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A Prospective Cohort Study of Metabolic Syndrome and Endometrial Cancer Survival

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A Prospective Cohort Study of Metabolic Syndrome and Endometrial Cancer Survival

by

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A THESIS

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Abstract

Background: Metabolic syndrome has been previously associated with increased endometrial cancer risk, but the relationship with metabolic syndrome and endometrial cancer survival remains unclear.

Objectives: To determine the associations between metabolic syndrome using the harmonized criteria with disease-free survival, overall survival, endometrial cancer-specific survival and time to recurrence among endometrial cancer survivors. Second, to determine the association between the number of metabolic syndrome components as well as each individual metabolic syndrome component with these prognostic outcomes.

Methods: A prospective cohort of 540 endometrial cancer survivors diagnosed between 2002 and 2006 participated in the Alberta Endometrial Cancer Cohort and were followed until death or March 20, 2019. Baseline in-person interviews, direct anthropometric measurements and fasting blood samples were used to assess metabolic syndrome. Recurrence and survival data were obtained via medical chart abstraction and vital status updates.

Results: Compared to endometrial cancer survivors without metabolic syndrome, survivors with metabolic syndrome had worse overall survival when assessed with the harmonized criteria. Of the individual metabolic syndrome components, only waist circumference was associated with recurrence and survival outcomes. Lifetime recreational physical activity prior to diagnosis was observed to modify the associations between metabolic syndrome and its components with overall survival and disease-free survival.

Conclusion: The metabolic syndrome, especially waist circumference, was associated with worse overall and disease-free survival among endometrial cancer survivors. Future research should aim to confirm these results and improve our understanding of the role lifestyle factors

such as physical activity have in the association between metabolic syndrome and endometrial cancer survivors' prognosis.

Preface

Chapter Four includes the main manuscript from this thesis which addresses the association between metabolic syndrome and its components defined by harmonized criteria with disease-free survival, overall survival, endometrial cancer-specific survival and recurrence among endometrial cancer survivors from the Alberta Endometrial Cancer Cohort Study.

For this manuscript Renee Kokts-Porietis led the formal analysis and interpretation of data, as well as drafting, writing, reviewing and editing of the manuscript. All authors were involved in conceptualization and provided critical review of this manuscript. Kerry Courneya, Linda Cook and Christine Friedenreich were involved in the funding acquisition, methodology, investigation and project administration of the larger project. Finally, Jessica McNeil, Gregg Nelson and Christine Friedenreich provided supervision and guidance to Renee Kokts-Porietis at each stage of the project.

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List of Symbols, Abbreviations & Nomenclature

Symbols & Abbreviations	Definition
>	Greater than
<	Less than
\geq	Greater than or equal to
\leq	Less than or equal to
\pm	Plus or minus
BMI	Body Mass Index
CI	Confidence Interval
DBP	Diastolic Blood Pressure
EC	Endometrial Cancer
ESMO	European Society of Medical Oncology
FIGO	International Federation of Gynecology and Obstetrics
FU	Follow-up
HR	Hazard Ratio
HDL	High-Density Lipoprotein
HUNT	Health Surveys in North-Trondelag study
IARC	International Agency for Research on Cancer
IDF	International Diabetes Federation
IGF	Insulin-Like Growth Factor
LDL	Low Density lipoprotein
Me-Can	Metabolic Syndrome and Cancer Project

MET	Metabolic-Equivalent Task
NCEP-ATP III	National Cholesterol Education Program Adult Treatment Panel III
NIH-AARP	National Institutes of Health- American Association of Retired Persons
NOS	Not Otherwise Specified
NR	Not Reported
OR	Odds Ratio
PCOS	Polycystic Ovary Syndrome
RR	Risk Ratio
SBP	Systolic Blood Pressure
SEER	Surveillance, Epidemiology, and End Results Database
SMR	Standardized Mortality Rate
SUCCEED	Survivors of Uterine CanCer Empowered by Exercise and Healthy Diet
TNM	Tumour, Lymph Node, Metastasis stage
WCRF-CUP	World Cancer Research Fund-Continuous Update Project

CHAPTER ONE: INTRODUCTION

1.1. Background

Endometrial cancer is the sixth most commonly diagnosed cancer among women worldwide.¹ Endometrial cancer accounts for 75-80% of all uterine cancers and occurs most often in women after age sixty.^{2,3} Based primarily on histology, endometrial cancer has been classified into two broad types: Types I and II. Type I endometrial cancers include low International Federation of Gynecology and Obstetrics (FIGO)-grade endometrioid adenocarcinomas and make up 80-90% of all endometrial cancer cases.³ These tumours typically arise following endometrial hyperplasia in the presence of hormonal imbalances, specifically high levels of unopposed estrogens.⁴ Lower FIGO grades (grades 1 and 2) generally have better prognosis which likely contributes to the higher survival rates observed among women living with Type I endometrial cancers.³ Type II endometrial cancers are less common and include non-endometrioid and high grade (FIGO grade 3) endometrioid tumours.³ These tumours are thought to develop in an atrophic environment and are considered more aggressive with higher rates of recurrence and mortality.^{3,4}

Specific features of endometrial cancer diagnosis including histology, grade and age at diagnosis are associated with endometrial cancer survival. Relative to women with low-grade endometrioid cancer, women with high-grade endometrioid (hazard ratio (HR)=6.69, 95% confidence interval (CI)=4.03-11.10), serous, clear cell, mixed endometrioid and serous/clear cell (HR=4.00, 95% CI=2.40-6.65), and carcinosarcoma (HR=10.20, 95% CI=5.58-18.60) have reduced endometrial cancer-specific survival.⁵ Moreover, high grade endometrial cancer (HR_{stage 4 vs 1}=9.69, 95% CI=5.22-18.00) has been associated with decreased cancer-specific survival.⁵

Increasing age at diagnosis has also been related to reduced endometrial cancer-specific survival ($HR_{\text{per year}}=1.06$, 95% CI=1.04-1.09).⁵

Endometrial cancer survivors have a greater prevalence of obesity, diabetes/elevated blood glucose levels (i.e. hyperglycemia), high blood pressure (i.e. hypertension) and high cholesterol (i.e. hypercholesterolemia) than the general population.⁶ Women living with obesity or diabetes are known to have an increased risk of developing endometrial cancer and nearly 20% of all Canadian endometrial cancer cases identified in 2015 were attributable to excess body fatness.⁷ In comparison genetic mutations such as Lynch and Cowden syndromes only accounted for approximately five percent of endometrial cancer cases.³ There is currently insufficient evidence to suggest that survival rates for women with Lynch syndrome-related endometrial cancer are different from survivors with sporadic endometrial cancer.⁸ However, endometrial cancer survivors living with obesity, diabetes or cardiovascular disease may experience reduced survival.⁵ The relationship between these cardiometabolic risk factors and endometrial cancer survival has been investigated to varying degrees and will be described in Chapter Two. This thesis will focus on the associations between the clustering of cardiometabolic risk factors, namely the metabolic syndrome, and survival outcomes in women living with endometrial cancer.

