International Journal of Cardiology Hypertension 9 (2021) 100085

Contents lists available at ScienceDirect

International Journal of Cardiology Hypertension

journal homepage: www.sciencedirect.com/journal/international-journal-of-cardiology-hypertension

Research Paper

Arterial stiffness is associated with cardiovascular and cancer mortality in cancer patients: Insight from NHANESIII

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ARTICLE INFO

Keywords:
Arterial stiffness
Cardio-oncology
CVD

ABSTRACT

Background: Cancer survivors are at greater risk for cardiovascular disease (CVD) than second malignancy, resulting in a decreased quality of life and increased cost of care. Additional knowledge of CVD prevention by identifying possible risk factors has clinical relevance. Our main objective was to determine the relevance of a clinical index of arterial stiffness, pulse pressure, in predicting CVD mortality in cancer patients, with a second objective to examine its relationship with cancer mortality.

Methods: We retrospectively analyzed 781 cancer patients from Third National Health and Nutrition Examination Survey and Linked Mortality File, including demographic, anthropometric, blood pressure, and cause of death. Kaplan-Meier survival curve and Cox hazard regression analyses were performed to assess the relationship between pulse pressure and cardiovascular, cancer, and all-cause mortality.

Results: During a mean follow-up time of 8.1 years, 603 deaths, 257 cancer and 151 CVD, occurred. In unadjusted models, the risk of CVD, cancer, and all-cause mortality were 3.8-fold, 5.3-fold, and 1.6-fold higher, respectively, for pulse pressure ≥70 mmHg compared to <50 mmHg. Adjusted analyses revealed a higher CVD mortality in cancer patients <65 years with a pulse pressure 60–70 mmHg (adjusted hazard ratio, 5.26; 95%CI, 1.12–24.78) when compared to pulse pressure of <50 mmHg. Pulse pressure was not associated with risk of all-cause, CVD, or cancer in those ≥65 years.

Conclusion: Pulse pressure, an index of arterial stiffness, is predictive of CVD mortality in cancer patients. Our findings support non-invasive office-setting measurements of arterial stiffness to identify high risk patients.

1. Introduction

Over the last half century improvements in cancer treatments and technological advancements have led to an overall decline in cancer-related mortality, with more patients surviving cancer and living long enough to develop a secondary chronic disease. Recent studies, across a spectrum of cancer types, have demonstrated that many patients who survive their cancer diagnosis have a higher risk of death from cardiovascular disease (CVD) compared to the general population, with reports of a greater risk of CVD death than secondary malignancy [1,2]. This increased chronic disease burden not only diminishes quality of life but is also a significant driver of the escalated cost of care in cancer survivorship [3]. Thus, advancing our understanding of the predictors of CVD in the nearly 17 million cancer survivors, representing approximately 5% of the population in the United States, is fundamentally important in improving cardio-oncology care for this population [4].

In an effort to mitigate risk of CVD in current cancer patients and survivors, current cardio-oncology guidelines are directed towards monitoring overt structural changes in left ventricular function for the detection of cardiovascular toxicity [5,6]. However, there is increasing

Abbreviations: BMI, Body mass index; CVD, Cardiovascular disease; MAP, Mean arterial pressure; NDI, National Death Index; NHANES III, Third National Health and Nutrition Examination Survey; PP, Pulse Pressure.

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https://doi.org/10.1016/j.ijchy.2021.100085
Received 29 January 2021; Received in revised form 14 April 2021; Accepted 23 April 2021
Available online 28 April 2021

evidence by our group and others that adverse vascular changes, specifically increases in arterial stiffness, manifest into cancer survivorship and can occur independent of cardiac dysfunction [7–11]. Because arterial stiffness is an established surrogate endpoint for CVD and is a strong predictor of future major adverse cardiovascular events and all-cause mortality in non-cancer patients and otherwise healthy populations [12–14], it has the potential to provide predictive utility in those previously diagnosed with cancer.

