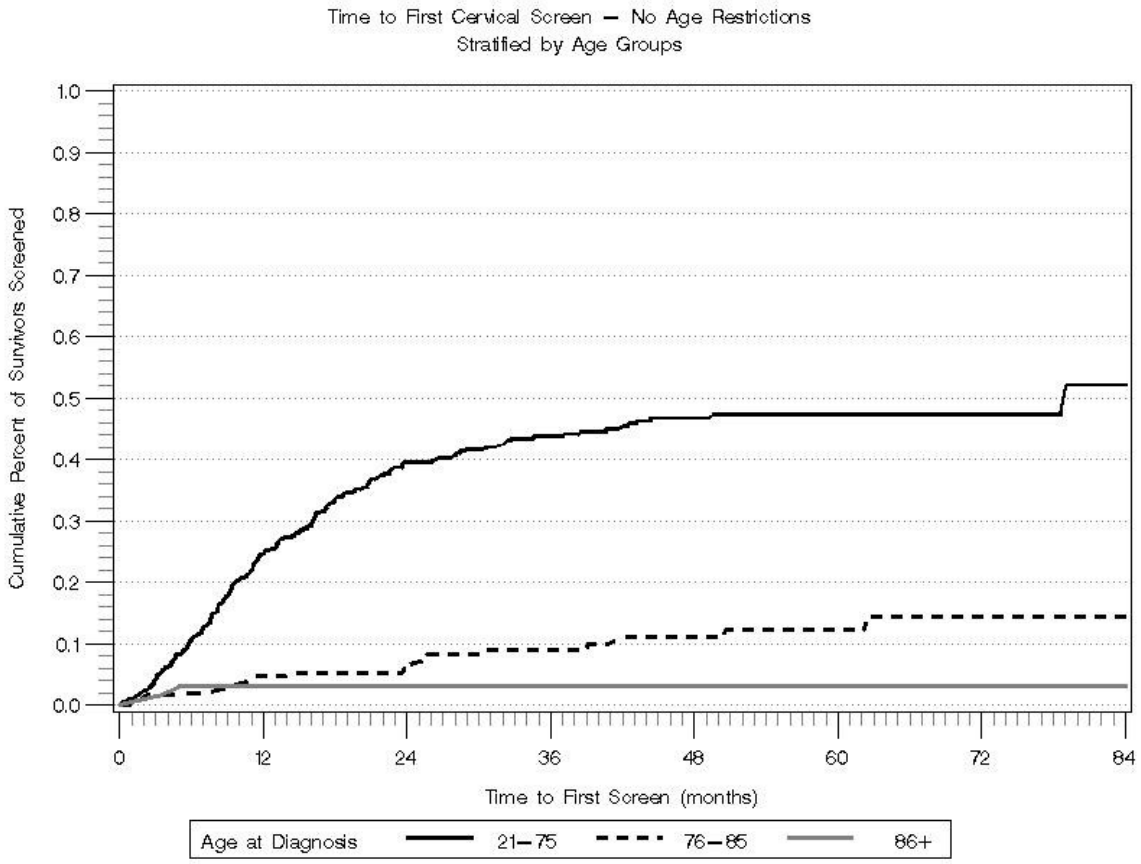
[*] Breast cancer pre-diagnosis screening: within the 3 years prior to diagnosis. Cervical cancer pre-diagnosis screening: within the past 4 years

[Ω] Proportional assumption was not met, therefore compared using Kaplan Meier curve Log Rank test