1.1.1. Descriptive Epidemiology

In 2018, the International Agency for Research on Cancer (IARC) estimated that 382,069 new cases of endometrial cancer and 89,929 endometrial cancer-specific deaths occurred globally¹ with the highest rates occurring in North America and Central and Eastern Europe.^{1,9} Approximately 7,400 new diagnoses and 1,300 endometrial cancer-specific deaths are estimated

to occur in 2020, and the lifetime probability of dying from endometrial cancer in Canada is currently one in 147.^{10,11} In recent years, uterine cancer mortality rates increased two percent annually in Canada and the USA, making endometrial cancer one of the few cancer types with both increasing incidence and mortality rates.^{11,12}

The median age for peak uterine cancer incidence has decreased between 1992 and 2010 from 66 years to 62 years of age among Canadian women,² whereas the median age of death has increased during this time with the highest mortality rates occurring among survivors over the age of 85 years.² Within the American context, White women experience greater incidence of endometrial cancer and are typically diagnosed at a younger age than Black women.^{4,13} In contrast, Black women experience nearly double the rate of endometrial cancer-specific mortality.¹³

1.1.2. Analytical Epidemiology

The World Cancer Research Fund Continuous Update Project (WCRF-CUP) investigates diet, nutrition and physical activity factors related to cancer prevention and survival.⁹ While several risk factors have been investigated in the etiology of endometrial cancer, only greater body fatness including abdominal fatness and adult weight gain, has been deemed a convincing cause of endometrial cancer.⁹ The WCRF has reported that there is probable evidence that physical activity, coffee consumption, adult attained height as a proxy for developmental factors during childhood and glycemic load are related to endometrial cancer risk, while there is limited evidence that suggests sedentary behavior is related to the risk of endometrial cancer.⁹ Reproductive life events, medication use and chronic conditions have also been associated with endometrial cancer incidence and survival to varying degrees.⁹

1.1.2.1. Lifestyle Factors

Currently, Body Mass Index (BMI, kg/m^2) is the most commonly used method for assessing body fatness and classify individuals as overweight (25-29.9 kg/m^2) or obese ($> 30 \text{ kg}/\text{m}^2$).¹⁴ However, it has been suggested that central adiposity (waist circumference) may be more relevant for morbidity and mortality outcomes.¹⁴ Obesity is considered to be a convincing cause of endometrial cancer as many pathological features of body fatness such as metabolic disruptions, hormonal and growth factor imbalances, and chronic inflammation prompt tumour growth.¹⁴⁻¹⁶ Individuals living with cancer and obesity also experience reduced responses to standard treatments, higher rates of metastatic disease and generally poorer prognoses than normal weight individuals.¹⁶ The link between adipose tissue and female sex hormones is thought to drive the association between obesity and endometrial cancer pathogenesis.¹⁴ Adipose tissue can convert androgens and androgenic precursors into the female sex steroid estrogen. In individuals with obesity, excess adipose tissue results in greater conversion rates and thus higher estrogen levels.¹⁴ Unopposed estrogen in the endometrium stimulates cell proliferation and inhibition of apoptosis, which then promotes tumourigenesis.¹⁴ This mechanism of endometrial cancer pathogenesis is known as the unopposed estrogen hypothesis. In a systematic review and meta-analysis, Aune et al.¹⁵ reported a non-linear increase in endometrial cancer risk for every five-unit increase in BMI, with greater risk being observed in the overweight and obese BMI ranges. Moreover, for each ten cm increase in waist circumference the risk of endometrial cancer increased 1.27 (95% CI=1.17-1.39) times.¹⁵ Obesity may also decrease endometrial cancer-specific survival, as well as overall survival in women living with endometrial cancer.¹⁴

Endometrial cancer survivors with obesity have a statistically significant decrease in overall survival per five-unit increase in BMI ($HR_{\text{per } 5 \text{ kg/m}^2}=1.11$, 95% CI=1.01-1.22).⁵

Women with high compared to low physical activity levels have a reduced risk of endometrial cancer (risk ratio (RR)=0.80, 95% CI=0.75–0.85),¹⁷ whereas high rather than low amounts of sedentary behaviour may increase the risk of endometrial cancer by approximately 34%.¹⁸ A recent meta-analysis reported that post-diagnosis physical activity was associated with improved overall survival in a combined estimate of all female reproductive cancers ($HR=0.66$, 95% CI=0.49-0.88).¹⁹ No relationship was observed in this meta-analysis for pre-diagnosis physical activity or cancer-specific survival for female reproductive cancers survivors.¹⁹

There is limited evidence whether or not dietary patterns or specific foods impact endometrial cancer risk.⁹ The WCRF-CUP reported a 15% increased risk in endometrial cancer per 50 units of glycemic load increase per day ($RR_{\text{per } 50 \text{ glycemic load units/day}}=1.15$, 95% CI=1.06-1.25).⁹ It has also been suggested that prolonged high glycemic load diets can lead to hyperinsulinemia and result in greater bioavailability of insulin-like growth factor-1 (IGF),²⁰ which can directly promote endometrial cancer cell division and growth.²⁰ Currently there is no available evidence on the relationship between glycemic load and endometrial cancer recurrence or survival, and a null association has been reported for the relationship between glycemic load and overall survival among women in the general population ($RR=1.06$, 95% CI=0.90-1.25).²¹

There is some evidence that greater adult attained height is associated with increased endometrial cancer risk. The WCRF-CUP reported that for every five cm increase in adult attained height the risk of endometrial cancer increased seven percent (95% CI=3-11%) in a meta-analyses of ten studies.⁹ Adult height is a marker of developmental factors during childhood such as the rate of growth, the number of cell divisions, age of sexual maturity and is a

proxy for nutritional exposures which affect several hormonal and metabolic mechanisms.⁹ Specifically, taller women may have been exposed to greater insulin levels, pituitary-derived growth hormone and IGFs.⁹

Greater coffee consumption, including decaffeinated coffee, may reduce the risk of endometrial cancer (RR=0.74, 95% CI=0.68–0.81).^{9,22} While the specific biological mechanism remains unknown, the link between coffee consumption and reduced risk of endometrial cancer may be related to lower circulating levels of estrogen or insulin as well as higher insulin sensitivity.⁹ Coffee has also been associated with reduced obesity, inflammation and bioavailability of estrogens, which may partially explain its protective association with endometrial cancer.^{9,22} The association between coffee consumption and recurrence or survival outcomes among endometrial cancer survivors has not been assessed in the literature.