Importantly, several recent reviews have also highlighted the shared biological mechanisms mediating cancer and cardiovascular disease risk [15–17]. In this context, arterial stiffness, which is a well-known predictor of mortality in the general population [12–14], may also serve as a unique risk-stratification tool for cancer outcomes. While, both traditional and non-traditional cardiovascular disease risk factors have been associated with an increased risk for incident cancer [16–19], there remains a paucity as it relates to arterial stiffness. Therefore, given the complex mortality risks in those following cancer diagnosis, evaluation of additional potential predictors, like arterial stiffness, for both disease entities in this population is essential. Therefore, the first goal of this investigation was to evaluate whether pulse pressure, a clinical index of arterial stiffness [20,21], is a significant predictor of CVD mortality. Since cancer and CVD share several common biological mechanisms [15] and underlying CVD increases cancer risk [17], the second goal was to examine the influence of pulse pressure as a predictor of cancer mortality. Identification of these relationships could assist in stratifying mortality risk in cancer populations during routine visits in the clinic without additional imaging procedures.

2. Methods

2.1. Study design and population

Data were obtained from the Third National Health and Nutrition Examination Survey (NHANES III) which spanned from 1988 to 1994 and was collected by the US National Center for Health Statistics. NHANES III was conducted using a stratified, multistage, and cluster sampling design to obtain a randomized representative sample of the noninstitutionalized civilian U.S. population. The survey included in-depth, in-person interviews, physical examination, physiological measurements, laboratory assessments, and health history questionnaire. The methodology of the NHANES III, as well as the data, are publicly available and can be accessed online (https://www.cdc.gov/nchs/nhanes/index.htm). The original NHANES III sample size included ~33,994 individuals. The inclusion criteria for our study consisted of participants ≥17 years old with a history of a physician diagnosed cancer. Cancer types included bladder, breast, cervical, colorectal, prostate, uterine, bone, brain/neurological, esophageal, gallbladder, and Hodgkin's disease for a final sample size of 781 subjects. We did not exclude any participants based on location or type of cancer. NHANES III was reviewed and approved by the NCHS Institutional Review Board. Our initial analysis examined pulse pressure as a predictor of cardiovascular, cancer, and all-cause mortality in all cancer patients. We performed a secondary analysis after dividing the cohort into two groups based on age (<65 years and ≥65 years) since the average age at cancer diagnosis is approximately 65–66 years old [22] and there are reported differences in CVD risk among younger and older cancer populations. After performing the initial analysis this rationale was confirmed as age was a significant predictor of cardiovascular, cancer, and all-cause mortality.

2.2. Arterial pulse pressure

Serial brachial blood pressure measurements were taken in triplicate in the seated position after 5 min of rest with the arm rested on a table and positioned at heart level. To calculate mean pulse pressure, we calculated the algebraic mean systolic and diastolic blood pressure for each participant and then calculated the difference between the systolic and diastolic pressures [23].

2.3. Outcome variables

The primary outcome variables of the study were cardiovascular, cancer, and all-cause mortality, obtained from the NHANES III Linked Mortality File, collected by the National Center for Health Statistics through December 31st, 2011. All mortality outcomes were based on the NHANES III Linked Mortality file (ICD-10; 13 underlying causes of death) and were linked with the National Death Index (NDI). Pertinent to this study, cancer (ICD-10 codes: C00–C97) and cardiovascular (ICD codes: I00–I78) related deaths were coded by NDI. Follow-up for each person was calculated as the difference between the time from the NHANES III examination date and the last known date alive or censored from the NHANES III mortality file.