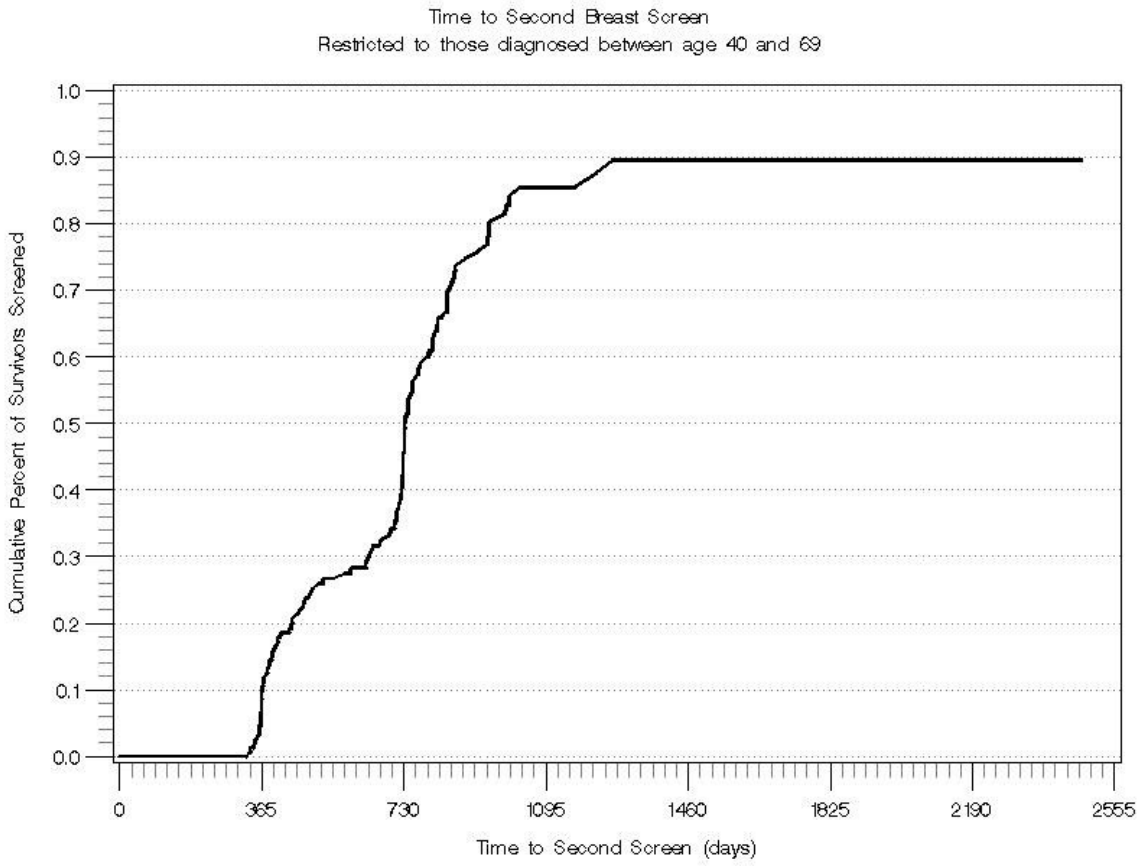
Bolded hazard ratios are statistically significant