Although not included in the WCRF-CUP because it was outside the scope of that report, cigarette smoking has been found to reduce endometrial cancer risk.²³ Results from a meta-analysis suggest that postmenopausal women who currently smoke have between a 30-40% lower risk of endometrial cancer compared to never smokers.²³ While this association was slightly attenuated among ever smokers, a 20-30% reduction in risk of endometrial cancer was observed for ever compared to never smokers.²³ These findings may be related to lower BMI commonly observed among individuals who smoke and thus reduced endogenous estrogen levels, as well as higher progesterone levels reported among smokers.⁴ However, it is important to note that while current smokers may be at a reduced risk of endometrial cancer, they experience half the overall survival as never smokers.²⁴ Additionally, endometrial cancer survivors who smoke have reduced endometrial cancer-specific survival (HR=1.38, 95%

CI=1.09-1.75) and overall survival (HR=1.41, 95% CI=1.20-1.66) compared to survivors who are non-smokers.²⁵

1.1.2.2. Events of Reproductive Life

Reproductive factors such as age at menarche, menopausal age, parity and anovulation have been previously associated with the risk of endometrial cancer.⁴ These reproductive events are closely linked to endogenous hormonal levels, namely estrogens which are central to endometrial cancer etiology.⁴ As mentioned above, the unopposed estrogen hypothesis suggests that high levels of estrogen in the absence of sufficient progesterone increases the risk of endometrial cancer by promoting endometrial proliferation that can lead to malignant transformations.^{4,26} Women living with polycystic ovary syndrome (PCOS) experience chronic anovulation which results in high unopposed estrogen levels.⁴ Subsequently, women with PCOS are at an elevated risk of endometrial cancer (odds ratio (OR)=2.79, 95% CI=1.31-5.95).²⁷ To date, there are no known studies that have assessed the association between PCOS and survival among endometrial cancer survivors. Although there is some evidence that women living with PCOS in the general population may have reduced overall survival, these association did not reach statistical significance (OR=1.21, 95% CI=0.91-1.60).²⁸ Older age at menarche may be protective for endometrial cancer incidence later in life ($RR_{\text{older vs younger}}=0.68$, 95% CI=0.58-0.81),²⁹ while later age of menopause onset has been associated with an increased risk of endometrial cancer.²⁶ Specifically among studies from North America, women with the oldest age at menopause onset had 1.60 (95% CI=1.37-1.86) times the risk of endometrial cancer compared to women with the youngest age at menopause onset.²⁶ No studies have assessed the relationship between age of menopause and subsequent endometrial cancer recurrence or

survival. A meta-analysis of epidemiologic studies reported an overall protective association between parity and endometrial cancer risk ($RR_{\text{parity vs nulliparous}}=0.69$, 95% CI=0.65-0.74).³⁰ Parity may also improve overall survival ($HR_{\text{parity vs nulliparous}}=0.69$, 95% CI=0.58-0.82).³¹ It is hypothesized that the relationship between parity and endometrial cancer is related to the hormonal changes that occur during pregnancy.³²

1.1.2.3. Exogenous Hormones

The use of pre- and post-menopausal estrogen only hormones has been consistently shown to increase the risk of endometrial cancer, while there have been inconsistent findings associated with combined use of estrogen and progestin.³³ Several reasons exist for the lack of direct associations between combined hormone therapy use and endometrial cancer risk. The most important being the protective effect of progestins on endometrial cancer risk, as well as the wide range of regimens of combined estrogen and progestin that are commonly utilized.⁴ Endometrial cancer recurrence was not associated with estrogen only hormone therapy at the time of diagnosis (OR=0.78, 95% CI=0.38-1.57) and a protective association was observed in a meta-analysis of observational studies with combined estrogen and progestin use (OR=0.23, 95% CI=0.08-0.66).³⁴

There has been limited research on hormonal therapy use and survival among endometrial cancer survivors. Most recently, Felix et al.³⁵ observed that pre-diagnosis use of estrogen and progestin therapy was associated with better ten-year overall survival (HR=0.65, 95% CI=0.43-0.99) and endometrial cancer-specific survival (HR=0.51, 95% CI=0.26-0.98) within the National Institutes of Health-American Association of Retired Persons cohort (NIH-

AARP). Since these estimates were based on a small number of deaths (29 and 11 deaths, respectively), further research is warranted to confirm these results.³⁵

1.1.2.4. Chronic Conditions

Women living with diabetes have nearly double (RR=1.72, 95% CI=1.48-2.01) the risk of endometrial cancer.³⁶ Increased fasting glucose levels and insulin resistance are hallmarks of diabetes.³⁷ Bjorge et al.³⁸ previously reported that women in the highest quintile of fasting glucose levels (mmol/L) compared to the lowest had 1.57 (95% CI=1.27-1.95) times the risk of endometrial cancer. Similarly, Arthur et al.³⁹ observed double (RR=1.99, 95% CI=1.36-2.49) the risk of endometrial cancer for women with fasting glucose levels ≥ 100 mg/dL compared to < 100 mg/dL. Elevated glucose levels can provide tumours with the energy needed to promote cancer growth, cancer progression and ultimately lead to decreased survival.¹⁴ While diabetes has been found to decrease both cancer-specific survival and overall survival in women with endometrial cancer, the body of literature on this topic remains inconclusive.³⁷ In a population-based study of endometrial cancer survivors in the Netherlands, five-year overall survival rates were significantly lower for endometrial cancer survivors with diabetes (68%) compared to survivors without diabetes (84%).⁴⁰ Endometrial cancer survivors with diabetes have been reported to experience a 1.6-fold decrease in overall survival compared to survivors without diabetes (HR=1.58, 95% CI=1.07-2.33,⁴¹ HR=1.7, 95% CI=1.1-2.5).⁴² More recently, Nagel et al.⁵ reported that endometrial cancer survivors living with diabetes also had poor endometrial cancer-specific survival (HR=2.09, 95% CI=1.31-3.35).