2.4. Covariate assessment

Covariates included in the multivariate models were identified based on their clinical relevance and current use in CVD risk stratification [21,23,24]. These included age (years), sex (male or female), race (specified as black or nonblack), total cholesterol (mg/dL), HDL cholesterol (mg/dL), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), hypertensive medications, history of diabetes mellitus, and smoking status (each as binary variables). Information for age, sex, race, use of hypertension medication, diabetes status, and smoking status were self-reported using standardized questionnaires during interview and were coded as dichotomous "yes/no" variables in the NHANES database. Race/ethnicity were classified dichotomously as non-Hispanic white/Mexican American/Other and non-Hispanic Black [21]. Serum total cholesterol and high density-lipoprotein (HDL) cholesterol was collected and analyzed as previously described [25].

2.5. Statistical analysis

Continuous data are presented as mean ± SD. Categorical data are presented as counts and percentages. Kaplan–Meier plots were used to show the difference in time to event by pulse pressure quartile and statistically compared with the log-rank test. Cox proportional hazard regression analysis was used to compare the risk of cardiovascular, cancer, and all-cause mortality with pulse pressure as a continuous variable and across pulse pressure quartiles. For the analyses in younger and older patient cohorts, pulse pressure was binned into four categories: PP_1<50; 50 ≤ PP_2 >60; 60 ≤ PP_3 >70; 70 ≤ PP_4, similar to previous investigations [26]. In the younger and older cohorts, the assumption of linearity was violated and therefore required categorization. All primary analyses were also performed without pulse pressure, using only the above defined CVD risk factors. The predicted performance of the models with and without pulse pressure were evaluated by concordance index (C index) and the likelihood ratio χ^2 statistic [27]. A C index of 0.5 indicates a random predictor, while 1.0 indicates a perfect predictor. Statistical analyses were conducted using survival package in publicly available R software (version 3.5) [28]. All significance tests were two-sided using $p < 0.05$ as the level of statistical significance.

3. Results

Baseline demographics and subject characteristics are outlined in Table 1. A total of 781 adults (307 men, 474 women) with a history of a cancer diagnosis were included in the analysis, with an average follow-up of 8.1 years. During the follow-up period, there were 603 deaths (77% of the participants) including 257 cancer related deaths (43%) and 151 cardiovascular related deaths (25%). The <65-year subcohort included a total of 301 subjects (80 men, 221 women) with an average

Table 1
Baseline cardiovascular risk factors by pulse pressure category in participants with cancer, NHANES III 1998–1994.

	PP1	PP2	PP3	PP4
Entire Cancer Cohort, n =781				
Systolic blood pressure, mmHg	116.09 ± 12.27	129.38 ± 10.06	138.96 ± 12.31	159.10 ± 19.96
Diastolic blood pressure, mmHg	76.53 ± 9.89	75.47 ± 9.76	74.62 ± 11.96	73.17 ± 14.84
Age, y	52.91 ± 17.10	65.07 ± 15.85	71.35 ± 12.44	75.85 ± 9.66
Total cholesterol, mg/dL	216.56 ± 40.01	223.21 ± 41.57	212.20 ± 45.65	218.67 ± 41.20
HDL cholesterol, mg/dL	52.90 ± 14.81	52.35 ± 41.57	50.25 ± 14.08	50.71 ± 14.19
Race, % black	25%	15%	12%	8%
Sex, % women	67%	61%	54%	58%
Diabetes, %	6%	12%	14%	14%
HTN meds, %	82%	83%	88%	88%
Cigarette smokers, %	40%	25%	24%	12%
Young Cohort (<65 years), n=301				
Systolic blood pressure, mmHg	115.11 ± 11.73	128.85 ± 10.16	141.17 ± 15.15	158.53 ± 23.44
Diastolic blood pressure, mmHg	76.78 ± 9.15	75.16 ± 9.40	77.19 ± 14.00	77.16 ± 18.15
Age, y	44.69 ± 12.12	50.50 ± 13.27	54.95 ± 9.67	55.32 ± 12.81
Total cholesterol, mg/dL	211.75 ± 37.37	219.79 ± 39.86	207.33 ± 36.36	233.74 ± 45.02
HDL cholesterol, mg/dL	53.42 ± 14.31	50.93 ± 11.25	49.85 ± 13.60	56.05 ± 12.64
Race, % black	27%	4%	26%	21%
Sex, % women	76%	70%	64%	79%
Diabetes, %	6%	10%	15%	16%
HTN meds, %	74%	78%	87%	84%
Cigarette smokers, %	49%	44%	51%	32%
Old Cohort (≥ 65 years), n =480				
Systolic blood pressure, mmHg	144.67 ± 54.67	129.76 ± 10.03	138.19 ± 11.14	159.16 ± 19.67
Diastolic blood pressure, mmHg	75.89 ± 11.61	75.70 ± 10.05	73.73 ± 11.10	72.79 ± 14.49
Age, y	73.81 ± 7.25	75.48 ± 6.68	77.01 ± 7.13	77.79 ± 6.60
Total cholesterol, mg/dL	228.81 ± 44.01	225.53 ± 42.81	213.88 ± 48.47	217.25 ± 40.66
HDL cholesterol, mg/dL	52.90 ± 14.81	52.35 ± 12.52	50.23 ± 14.08	50.71 ± 14.19
Race, % black	21%	12%	5%	7%
Sex, % women	57%	55%	50%	56%
Diabetes, %	7%	13%	14%	14%
HTN meds, %	93%	87%	88%	89%
Cigarette smokers, %	16%	11%	15%	10%