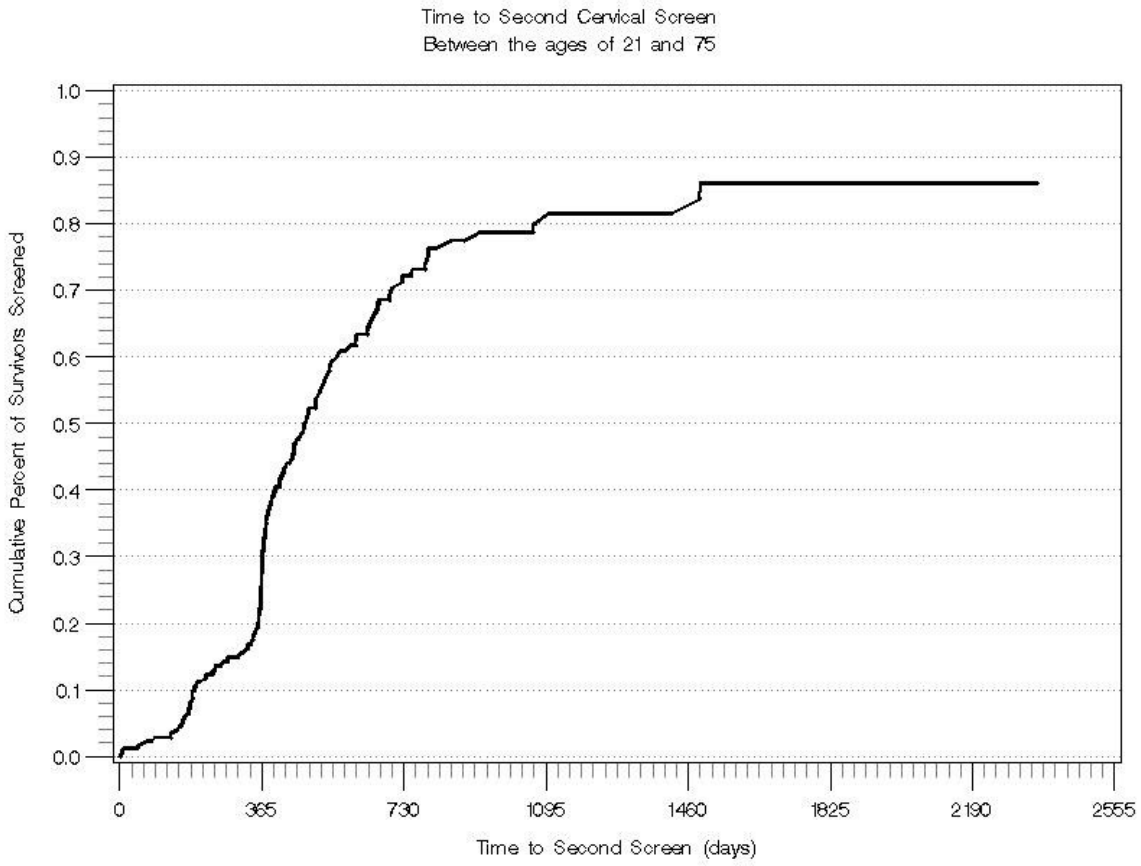
<u>Figure 6</u> – Time to First Breast Cancer Screen in entire colorectal cancer survivor cohort, stratified by age at diagnosis



<u>Figure 7</u> – Time to First Cervical Cancer Screen in entire colorectal cancer survivor cohort, stratified by age at diagnosis



<u>Figure 8</u> – Time to Second Breast Cancer Screen within the Nova Scotia screening guideline recommended age group of 40-69



<u>Figure 9</u> – Time to Second Cervical Cancer Screen within the Nova Scotia screening guideline recommended age group of 21-75

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Chapter 4 – Discussion

In this chapter, I will begin by recapping key findings from this thesis project. I will then discuss some limitations of this study and recommendations for future researchers. Finally, I will conclude with implications of these findings for healthcare providers, policy makers, and other administrative decision-makers, such as cancer program managers.

4.1 Key Findings

The objectives of this thesis project were to synthesize evidence comparing the receipt of screening for new primary cancers between cancer survivors and non-cancer controls, and to describe patterns of breast and cervical cancer screening among a cohort of Nova Scotian colorectal cancer survivors. To meet these objectives, we conducted two studies: a systematic review and meta-analysis, and a population-based study of Nova Scotian colorectal cancer survivors.

While it has been previously hypothesized that a cancer survivor's previous cancer diagnosis may shift healthcare workers' attention away from administering preventive health services[1], we found that cancer survivors received were more likely to receive breast, cervical, colorectal, and prostate cancer screening for new primary cancers than the general population in our systematic review (increased by 19%, 22%, 19%, and 22%, respectively). This result could indicate that healthcare providers preferentially encourage cancer survivors to undergo screening for new primary cancers, realizing that many cancer survivors are at an increased risk of developing second primary cancers, or

cancer survivors are more likely to be screened than the general population simply because of their increased contact with the health care system[2-4]. However, we noted in our colorectal cancer survivor cohort study increasing numbers of primary care physician visits was not associated with increased receipt of breast or cervical cancer screening. Further exploration of the reasons cancer survivors choose to undergo screening for new primary cancers is warranted.