Several cardiovascular disease risk factors are also closely associated with endometrial cancer risk. Participants of the Women's Health Initiative cohort study with low high-density

lipoprotein (HDL) cholesterol (< 50 mg/dL) or elevated triglycerides levels (\geq 150 mg/dL) had 1.65 (95% CI=1.22-2.23) and 1.34 (95% CI=0.97-1.85) times the risk of endometrial cancer compared to participants with normal lipid level, respectively.³⁹ Bjorge et al.³⁸ also noted that in contrast to women with the lowest quintile of triglycerides, those with the highest levels had a greater risk of endometrial cancer (RR=1.61, 95% CI=1.29-2.02, p-trend <0.01). Moreover, Kitson et al.⁶ reported that significantly more (88.7% versus 54.3%) endometrial cancer survivors had undiagnosed or undertreated cardiovascular disease risk factors compared to women in the overall UK population. The authors also noted that despite endometrial cancer survivors already taking significantly more antihypertensive medication compared to the general population, nearly 50% of survivors were still classified as hypertensive.⁶ Hypertension has been shown to elevate endometrial cancer risk ($HR_{\text{per unit z-score}}=1.20$, 95% CI=1.13-1.28).³⁸

Five years after an endometrial cancer diagnosis, Ward et al.⁴³ reported that the most frequent cause of death for endometrial cancer survivors becomes cardiovascular disease rather than endometrial cancer. In the Surveillance, Epidemiology, and End Results (SEER) Database, endometrial cancer survivors were reported to have greater cardiovascular disease mortality (standardized mortality rate (SMR)=8.8, 95% CI=8.7-9.0) and all-cause mortality (SMR=15.9, 95% CI=15.8-16.0) than the general population.⁴⁴ However, results from the Iowa Women's Health Study suggest that women living with endometrial cancer have a reduced risk of cardiovascular disease mortality (HR=0.75, 95% CI=0.56-0.99), and a greater risk of all-cause mortality (HR=1.50, 95% CI=1.30-1.74) than the general population, after adjusting for both BMI and diabetes in the analysis.⁴⁵ These findings highlight the discrepancy that currently exists in the literature regarding the contributions of obesity, diabetes and cardiovascular disease with survival outcomes among endometrial cancer survivors.

1.1.3. Metabolic Syndrome

Metabolic syndrome is defined as the clustering of cardiovascular and metabolic disease risk factors including central adiposity (waist circumference ≥ 88 cm), hypertension (systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg), hyperglycemia (fasting blood glucose levels ≥ 100 mg/dL), and dyslipidemia (triglyceride levels ≥ 150 mg/dL and/or low HDL cholesterol levels < 50 mg/dL).⁴⁶ The specific characteristics of the metabolic syndrome have evolved since the first formalized definition was proposed by the World Health Organization in 1998.⁴⁶ A consensus statement was put forth in 2009 to harmonize the criteria of metabolic syndrome by the International Diabetes Federation (IDF), and the American Heart Association/ National Heart, Lung, and Blood Institute who had adopted the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines.⁴⁶ Specific criteria of metabolic syndrome definitions are outlined in **Table 1**. Of note, metabolic syndrome defined with the harmonized criteria is categorized using country- and sex-specific waist circumference criteria.⁴⁶ Moreover, medication use for the treatment of hypertension, dyslipidemia or hyperglycemia are considered to be alternative indicators for this metabolic syndrome criteria (i.e. medication alternative metabolic syndrome criteria).⁴⁶

Table 1. Metabolic Syndrome Definitions

Definition	IDF 2005 ⁴³	NCEP-ATP III 2005 ⁴⁶	Harmonized 2009 ⁴⁶
	Waist Circumference and any two other components	Any three of the components	Any three of the components
Obesity			
<i>Waist Circumference</i>	≥ 80 cm ^{a**}	≥ 88 cm	≥ 88 cm ^b
Hyperglycemia			
<i>Fasting Plasma Glucose</i>	≥ 100 mg/dL or previously diagnosed Type 2 diabetes	≥ 110 mg/dL	≥ 100 mg/dL*
Hypertension			
<i>Blood Pressure</i>	SBP ≥ 130 mmHg or DBP ≥ 85 mmHg *	SBP ≥ 130 mmHg or DBP ≥ 85 mmHg	SBP ≥ 130 and/or DBP ≥ 85 mmHg*
Dyslipidemia			
<i>Triglycerides</i>	≥ 150 mg/dL*	≥150 mg/dL	≥150 mg/dL*
<i>HDL Cholesterol</i>	< 50 mg/dL*	<50 mg/dL	<50 mg/dL*

*Drug treatment of condition is an alternate indicator

**If BMI is >30 kg/m², central obesity can be assumed

^aEuropeans ethnic group

^bCanadian Specific

Although prevalence estimates differ by the metabolic syndrome definition that is used, it is estimated that approximately one quarter of the world population has metabolic syndrome and one in five Canadians have metabolic syndrome.⁴⁷⁻⁴⁹ Moreover, endometrial cancer survivors have a greater prevalence of obesity, diabetes, non-diabetic hyperglycemia, hypertension and hypercholesterolemia compared to women in the general population.⁶ Additionally, most endometrial cancer survivors are expected to have more than one metabolic syndrome risk factor.⁶

While metabolic syndrome is known to increase the risk of diabetes fivefold and cardiovascular disease threefold,⁴⁹ it has more recently been associated with an increased risk of cancer.^{50,51} The estimated risk of developing endometrial cancer for women with metabolic syndrome is 1.89 (95% CI=1.34-2.67)⁵² to 2.20 (95% CI=1.61-3.02)³⁹ times that experienced among women without this syndrome. Additionally, for every increase in standard deviation of a

continuous metabolic risk score, Stocks et al.⁵³ observed a 56% (95% CI=42-70%) increased risk of endometrial cancer.

Women diagnosed with metabolic syndrome in the Third National Health and Nutrition Examination Survey experienced a 33% (95% CI=4-71%) decrease in total cancer-specific survival.⁵⁴ A positive relationship was identified between the number of metabolic syndrome risk factors and total cancer-specific mortality in this study (p-trend <0.01), such that compared to individuals without metabolic syndrome, those with three, four and five metabolic syndrome components had 1.25 (95% CI=0.93-1.67), 1.33 (95% CI=0.94-1.86), and 1.73 (95% CI=1.12-2.68) times the hazard of cancer-specific mortality, respectively.⁵⁴ No association between metabolic syndrome and obesity-linked (breast, colorectal, pancreatic and endometrial) cancer survival reached statistical significance in this study.⁵⁴ Among endometrial cancer survivors, only four studies have assessed the association between metabolic syndrome and survival outcomes.^{38,55-57} Generally, metabolic syndrome has been associated with reduced endometrial cancer-specific survival^{38,55} and overall survival^{56,57} among women living with endometrial cancer.

1.2. Rationale for Study

The associations between endometrial cancer incidence and metabolic syndrome as well as its components have been previously identified.^{39,58} Despite the biological plausibility that metabolic syndrome may be associated with endometrial cancer recurrence and survival,^{14,54} limited information on survival outcomes currently exists. Therefore, additional research is needed to understand recurrence and survival outcomes among endometrial cancer survivors associated with metabolic syndrome.