Data are presented as mean ± standard deviation.
*Significantly different vs. PP1 ($P < 0.05$).

follow-up cancer duration of 18 years and 136 total deaths [103 cancer related deaths (75%) and 22 cardiovascular related deaths (16%)]. The ≥65 years subcohort consisted of 480 subjects (227 men, 253 women) with an average follow-up time of 8 years and 467 total deaths [154 cancer related deaths (33%) and 129 cardiovascular related deaths (28%)]. Baseline demographics and subject characteristics based on pulse pressure levels are shown in Table 1.

The four indexes of arterial blood pressure were positively and significantly correlated with each other as determined via product-moment (Pearson) simple correlations. The correlation coefficients of pulse pressure with other blood pressure parameters were $R = 0.4$ ($P < 0.0001$) with MAP, $R = 0.85$ ($P < 0.0001$) with SBP, and $R = -0.14$ ($P < 0.0001$) with DBP.

3.1. Associations of pulse pressure with cardiovascular mortality

The unadjusted Cox analysis revealed that in the entire cancer cohort, pulse pressure was a significant determinant of cardiovascular mortality with a hazard ratio of 1.03 (95% confidence interval, 1.02–1.03) for every 10 mm Hg increase ($P < 0.001$). Moreover, Kaplan-Meier curve analysis revealed significant differences in cardiovascular survival probabilities between pulse pressure categories for the entire cancer cohort ($P < 0.0001$) (Fig. 1A), such that each level of elevated pulse pressure category was significantly predictive of mortality (Table 2). In younger cancer survivors a significant association between pulse pressure levels (PP_2, PP_3, and PP_4) and cardiovascular mortality was observed ($P = 0.00025$) (Table 3) (Supplemental Fig. 1). The overall predictive model that included pulse pressure and the traditional cardiovascular risk factors was significant (C index = 0.86, $\chi^2 = 38.45$, $P < 0.0001$). In this model, a pulse pressure of 60–70 mmHg (PP_3) showed significant increase in the risk for cardiovascular mortality, with highest pulse pressure category [(>70 mmHg (PP_4)] approaching significance ($P < 0.1$). Compared to the model containing only risk factors, the modeling including pulse pressure was incrementally more predictive of cardiovascular mortality. In the older cohort of cancer survivors pulse pressure was not predictive of cardiovascular mortality in univariate or multivariate analysis (Table 3).