We observed significant heterogeneity in our breast, cervical, and colorectal cancer screening meta-analyses, however very little of this heterogeneity could be explained in our subgroup and sensitivity analyses. A key contextual factor, how local screening programs recruited participants, was not reported in the primary literature, and is a likely source of heterogeneity that we could not measure in our review. Other potential sources of heterogeneity are likely hidden within the studies, and could not be analyzed. We encourage future researchers to describe how local screening programs operate in order to provide more meaningful feedback to health policy makers.

While we found that cancer survivors were more likely to receive screening for new primary cancers than the general population, we also observed that a significant proportion of cancer survivors (along with the general population) did not receive screening. This remains a concern, as many cancer survivor populations are at an increased risk of developing many secondary cancers[5-10]. In addition, we observed a lack of Canadian literature, with only two Canadian studies sharing overlapping study populations identified in our systematic review[11, 12]. The study by Grunfeld *et al.*[11], the larger of the two studies, examined several subpopulations of cancer survivors, including breast, colorectal, endometrial, and Hodgkin's lymphoma survivors. While the pooled

receipt of cancer screening across all these subpopulations was similar to the findings of our meta-analysis, this study found that colorectal cancer survivors were less likely to receive breast cancer screening than the general population, and no more likely to receive cervical cancer screening, results which differ from our predominately U.S.-based meta-analysis.

In our analysis of Nova Scotian colorectal cancer survivors, we found that a significant proportion of survivors within cancer screening guideline age recommendations never received breast and cervical cancer screening after their colorectal cancer diagnosis (30.1% never received a breast cancer screen, 47.9% never received a cervical cancer screen). 46.4% of our breast cancer screening cohort between the ages of 50 and 69 received a screening mammogram within two years of their colorectal cancer diagnosis, which is comparable to the Nova Scotia general population aged 50-69 between 2006-2007 (the latest two full years which were also examined during our study), where 48.03% was screened[13]. It is plausible that after age adjustment, our colorectal cancer survivor cohort could be more likely to receive breast cancer screening, as our cohort between ages 50-69 is skewed towards slightly older ages.

Among our age restricted cohorts, the most significant predictive factor of receiving both breast and cervical cancer screening during the survivorship period was the receipt of pre-colorectal cancer diagnosis screening (Breast cancer screening, HR: 4.71, 95% C.I. 3.42 – 6.51; Cervical cancer screening, HR: 6.83, 95% C.I. 4.58 – 10.16). We observed a similar effect in our time to second screen analysis, where a very high proportion of those who were screened during the survivorship period received a second screen during the survivorship period (Breast cancer screening, 89.6%; Cervical cancer

screening, 82.2%). We believe these findings are largely a result of the Nova Scotia Breast Screening Program, which sends reminder cards to those enrolled in the screening program. Cervical cancer screening is also likely influenced by these reminder cards, as one of the top self-reported reasons for undergoing a Pap smear was the reminder card sent by the Nova Scotia Breast Screening Program.

Not surprisingly, receipt of screening varied substantially between survivors within and outside screening guideline-recommended age groups. Those outside of guideline recommendations were less likely to receive breast and cervical cancer screening. Within our age restricted cohort, younger colorectal cancer survivors were more likely to receive cervical cancer screening (five year increase in age, HR: 0.76, 9%% C.I. 0.71 – 0.86), however this effect was not observed for breast cancer screening within our age restricted cohort

4.2 Study Limitations

Our systematic review limitations largely reflect the limitations of the included literature. As only 20 studies were identified, subgroup and sensitivity analyses were likely underpowered to detect potential differences. In addition, the majority of included studies were conducted in the United States. Only two Canadian studies using overlapping study populations were identified, demonstrating the need for further comparative studies examining Canadian cancer survivors.