1.3. Aim and Objectives

The aim of this thesis was to examine the associations between metabolic syndrome and its components with recurrence and survival outcomes among endometrial cancer survivors. The first objective was to determine the associations between metabolic syndrome using the harmonized criteria and the medication alternative harmonized definition,⁴⁶ with disease-free survival, overall survival, endometrial cancer-specific survival and time to recurrence among endometrial cancer survivors in the Alberta Endometrial Cancer Cohort. The second objective was to determine the relationships between the number of metabolic syndrome components as well as each individual metabolic syndrome component with these prognostic outcomes.

1.4. Ethics Approval

Ethical approval for the “Metabolic Syndrome and Lifestyle Risk Factors in Endometrial Cancer Etiology and Survival” project was obtained from the Health Research Ethics Board of Alberta– Cancer Committee (Ethics ID 17-0574). The addition of Renee Kokts-Porietis as a student co-investigator to undertake this thesis was approved on August 23, 2019.

CHAPTER TWO: LITERATURE REVIEW

2.1. Metabolic Syndrome and Endometrial Cancer Survival

A comprehensive literature search was conducted to summarize the available evidence on the relations between metabolic syndrome and its components with recurrence and survival outcomes among endometrial cancer survivors. The search was completed using the MEDLINE (Ovid) and EMBASE (Ovid) databases from 1990 up to and including March 19, 2020. Three concepts were included in each database search: endometrial cancer, metabolic syndrome and its individual components, and recurrence/survival. Database subject headings (e.g. MEDLINE Subject Heading), title abstract keywords and Boolean operators were used to define and combine these concepts. The complete search strategies are provided in the Appendix A. Additional relevant literature was included at the full text stage. An overview of the article screening process is presented in **Figure 1**.

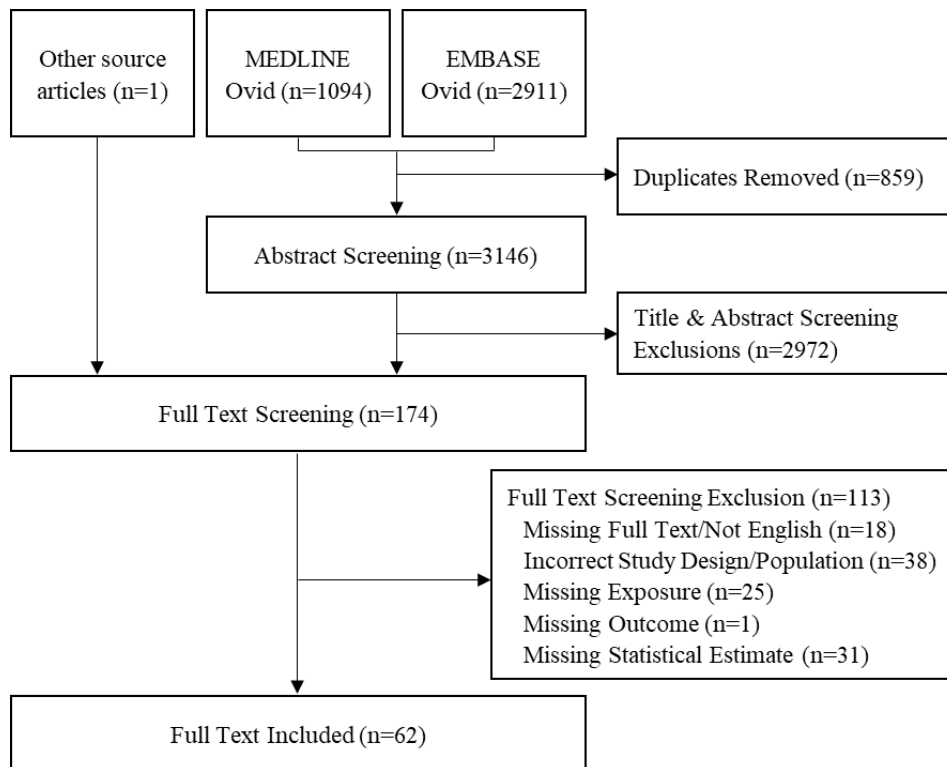


Figure 1. Literature Search and Screening Diagram

Sixty-two full text publications reported estimates for the relationship between either metabolic syndrome or at least one of its components with overall survival, endometrial cancer-specific survival, and endometrial cancer recurrence. Forty-five^{5,38,41,42,55,59-98} of these articles provided estimates for obesity, sixteen of which were included in a systematic review and meta-analysis that summarizes the association between BMI and survival in articles published prior to June 2013.⁹⁹ A total of thirty^{5,38,40-42,55,70,71,75-80,84,88,90,91,94,95,100-109} articles reported estimates for hyperglycemia, glucose levels or diabetes and recurrence or survival outcomes. There were eighteen^{38,40,41,55,63,70,75,77,80,84,88,91,94,95,101,109-111} articles that included hypertension estimates and five^{38,55,70,84,91} studies presented dyslipidemia estimates with the prognostic outcomes. Only four articles^{38,55-57} provided estimates specific to metabolic syndrome, although most of these studies used proxy metabolic syndrome criteria⁵⁵⁻⁵⁷ or study-specific metabolic syndrome definitions.^{38,56,57} A summary of the literature that reports estimates of the associations for metabolic syndrome or more than one metabolic syndrome component and endometrial cancer recurrence or survival outcomes is presented in **Table 2**. Most of this literature was conducted as retrospective analyses of large prospective cohorts or databases,^{38,40,55,70,77,79,94,95,101,109} twelve were retrospective cohorts derived from hospital medical records^{41,56,57,63,75,76,78,80,84,88,90,91} and three studies were conducted prospectively.^{5,42,71} Of note, while the language used to describe survival outcomes in the literature differed by study, all statistical estimates are presented in terms of recurrence or mortality events. The main findings from all identified studies are summarized in terms of survival outcomes in the following sections of this chapter.