3.2. Associations of pulse pressure with cancer mortality

Similar to cardiovascular mortality analyses, the unadjusted Cox analysis revealed that in the entire cohort, pulse pressure was a significant determinant for cancer mortality with a hazard ratio of 1.02 (95% confidence interval, 1.01 – 1.02, $P < 0.001$). In addition, statistically significant differences were found in the Kaplan-Meier curve analyses

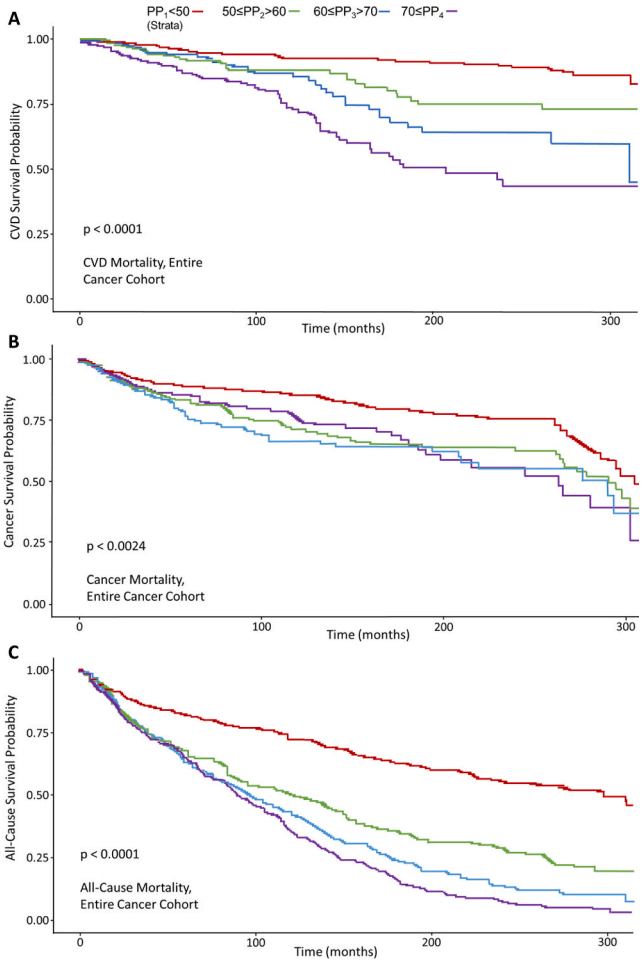

Fig. 1. Kaplan-Meier curve analysis of **A)** cardiovascular, **B)** cancer, and **C)** all-cause mortality in the entire cancer cohort across pulse pressure level. CV indicates cardiovascular mortality.

Table 2
Association of pulse pressure with cardiovascular, all-cause, and cancer mortality on unadjusted analysis in participants with cancer, NHANES III 1998–1994.

	Unadjusted	p Value
Outcome	HR (95% CI)	
Cardiovascular Mortality		
PP1	–	
PP2	2.05 (1.21–3.49)	0.007
PP3	3.15 (1.88–5.28)	<0.001
PP4	5.34 (3.34–8.44)	<0.001
All-Cause Mortality		
PP1	–	
PP2	2.27 (1.78–2.92)	<0.001
PP3	3.11 (2.43–3.98)	<0.001
PP4	3.78 (3.01–4.76)	<0.001
Cancer Mortality		
PP1	–	
PP2	1.52 (1.09–2.12)	0.014
PP3	1.85 (1.31–2.63)	0.0005
PP4	1.60 (1.13–2.26)	0.008

HR = Hazard Ratio, CI = confidence interval.

Table 3
Association of pulse pressure with cardiovascular, all-cause, and cancer mortality on unadjusted and multivariate-adjusted analysis in participants with cancer, stratified by age, NHANES III 1998–1994.