Important contextual factors were not available for analysis in our systematic review, such as how screening programs local to each study operate. This could be a

potential source of heterogeneity which we could not have measured in our study. There were inconsistencies observed in studies' use of screening timeframes, which often did not reflect national recommendations for population-based cancer screening. One common example was when studies did not use upper or lower age limits to compare receipt of cancer screening between cancer survivors and non-cancer controls. While we did not find this to be a significant source of bias in our subgroup analysis, none of the studies that did not use age limits reported separate results for those within and outside guideline recommended age limits.

One way we could have overcome several of the limitations in the identified literature was through use of an individual patient data meta-analysis. However, this was not feasible given the timeframe of this thesis project.

The two main limitations from our population-based study of Nova Scotian colorectal cancer survivors stem from data access and availability. Due to data access limitations, we were unable to compare screening receipt between our cohort of colorectal cancer survivors and a matched cohort of non-cancer controls. We found non-age standardized general population mammography screening rates were similar to that of our colorectal cancer survivor cohort. This comparison could have been improved through comparison with an age-standardized screening rate, however this was not available.

The majority of our cohort was censored due to a lack of available data, which was only available to March 31st, 2008. As we included incident colorectal cancer cases until December 31st, 2005, some survivors analyzed in our cohort had less than two and a half years of follow-up on our study. We minimized the impact of the variable lengths of

follow-up in our study by only examining screening receipt prior to our censorship criteria, and using time to event analysis techniques.

Surprisingly, we did not observe increased breast and cervical cancer screening among those with higher quartiles of primary care physician visits, which is in contrast to previously published literature[3, 4]. Previous research has shown in a population of breast cancer survivors that physician utilization changes over the course of the survivorship period, with an increasing number of primary care physician and decreasing number of oncology specialist visits over time[14]. We measured physician utilization in an annualized rate measure that would not have captured these changes. This could have biased our results towards the null if those with shorter follow-up lengths were less likely to be screened, and had artificially inflated annualized physician visit rates

As we did not have access to test results or family history, we could not examine possible overutilization of cancer screening in our cohort. We also could not measure clinical or prognostic factors such as frailty, post-operative complications, or treatment side effects which could have influenced receipt of cancer screening due to poor prognosis.

Study power was also a limitation. While our study population included all diagnosed colorectal cancer cases in Nova Scotia over a five year period, we were only able to obtain an 80% power to detect hazard ratios of 1.53 and 1.43 for our breast and cervical cancer screening Cox proportional hazards models, respectively

4.3 Implications for decision makers

The decision of whether it is beneficial to screen cancer survivors for new primary cancers is made complex by the competing demand of a cancer survivors' initial cancer diagnosis. The key component of this competing demand is life expectancy: the overall 5-year life expectancy of those diagnosed with colorectal cancer is 63%[15], with poorer survival rates for those diagnosed with later stage cancers. Some individuals who are diagnosed with colorectal cancer would not receive any benefit from screening for new primary cancers due to their short anticipated life expectancy.

In our colorectal cancer survivor analysis, we attempted to select a cohort of 'well' cancer survivors through the use of exclusion and censoring criteria available in administrative databases. These included important prognostic factors, such as age, stage at diagnosis, and receipt of curative-intent resection surgery. We believe this approach selected a cancer survivor cohort which better represents the cancer survivors in which healthcare providers should actively target to increase uptake of screening for new primary cancers. Despite this, we still observed a large proportion of colorectal cancer survivors did not ever receive breast and cervical cancer screening after their colorectal cancer diagnosis.

In the absence of evidence which directly examines screening efficacy among cancer survivors, several studies have demonstrated that many cancer survivor populations are at an increased risk of developing second primary cancers[5-10]. Long-term cancer survivors, or short-term cancer survivors who are likely to survive long-term based on the clinical characteristics of their disease, should be encouraged to meet population-based screening recommendations. Their risk of developing a second cancer is at least as

great as the general population, and often will be higher. Future research should directly measure the efficacy and cost-effectiveness of cancer screening among cancer survivors, and also seek to determine whether the optimal screening frequency for cancer survivors should be different than the general population.