Table 2. Literature Summary of Metabolic Syndrome and Multiple Metabolic Syndrome Components with Endometrial Cancer Recurrence and Survival Outcomes

Author, Year, Reference, Location	Study and Population Characteristics (number of events/ analytical sample size)	Metabolic Syndrome Components Assessed	Results		
			Cancer-Specific Mortality Estimates	Overall Mortality Estimates	Recurrence Estimates
Bjorge 2010, ³⁸ Austria, Norway, Sweden	129 EC-deaths/ 28,7320 women Metabolic Syndrome and Cancer Project FU: 1974-2005	Metabolic syndrome			
		HR per unit Z-score	1.56 (1.32-1.84)		
		BMI (kg/m²)			
		HR per unit Z-score	1.60 (1.39-1.85)		
		HR Quintile 5 vs 1	5.35 (2.43-11.80)		
		Glucose (mmol/L)			
		HR per unit Z-score	1.06 (0.91-1.23)		
		HR Quintile 5 vs 1	1.32 (0.74-2.36)		
		Blood Pressure (mmHg)			
		HR per unit Z-score	1.17 (0.98-1.39)		
		HR <i>SBP</i> Quintile 5 vs 1	2.22 (0.97-5.12)		
		HR <i>DBP</i> Quintile 5 vs 1	1.86 (0.95-3.65)		
		Cholesterol (mmol/L)			
		HR per unit Z-score	0.92 (0.76-1.12)		
HR Quintile 5 vs 1	0.82 (0.45-1.51)				
Jin 2020, ⁵⁵ USA	1,786 EC-deaths/ 10,090 EC survivors Surveillance, Epidemiology, and End Results-Medicare database FU: median 72 mo.	Metabolic syndrome			
		HR Yes vs No			
		<i>Stage I/II</i>	1.28 (1.09-1.53)		
		<i>Stage III/IVa</i>	1.18 (0.93-1.49)		
		Obesity			
		HR Yes vs No			
<i>Stage I/II</i>	0.86 (0.62-1.17)				
<i>Stage III/IVa</i>	0.67 (0.41-1.04)				

		Glucose/ Diabetes		
		HR Yes vs No		
		<i>Stage I/II</i>	1.07 (0.93-1.23)	
		<i>Stage III/IVa</i>	1.20 (1.00-1.46)	
		Hypertension		
		HR Yes vs No		
		<i>Stage I/II</i>	1.14 (0.99-1.30)	
		<i>Stage III/IVa</i>	1.09 (0.40-1.04)	
		Dyslipidemia		
		HR Yes vs No		
		<i>Stage I/II</i>	0.94 (0.82-1.07)	
		<i>Stage III/IVa</i>	0.89 (0.74-1.06)	
		Hypertriglyceridemia		
		HR Yes vs No		
		<i>Stage I/II</i>	0.86 (0.35-2.09)	
		<i>Stage III/IVa</i>	0.24 (0.01-1.09)	
Ni 2015,⁵⁶	Deaths NR/385 EC survivors	Metabolic syndrome		
		HR Yes vs No		6.65 (1.93-47.79)
China	Zhejiang Cancer Hospital			
	FU: 2-144 mo.			
Shou 2020,⁵⁷	54 deaths/139 non-endometrioid uterine survivors	Metabolic syndrome		
		HR Yes vs No		2.22 (1.45-3.45)§
China	Zhejiang Cancer Hospital			
	FU: median 63.5 mo.			
Akbayir 2012,⁶³	17 deaths, 22 recurrences/194 EC survivors	BMI (kg/m²)		
		HR < 25	Reference	Reference
		25-29.9	0.82 (0.15-4.29)	1.92 (0.48-7.50)
Turkey	Kanuni Sultan Suleyman Hospital	≥ 30	0.55 (0.13-2.34)	1.17 (0.41-3.43)
	FU: mean 59.1 mo.	Hypertension		
		HR Yes vs No	0.32 (0.05-1.69)	0.28 (0.08-0.89)

Boll 2011, ¹⁰¹	Deaths NR/1,770 EC survivors	Diabetes HR Yes vs No		2.9 (2.2-4.0)
Netherlands	Eindhoven Cancer Registry	Hypertension HR Yes vs No		1.8 (1.4-2.4)
	FU: 1–14 yr.			
Chia 2007, ⁴²	166 deaths, 43 EC-deaths/ 745 EC survivors	BMI (kg/m ²) HR < 25	Reference	Reference
USA		25-29.9	1.10 (0.40-2.70)	1.20 (0.80-2.00)
	Female residents of Wisconsin, aged 40–79 years, with invasive EC	≥ 30 HR per kg/m ²	2.00 (0.80-5.10)	1.60 (1.00-2.50)
	FU: mean 9.3 yr.	Diabetes HR Yes vs No	0.80 (0.30-2.20)	1.7 (1.10-2.50)
Edlinger 2013, ⁷⁰	89 deaths, 49 EC-deaths/ 242 EC survivors	BMI (kg/m ²) HR per kg/m ²		0.99 (0.95-1.03)
Austria	Vorarlberg Health Monitoring and Promotion Programme	Glucose (mg/dl) HR per mg/dl		1.00 (0.99-1.00)
	FU: median 11.9 yr.	Hypertension HR Yes vs. No		1.51 (0.87-2.60)
		Total cholesterol (mg/dl) HR per mg/dl		1.00 (1.00-1.01)
		Triglycerides (mg/dl) log ₁₀ HR per mg/dl		1.40 (0.48-4.05)
Felix 2015, ⁷¹	100 deaths/2,278 Low grade EC survivors	BMI (kg/m ²) <i>Low Grade EC HR</i> < 18.5	3.61 (0.53-24.61)	
USA		18.5-24.9	Reference	
	116 deaths/614 High grade EC survivors	25-29.9	1.04 (0.47-2.30)	
		30-34.9	0.86 (0.38-1.91)	
	NRG Oncology/ Gynecologic Oncology Group 210 Trial	35-39.9	2.29 (1.06-4.98)	
		> 40 <i>High Grade EC HR</i>	1.92 (0.86-4.31)	
	FU: Median 60 mo.	< 18.5	2.94 (0.19-45.13)	
		18.5-24.9	Reference	

		25-29.9	1.24 (0.69-2.22)	
		30-34.9	1.01 (0.52-1.95)	
		35-39.9	1.02 (0.47-2.23)	
		> 40	1.30 (0.66-2.54)	
		Diabetes		
		HR Yes vs No		
		<i>Low Grade</i>	0.73 (0.38-1.92)	
		<i>High Grade</i>	0.92 (0.55-1.54)	
Giannini 2020,⁷⁵	Deaths NR/100 EC survivors	BMI (kg/m²)		
UK	Royal Infirmary Hospital of Edinburgh, Edinburgh.	HR per kg/m ²	0.96 (0.89-1.02)	0.98 (0.93-1.02)
	FU: ~3 yr.	Diabetes		
		HR Yes vs No	1.12 (0.30-4.21)	0.87 (0.32-2.37)
		Hypertension		
		HR Yes vs No	1.60 (0.49-5.25)	1.40 (0.60-3.28)
Hein 2020,⁷⁶	113 deaths, 57 recurrences/ 287 EC survivors	BMI (kg/m²)		
Germany	Department of Gynecology at the University of Erlangen	HR per kg/m ²	1.03 (1.00-1.07)	0.99 (0.93-1.04)
	FU: ~10 yr.	Diabetes		
		HR Yes vs No	1.47 (0.94-2.29)	1.43 (0.69-2.98)
Khan 2006,⁷⁷	22 EC-deaths/63,541 women	BMI (kg/m²)		
Japan	Japan Collaborative Cohort Study	RR < 18.5	Reference	
	FU: mean 13.3 yr.	18.5-25	1.42 (0.19-10.72)	
		≥ 25	0.79 (0.08-7.70)	
		Diabetes		
		RR Yes vs No	1.64 (0.17-9.60)	
		SBP (mmHg)		
		RR < 130 vs > 130	1.89 (0.50-7.15)	
Ko 2014,⁷⁸	Deaths NR/1,411 EC survivors	BMI (kg/m²)		
USA	University of North Carolina Hospital, Chapel Hill and	HR per kg/m ²		
		<i>EC Type I</i>	0.99 (0.96-1.01)	0.98 (0.96-1.00)
		<i>EC Type II</i>	1.01 (0.99-1.04)	1.01 (0.99-1.03)