	Younger Cohort (<65 years)		*Older Cohort (≥65 years)*	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Outcome	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Cardiovascular Mortality				
PP1	–	–	–	–
PP2	0.94 (0.25–3.50)	0.88 (0.21–3.69)	1.08 (0.59–1.99)	0.82 (0.44–1.54)
PP3	5.65 (2.08–15.39)***	5.26 (1.12–24.78)**	0.87 (0.47–1.58)	0.57 (0.29–1.10)*
PP4	4.85 (1.29–18.31)**	7.28 (0.73–72.18)*	1.37 (0.81–2.31)	0.88 (0.44–1.77)
All-Cause Mortality				
PP1	–	–	–	–
PP2	1.78 (1.18–2.70)***	1.31 (0.82–2.07)	1.29 (0.94–1.78)	1.12 (0.80–1.56)
PP3	3.16 (2.01–4.98)***	1.65 (0.90–3.02)	1.16 (0.85–1.59)	0.97 (0.69–1.37)
PP4	2.86 (1.59–5.15)***	1.71 (0.69–4.27)	1.28 (0.96–1.70)*	1.14 (0.78–1.67)
Cancer Mortality				
PP1	–	–	–	–
PP2	1.28 (0.80–2.06)	1.22 (0.72–2.06)	1.04 (0.63–1.73)	1.09 (0.65–1.86)
PP3		1.49 (0.69–3.17)	0.95 (0.58–1.55)	1.11 (0.63–1.94)
PP4	1.52 (0.69–3.34)	1.53 (0.52–4.45)	0.74 (0.46–1.18)	1.06 (0.55–2.05)

Multivariate model adjusted for age (years), sex (male or female), race (specified as black or nonblack), total cholesterol (mg/dL), HDL cholesterol (mg/dL), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), hypertensive medications, history of diabetes mellitus, and smoking status (each as binary variables).
HR = Hazard Ratio, CI = confidence interval.
*P < 0.1.
**P < 0.05.
***P < 0.01.

between different pulse pressure levels and cancer survival probabilities in the entire cancer cohort analysis (Fig. 1 B), P = 0.0024). Univariate Cox regression analysis, but not adjusted, suggest that compared to the reference PP_1, the risk of cancer mortality were 1.52-fold, 1.85-fold, and 1.60-fold higher for those patients with elevated pulse pressures in PP_2, PP_3, and PP_4 groups, respectively (Table 2). In younger cancer survivors a significant association between 60 to 70 mmHg (PP_3) and cancer mortality was observed (Table 3) (Supplemental Fig. 2). However, on multivariate analysis in both <65 year and ≥65 years cohorts this relationship was no longer significant (Table 3).

3.3. Associations of pulse pressure with all-cause mortality

Arterial pulse pressure was associated with all-cause mortality (unadjusted HR: 1.01 (95% CI: 1.001 - 1.02, P = 0.03). However, this only equated to a <1% increased risk for every 10 mm Hg increase in pulse pressure. Kaplan-Meier curve analyses revealed statistically significant differences in all-cause survival probabilities between different pulse pressure levels in the entire cancer cohort (P < 0.0001) (Fig. 1C). Across the entire cohort, compared to the reference (PP_1), the risk of all-cause mortality were 2.27-fold, 3.11-fold, and 3.78-fold higher for cancer patients with an arterial pulse pressure 50–60 mmHg (PP_2), 60–70 mmHg (PP_3), and ≥70 mmHg (PP_4), respectively (Table 2). All-cause mortality was significantly associated with elevated pulse pressures in the younger cancer survivors across all categories (Table 3). In the fully adjusted analyses, pulse pressure was no longer a significant predictor for all-cause mortality. However, the combination of pulse pressure and these risk factors revealed slightly better model for predicting all-cause mortality (C index = 0.77, $\chi^2 = 126.8$) compared to only the traditional CVD risk factors alone (C index = 0.76, $\chi^2 = 124.0$). In the older cohort, there were no differences in all-cause survival probabilities between the different levels of pulse pressure (P = 0.32). Cox regression analysis revealed pulse pressure was not independently predictive of all-cause mortality in the univariate analysis or the multivariate analyses. The model including pulse pressure with CVD risk factors as a whole significantly predicted all-cause mortality (C index = 0.65, $\chi^2 = 128.5$, P < 0.0001), but did not appear improve upon the model consisting of only traditional risk factors.