From our systematic review and meta-analysis, we found that while cancer survivors were more likely to receive screening for new primary cancers than the general population, a significant proportion of survivors did not receive screening. Cancer survivors should be encouraged to participate in population-based screening programs, as in some cancer survivor populations their risk of developing a second primary cancer is greater than that of the general population[5-10].

An important finding from our population-based study of colorectal cancer survivors was that pre-colorectal cancer diagnosis screening was strongly predictive of receiving post-diagnosis cancer screening. We also saw that high proportions of those who were screened during the survivorship period received a second cancer screen. This is likely due to the Nova Scotia Breast Screening Program, which sends out reminder cards to enrolled participants. This also indicates that those who aren't involved in breast and cervical cancer screening programs are a population at risk of not receiving cancer screening post-diagnosis, and are a group that should be targeted to encourage participation in screening programs.

Surprisingly, we did not observe increased breast and cervical cancer screening among those with higher quartiles of primary care physician visits. The Nova Scotia Breast Screening Program reports that the most frequently self-reported reason for

participating in the screening program is recommendation by a family physician, and this likely also holds true for the cancer survivor population as well. Targeting family physicians has been shown to increase uptake of breast cancer screening in the general population, and would likely also increase screening receipt among cancer survivors as well.

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Appendix A – PubMed Search Strategy

#55	Search #40 AND #45 AND #54	1048
#54	Search #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53	2263065
#53	Search "Neoplasms by Histologic Type"[Mesh]	1153087
#52	Search "Neoplasms by Site"[Mesh]	1420041
#51	Search "Neoplasms, Second Primary"[Mesh]	8006
#50	Search "Neoplasms, Multiple Primary"[Mesh]	24727
#49	Search malign* [tiab]	322530
#48	Search tumour [tiab]	125997
#47	Search tumor [tiab]	573419
#46	Search cancer [tiab]	728755
#45	Search #41 OR #42 OR #43 OR #44	611106
#44	Search "Preventive Health Services"[Mesh]	339610
#43	Search "Early Detection of Cancer"[Mesh]	759
#42	Search "Mass Screening"[Mesh]	79128
#41	Search screen* [tiab]	327138
#40	Search #33 OR #34 OR #35 OR #38 OR #39	51822
#39	Search "Survivors"[Mesh]	9554
#38	Search "previous malignancy"	103
#35	Search "previous cancer"	180
#34	Search "previous diagnosis"	1083
#33	Search survivor* [tiab]	46731

Appendix B – Systematic Review Data Abstraction Form

DATA ABSTRACTION FORM

INCLUDED: ☐ **EXCLUDED:** ☐

Study ID:

Study Reference:

STUDY ELIGIBILITY

1) Entire study population is eligible for screening procedure(s) used in study	Yes: ☐	No: ☐	Unsure: ☐
2) Exposed group are cancer survivors:	Yes: ☐	No: ☐	Unsure: ☐
3) Cancer survivors screening rates are compared to (either):	Yes: ☐	No: ☐	Unsure: ☐
a) Non-cancer unexposed	Yes: ☐	No: ☐	Unsure: ☐
b) Population rate (adjusted)			
4) Screening rates (any or all of):	Yes: ☐	No: ☐	Unsure: ☐
a) Breast	Yes: ☐	No: ☐	Unsure: ☐
b) Colorectal	Yes: ☐	No: ☐	Unsure: ☐
c) Cervical	Yes: ☐	No: ☐	Unsure: ☐
d) Prostate			

METHODS

Cancer Survivors

Inclusion/Exclusion Criteria

Characteristics (Age, Sex, Stage at Diagnosis, etc):

Location:

Data Source:

Administrative or Self-Reported (Exposure (Cancer Survivor) and Outcome (Screening):

Survivor Cancer Diagnosis Type (number of individuals per cancer type, stage):

Study Design:

Control Group:

Source (Matched non-cancer cohort, unmatched non-cancer cohort, adjusted population rate):

Inclusion/Exclusion Criteria:

Characteristics (Age, Sex, etc)

SCREENING TYPES MEASURED

Cancer Screened For (1):