	Duke Cancer Institute, Durham, N.C	Diabetes HR Yes vs No		
		<i>EC Type I</i>	2.21 (1.46-3.35)	1.55 (1.08-2.20)
	FU: 2005-2010	<i>EC Type II</i>	0.76 (0.43-1.34)	0.76 (0.47-1.25)
Kristensen 2017,⁹⁴	Deaths NR /4,330 EC survivors	BMI (kg/m²)		
		<i>EC Type I HR</i>		
		< 18.5	2.07 (1.20-3.55)	
Denmark	Danish Gynecological Cancer Database	18.5-24.9	Reference	
		25-29.9	1.04 (0.81-1.35)	
		30-34.9	1.06 (0.78-1.44)	
	FU: 2005-2012 until August 14, 2013	35-39.9	0.94 (0.59-1.49)	
		> 40	1.26 (0.80-1.98)	
		<i>EC Type II HR</i>		
		< 18.5	1.68 (1.03-2.74)	
		18.5-24.9	Reference	
		25-29.9	1.21 (0.89-1.64)	
		30-34.9	1.51 (1.01-2.26)	
		35-39.9	1.19 (0.71-1.99)	
		> 40	2.15 (1.12-4.11)	
		Diabetes		
		HR Yes vs No		
		<i>EC Type I</i>	0.76 (0.53-1.08)	
		<i>EC Type II</i>	0.73 (0.43-1.25)	
		Hypertension		
		HR Yes vs No		
		<i>EC Type I</i>	0.99 (0.79-1.23)	
		<i>EC Type II</i>	1.33 (1.02-1.73)	
Lemanska 2015,⁸⁰	Deaths NR /107 EC survivors	BMI (kg/m²)		
		Uni-HR per kg/m ²	1.01 (0.96-1.06)	
Poland	Poznan University of Medical Science	Plasma Glucose Level		
		Uni-HR per unit	1.00 (0.99-1.00)	
	FU: ~0-8.4 yr.	Hypertension		
		Uni-HR per unit	1.05 (0.43-2.60)	

Lindemann 2015,⁷⁹	166 deaths, 56 EC-deaths/ 337 EC survivors	BMI (kg/m²) HR < 25 vs >25	1.47 (0.69-3.11)	
Norway	Health Surveys in North-Trondelag	HR < 20		0.66 (0.08-5.43)
		20-24.9		Reference
		25-29.9		1.10 (0.69-1.75)
		30-34.9		1.10 (0.65-1.88)
	FU: median 6.7 yr.	≥ 35		1.34 (0.78-2.32)
		Diabetes		
		HR Yes vs No	2.62 (1.07-6.43)	2.14 (1.26-3.63)
		BMI < 25 kg/m ²		6.35 (1.90-21.14)
		BMI > 25 kg/m ²		1.80 (0.98-3.33)
Matsuo 2016,⁸⁴	59 EC-deaths, 94 recurrences/ 665 EC survivors	BMI (kg/m²) HR < 30 vs ≥ 30	1.19 (0.62-2.28)	1.44 (0.86-2.42)
USA	Los Angeles County Medical Center between 1999 and 2013	Diabetes Uni-HR Yes vs No	0.78 (0.44-1.37)	0.88 (0.57-1.37)
	FU: median 36.4 mo.	Hypertension Uni-HR Yes vs No	0.98 (0.58-1.63)	1.07 (0.71-1.61)
		Hypercholesterolemia Uni-HR Yes vs No	0.86 (0.47-1.56)	1.04 (0.66-1.64)
Nagle 2018,⁵	179 deaths, 123 EC-deaths/ 1,359 EC survivors	BMI (kg/m²) HR 18.5-24.9	Reference	Reference
Australia	Australian National Endometrial Cancer Study	25-29.9	0.63 (0.40-0.98)	0.74 (0.49-1.10)
		30-34.9	0.68 (0.38-1.23)	0.86 (0.53-1.40)
		> 35	1.01 (0.59-1.74)	1.56 (1.03-2.38)
	FU: median 7.1 yr.	per five kg/m ²	0.99 (0.87-1.14)	1.11 (1.01-1.22)
		Diabetes		
		HR Yes vs No	2.09 (1.31-3.35)	2.54 (1.72-3.74)
Nicholas 2014,⁴¹	Deaths NR/ 490 EC survivors	BMI (kg/m²) HR < 25		Reference
USA	Utah, USA	25-39		1.41 (0.83-2.40)
		> 40		1.40 (0.86-2.28)

	FU: median 4.5 yr.	Diabetes HR Yes vs No		1.58 (1.07-2.33)
		Hypertension HR Yes vs No		1.51 (1.06-2.15)
Olson 2012,⁹⁵	5,123 deaths, 1,691 EC-deaths/ 12,568 EC survivors	Diabetes HR Yes vs No		
USA		<i>White Women</i>	1.19 (1.06-1.35)	1.27 (1.18-1.36)
	SEER-Medicare database	<i>Black Women</i>	0.97 (0.73-1.30)	1.30 (1.08-1.56)
	FU: median 3.5 yr.	Hypertension HR Yes vs No		
		<i>White Women</i>	1.07 (0.96-1.19)	0.94 (0.89-1.01)
		<i>Black Women</i>	0.76 (0.55-1.05)	0.74 (0.60-0.92)
Ruterbusch 2014,⁸⁸	192 deaths, 43 EC-deaths/ 356 White EC survivors	BMI (kg/m²) HR Yes vs No		
USA		<i>White Women</i> ≥ 30 kg/m ²	0.89 (0.44-1.79)	1.04 (0.75-1.43)
	171 deaths, 66 EC-deaths/ 271 Black EC survivors	≥ 40 kg/m ² <i>Black Women</i>	0.72 (0.24-2.15)	1.33 (0.86-2.06)
	Henry Ford Health System	≥ 30 kg/m ²	0.81 (0.44-1.51)	1.04 (0.69-1.56)
		≥ 40 kg/m ²	1.04 (0.53-2.02)	1.07 (0.70-1.63)
	FU: 1990-2005 till December 31, 2012	Diabetes HR Yes vs No		
		<i>White Women</i>	1.00 (0.40-2.49)	1.63 (1.13-2.35)
		<i>Black Women</i>	0.71 (0.36-1.37)	1.17 (0.80-1.71)
		Hypertension HR Yes vs No		
		<i>White Women</i>	0.47 (0.23-0.98)	0.96 (0.70-1.32)
		<i>Black Women</i>	0.35 (0.19-0.67)	0.52 (0.34-0.79)