4. Discussion

This study is the first to demonstrate the association of pulse pressure, a clinical index of arterial stiffness [20,21], with CVD mortality in a large cancer cohort. Specifically, after dividing the cohort by age, we found in those less than 65 years old, a higher pulse pressure conferred an increased risk of all-cause and CVD-related mortality after controlling for multiple traditional CVD risk factors. Moreover, an increased arterial pulse pressure was also independently predictive of cancer mortality, highlighting the role of arterial stiffness as a potential common risk factor for both CVD and cancer. A critical innovative aspect of these findings includes the applicability to patients; specifically, the relative ease in which pulse pressure measures are obtained in the office setting, make it a valuable tool for straightforward assessment of CVD mortality risk upon adjustment for traditional risk factors.

Several investigations to date have demonstrated a relationship between CVD outcomes and elevated arterial pulse pressure. In 1991 Domanski and colleagues evaluated the role of arterial pulse pressure in predicting CVD outcomes in the general population using the NHANES I dataset. Their study revealed that every 10 mmHg increase in pulse pressure was associated with a 26% and 10% increased risk of cardiovascular death in individuals aged 25–45 years and 46–77 years old, respectively [21]. Similarly, Liu et al. [29] evaluated the relationship between pulse pressure and mortality in younger (i.e. <65 years) cancer and CVD free individuals and found that elevated pulse pressure was a predictor of both all-cause and cardiovascular mortality. Moreover, several reports support the premise that arterial pulse pressure provides important prognostic information in specific populations including patients with type II diabetes, heart failure, and chronic kidney disease [21,30–32]. None of these early works, however, focused on patients with a history of cancer specifically, even though they are at a higher risk for CVD compared with the general population [1,2,33].

There is a growing body of evidence suggesting a biological link

between cancer and cardiovascular disease [15]. Reasons for this include shared risk factors such as inflammation, smoking, obesity, hypertension, diabetes, diet, and physical inactivity [15,16,34]. Findings from a community based retrospective cohort study consisting of 36,236 cancer survivors support this notion. In a study conducted by Armenian et al. [1], cancer survivors were found to be more likely to have cardiovascular risk factors than cancer-free controls; additionally, cancer survivors with two or more CVD risk factors were more likely to develop CVD over time [1]. Most importantly, their analysis revealed cancer survivors who developed CVD had worse 8-year survival outcomes when compared to CVD free cancer survivors, independent of age, sex, cancer stage, and CVD risk factors. In another retrospective population-based study, Strongman and colleagues reported findings similar to Armenian et al. [33] with cancer survivors in this cohort were more likely to have baseline CVD risk factors and previous CVD when compared to cancer-free controls. Additionally, cancer survivors were also found to be at an increased risk of CVD than the general population and this association persisted after adjustment for shared risk factors for cancer and CVD. Findings from both of these studies indicate an increased prevalence of CVD related risk factors in cancer survivors when compared to cancer free controls, along with support for the notion that presence of CVD results in worsened outcomes in cancer survivors, further providing evidence for a shared biological link between cardiovascular disease and cancer.

To date, most studies evaluating the relationship between CVD risk and cancer have focused on the direct cardiotoxic effects, such as decreases in left ventricular function, following treatment with anti-cancer therapies including doxorubicin, trastuzumab, 5-fluorouracil, and androgen deprivation therapy [35–38]. Traditional therapies such as anthracyclines have been associated with a dose-dependent cardiotoxicity resulting in irreversible structural myocardial damage over time that manifests as decreased left ventricular mass and wall thickness, eventually leading to dilated cardiomyopathy and synchronous heart failure [39]. Characterization of this relationship has led to surveillance strategies in the cardio-oncology field that are centered around monitoring changes in left ventricular ejection fraction during and immediately after treatment [40]. However, it has come to light that vascular changes are occurring in this patient population that manifest as endothelial dysfunction, coronary vasospasm, and increased arterial stiffness [41–43]; and importantly, these changes often precede structural alterations in the myocardium [9,10]. Recently, our group performed an in-depth meta-analysis to demonstrate significant increases in arterial stiffness after exposure to anticancer therapies during cancer treatment and into survivorship, highlighting the vasculotoxicity associated with many chemotherapy agents [7]. This coupled with the findings of the current study highlight arterial stiffness as a possible treatable risk factor for the prevention of CVD following cancer treatment.