Screening tool used:

Relevant population screening guideline (e.g. age criteria):

Is the screening tool above applicable, valid, and recommended to entire study population?
□ Yes □ No □ Unsure (Why?):

Cancer Screened For (2):

Screening tool used:

Relevant population screening guideline (e.g. age criteria):

Is the screening tool above applicable, valid, and recommended to entire study population?
□ Yes □ No □ Unsure (Why?):

Cancer Screened For (3):

Screening tool used:

Relevant population screening guideline (e.g. age criteria):

Is the screening tool above applicable, valid, and recommended to entire study population?
□ Yes □ No □ Unsure (Why?):

Cancer Screened For (4):

Screening tool used:

Relevant population screening guideline (e.g. age criteria):

Is the screening tool above applicable, valid, and recommended to entire study population?
□ Yes □ No □ Unsure (Why?):

	OR/RR/Proportion, plus CI/p-value	Variables adjusted for in analysis
Screening Test (1):		
Screening Test (2):		
Screening Test (3):		
Screening Test (4):		
Screening Test (5):		

Notes:

STUDY RISK OF BIAS (Yes/No, if No is RoB Low/Medium/High)

Study Reference	
Was there bias in how the source or study population was selected?	
Cancer survivor definition appropriate, and described?	
Appropriate individuals (age/sex) screened in study? Guidelines listed?	
Screening rate measured appropriately and adequately?	
Confounders defined, measured, and accounted for?	
Free of other bias?	

Appendix C – Explanation of Risk of Bias categorization and coding

STUDY RISK OF BIAS (Yes/No, if No is RoB Low/Medium/High)	
Study Reference	
Was there bias in how the source or study population was selected?	High – Likely response bias, possibly due to low survey response rate (<60%) or clear bias in source/study population selection Moderate – Possible response bias, response rate >60% but <85% or response rate could have been influenced by cancer survivor status Low – Administrative database study, or survey with response rate >85%
Cancer survivor definition appropriate, and described?	High – Self-reported cancer diagnosis without further time since diagnosis/tumour characteristics reported High – Short-term cancer survivors (<2 years) Moderate – Self-reported with time since diagnosis indicating mostly longer-term cancer survivors Low – Exclusively self-reported longer-term cancer survivors, or administrative data selection of cancer survivors
Screening rate/receipt measured appropriately and adequately?	High – Screening receipt coded differently for cancer survivor and control groups Moderate – Self-reported cancer screening receipt Low – Administratively collected cancer screening receipt
Comparable/Matched cohorts, or confounders defined, measured, and accounted for?	High – crude rates reported, no confounders measured or used in analysis, unmatched cohorts with presence of potentially confounding variables Moderate – Somewhat comparable cohorts, not matched. (e.g. age-standardized analysis, sibling cohort) Low – Matched cohort used or multivariate adjusted used if cohorts were different
Free of other bias?	