Mechanistically increases in pulse pressure, via increases in arterial stiffness, increase the risk for cardiovascular events through alterations in the Windkessel effect. In health, each cardiac contraction sends energy waves across the periphery that are reflected back to the myocardium during early diastole to increase diastolic coronary perfusion, without increasing cardiac afterload. With increases in stiffness, the wave reflection returns to the myocardium during late systole and augments systolic pressure [44]. Coupled together, these factors augment total systolic ventricular load, decrease coronary perfusion pressure, and lead to an imbalance of myocardial oxygen delivery and demand [45,46].

4.1. Study strengths and limitations

Strengths of this study include the relatively large study population that consisted of a broad range of cancer types in both men and women. A second key strength is multiple adjustment analyses for competing risk factors, thus preventing the overestimation of the 'real' effect of pulse pressure on each outcome of interest. Furthermore, by evaluating subcohorts defined by age, the relationship between arterial pulse pressure and each outcome was specific to younger and older cancer populations, which have known differences in CVD risk [2,47]. Lastly, the use of pulse pressure to evaluate arterial stiffness versus other more costly and time-consuming techniques allows for easier translation of this work into the cardio-oncology clinic. Limitations of this study however must be taken into consideration. Specifically, with the NHANES III database, we were only able to utilize a snapshot in time of pulse pressure and we were not able to track these changes over time leading to the study endpoint. Further, our study does not have treatment information on the patients examined in this analysis. Because of this limitation, we cannot determine whether specific treatments or the diagnosis of cancer itself could have led to higher pulse pressure in this population.

5. Conclusion

In a large study of cancer patients from the NHANES III database, arterial pulse pressure adds valuable clinical information for CVD stratification. Given that pulse pressure is a readily available measurement in the office setting, our study supports the use of pulse pressure as a clinical tool to identify cancer patients and survivors who are at an enhanced risk of cardiovascular mortality. Future studies are warranted to examine whether this association is due to cancer treatments or the shared risk factors between cancer and cardiovascular disease.

Clinical perspectives

In cancer patients increases in arterial stiffness, assessed via arterial pulse pressure, are associated with an increased risk of cardiovascular and cancer mortality.

CRediT author statement

Shannon K. Parr: Conceptualization, Methodology, Formal analysis, Investigation, Data Curation, Writing – Original draft. **Catherine C. Steele:** Software, Formal analysis, Investigation. **Stephen T. Hammond:** Conceptualization, Writing - Review & Editing. **Vanessa Rose G. Turpin:** Conceptualization, Writing - Review & Editing. **Carl J. Ade:** Conceptualization, Methodology, Supervision, Project Administration, Writing - Review & Editing.

Disclosures

We state that this manuscript is not under consideration elsewhere and that the research reported will not be submitted for publication elsewhere until a final decision is made as to the acceptability of the manuscript. There is no financial or other relationship that influenced the outcome of this paper. In addition, this manuscript represents original work without fabrication, fraud or plagiarism and has been read and approved by all authors.

Funding

NA.

Declaration of competing interest

We state that this manuscript is not under consideration elsewhere and that the research reported will not be submitted for publication elsewhere until a final decision is made as to the acceptability of the manuscript. There is no financial or other relationship that influenced the outcome of this paper. In addition, this manuscript represents original work without fabrication, fraud or plagiarism and has been read and approved by all authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijchy.2021.100085.

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