Appendix D – Expanded Study Risk of Bias Table

First Author	Year	Selection Bias		Cancer Survivor Selection		Screening rate measurement		Comparable cancer survivors and controls, adjustment for confounding	
Aparicio-Ting	2003	M	82% rate in cancer-specific survey	H	Self-reported, no time since diagnosis	M	Self reported screening	H	Unadjusted
Bellizzi	2005	M	72% response rate in general population survey	M	Self-reported, majority have survived ≥5 years	M	Self reported screening	L	Multivariate adjusted analysis
Bishop	2010	H	48% response rate in cancer-specific survey	M	Used administrative data, majority have survived ≥5 years	M	Self reported screening	H	Unadjusted, matching process not described, cohorts are not similar
Breslau	2010	H	34% response rate in general population survey	M	Self-reported, majority have survived ≥5 years	M	Self reported screening	L	Multivariate adjusted analysis
Duffy	2006	M	69% response rate in general population survey	M	Self-reported, majority have survived ≥5 years	M	Self-reported, adequate screening different for survivors and controls	L	Matched cohort
Earle	2003	L	Administrative cohort selection	L	Used administrative data, all would be considered survivors	L	Used administrative data	L	Matched cohort
Earle	2004	L	Administrative cohort selection	L	Used administrative data, all would be considered survivors	L	Used administrative data	L	Matched cohort
Grunfeld	Unpub	L	Administrative cohort selection	L	Used administrative data, all would be considered survivors	L	Used administrative data	L	Matched cohort
Hudson	2009	H	80% participation rate, recruitment from GP clinic waiting room	H	Self-reported, no time since diagnosis	M	Self reported/chart review could miss screening outside GP office	L	Multivariate adjusted analysis
Khan	2010	L	Administrative cohort selection	L	Used administrative data, all survived ≥ 5 years	L	Used administrative data	L	Matched cohort
Kwon	2009	L	Administrative cohort selection	M	Included both short and long-term survivors	L	Used administrative data	M	Yellow - age-standardized comparison only
Mayer	2007	H	33% response rate in general population survey	M	Self-reported, mean 11 years since diagnosis	M	Self reported screening	L	Multivariate adjusted analysis
McBean	2008	L	Administrative cohort selection	L	Used administrative data, all survived ≥ 5 years	L	Used administrative data	L	Multivariate adjusted analysis
McBean	2009	L	Administrative cohort selection	M	Short and moderate-term follow-up (only up to 4 years after diagnosis)	L	Used administrative data	L	Multivariate adjusted analysis
Ng	2008	H	52% response rate in cancer-specific survey	L	Used administrative data, all survived ≥ 5 years	M	Self reported screening	M	Unadjusted, but sibling cohort
Oeffinger	2009	H	88% response rate to survey, but same source population as Yeazel 2003 (63% response rate)	L	Used administrative data, all survived ≥ 5 years	M	Self reported screening	M	Unadjusted, but sibling cohort
Snyder *(a)*	2009	L	Administrative cohort selection	M	Short and moderate-term follow-up of a single cohort of cancer survivors	L	Used administrative data	L	Matched cohort
Snyder *(b)*	2009	L	Administrative cohort selection	H	Cancer survivors are all short-term survivors (1st year of follow-up)	L	Used administrative data	L	Matched cohort
Trask	2005	M	72% response rate in general population survey	M	Self-reported, no time since diagnosis (same sample as Bellizzi 2005)	M	Self reported screening	L	Multivariate adjusted analysis
Yeazel	2004	H	63% response rate in cancer-specific survey	L	Used administrative data, all survived ≥ 5 years	M	Self reported screening	M	Secondary cancers were not excluded from both groups

Appendix E – Classification of Urban/Rural residency in the ACCESS database

The designation of a place of residence as rural or urban is largely based on a statistical area classification (SACtype) system developed by Statistics Canada[1] which classifies census subdivisions (CSDs) into the following categories:

- **Census Metropolitan Area (CMA):** A CMA has an urban population of at least 100,000 or more and includes all neighboring municipalities where 50% or more of the labor force commutes to the urban core.

- **Census Agglomeration (CA):** A CA has an urban core population of 10,000-99,999 and includes all neighboring municipalities where 50% or more of the labor force commutes to the urban core.

- **CMA/CA Influenced Zone (MIZ):** Census subdivisions outside of a CMA or CA are considered rural but are further classified according how influenced they are by all CMAs or CAs, as measured by commuting flows.

    - *Strong MIZ*: Between 30-49% of the employed workforce commutes to a CMA or CA.
    - *Moderate MIZ:* Between 5-30% of the employed workforce commutes to a CMA or CA.
    - *Weak MIZ:* Between 0-5% of the employed workforce commutes to a CMA or CA.
    - No MIZ**:** None of the employed workforce commutes to a CMA or CA, or, there are less than 40 people in the employed workforce.

Team *ACCESS* uses the following rural/urban classification system:

Urban	CMA Tracted CA Untracted CA Strong MIZ
Rural	Moderate MIZ Weak MIZ No MIZ Territories

References

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