Tuomi 2017,⁹⁰ Finland	98 recurrences/ 929 EC survivors Department of Obstetrics and Gynecology, Helsinki University Hospital FU: median 57 mo.	BMI (kg/m²)	
		OR ≥ 30 vs < 30	
		<i>Vagina</i>	1.00 (0.36-2.9)
		<i>Pelvis</i>	1.10 (0.49-2.3)
		<i>Intra-abdominal</i>	1.70 (0.78-3.6)
		<i>Extra-abdominal</i>	0.68 (0.31-1.5)
		Diabetes	
		OR Yes vs No	
Van Arsdale 2019,⁹¹ USA	543 deaths, 393 EC-deaths/ 1,732 EC survivors Treated at Montefiore Medical Center between 1999-2016 FU: median 3.4 yr.	BMI (kg/m²)	
		HR <i>EC Type I</i>	
		18.5-24.9	Reference
		25-29.9	1.16 (0.69-1.96)
		30-34.9	1.08 (0.64-1.83)
		35-39.9	0.64 (0.35-1.17)
		≥ 40	1.19 (0.69-2.07)
		HR <i>EC Type II</i>	
18.5-24.9	Reference		
25-29.9	0.77 (0.56-1.09)		
30-34.9	0.93 (0.66-1.30)		
35-39.9	0.59 (0.37-0.94)		
≥ 40	0.68 (0.43-1.09)		
Diabetes	Uni-HR Yes vs No	<i>EC Type I</i>	1.59 (1.13-2.24)
		<i>EC Type II</i>	1.24 (0.88-1.74)
		Hypertension	
		Uni-HR Yes vs No	
		<i>EC Type I</i>	1.20 (0.89-1.61)
<i>EC Type II</i>	0.84 (0.66-1.06)		

		Hyperlipidemia		
		Uni-HR Yes vs No		
		<i>EC Type I</i>	0.76 (0.56-1.01)	
		<i>EC Type II</i>	0.55 (0.43-0.71)	
Wang 2015,¹⁰⁹	29 recurrence/57 Uterine carcinosarcoma survivors	Diabetes		
USA		OR Yes vs No		0.40 (0.08-1.91)
	Cancer Genome Atlas Data Portal	Hypertension		
		OR Yes vs No		3.51 (1.03-11.90)
	FU: median 1.4 yr.			
Zander 2012,⁴⁰	Full cohort: 310 deaths/ 1,644 EC survivors	Diabetes		
Netherlands		HR Yes vs No	1.4 (0.7–2.6) [†]	1.3 (1.0-1.8)
	[†] Sub-cohort: Deaths NR/ 388 EC survivors	Hypertension		
		HR Yes vs No		0.9 (0.7-1.3)
	Eindhoven Cancer Registry			
	FU: ~5 yr.			

^aEstimates have been presented as published or limited to two decimal places. Hazard ratio (HR), Univariable (Uni-), Odds ratio (OR), Not reported (NR), Endometrial cancer (EC), Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Body Mass Index (BMI), Follow-up (FU), months (mo.) and years (yr.)

§ Reciprocal of original estimate

[†] Sub-cohort estimate

Only four observational epidemiologic studies have previously examined the relationship between metabolic syndrome and survival outcomes among endometrial cancer survivors. Ni et al.⁵⁶ used the presence of \geq three of the following risk factors: Type II diabetes history, medically-treated hypertension, diagnosed or treated hyperlipidemia and abdominal obesity defined as either waist circumference \geq 80 cm or BMI \geq 28 kg/m² to represent the metabolic syndrome. This study observed 64 deaths among women living with histologically confirmed endometrial cancer (n=385) in China.⁵⁶ Endometrial cancer survivors with metabolic syndrome had worse overall survival (HR=6.65, 95% CI=1.93-47.79) compared to those without the study-specific metabolic syndrome definition.⁵⁶ The same study-specific metabolic syndrome definition used by Ni et al.⁵⁶ was also associated with an approximate twofold decrease in overall survival among 139 Chinese non-endometrioid uterine cancer patients.⁵⁷

Jin et al.⁵⁵ recently examined the association between metabolic syndrome and endometrial cancer-specific survival in the SEER-Medicare database. This database included 10,090 women diagnosed with endometrial cancer between 1992 and 2011 over the age of 65 years. Survivors with metabolic syndrome Medicare claim (“dysmetabolic syndrome”) or claim codes for three of the five NCEP-ATP III metabolic syndrome criteria were considered to have this syndrome.⁵⁵ A total of 1,612 (16.0%) survivors met this criterion. This study⁵⁵ noted that metabolic syndrome was associated with decreased endometrial cancer-specific survival among stage I/II survivors (HR=1.28, 95% CI=1.09-1.53) but not survivors with stage III /IVa cancers (HR=1.18, 95% CI=0.93-1.49). Additionally, in the Metabolic Syndrome and Cancer Project (Me-Can), which collectively reported a total of 129 uterine corpus cancer deaths from a composite of six existing prospective cohort studies from Austria, Norway and Sweden, Bjorge et al.³⁸ observed that survivors with metabolic syndrome had 1.56 (95% CI=1.32-1.84) times the

hazard of endometrial cancer-specific death per one-unit increment of composite metabolic syndrome Z-score. However, only 58% of the 129 women who died of endometrial cancer were reported to have a prior diagnosis of incident endometrial cancer.³⁸ To date, no known study has assessed the association between metabolic syndrome and recurrence outcomes among endometrial cancer survivors.

2.2. Metabolic Syndrome Components and Endometrial Cancer Survival

2.2.1. Central Adiposity and Obesity

2.2.1.1. Overall Survival

There is no known literature that directly assessed the relationship between measured central adiposity (i.e. waist circumference) and overall survival among endometrial cancer survivors, therefore the following discussion is limited to BMI. A systematic review and meta-analysis of 18 cohort studies conducted by Secord et al.⁹⁹ observed a dose–response relationship between BMI and survival that reached statistical significance for women ≥ 40 kg/m² compared to < 25 kg/m² (OR=1.66, 95% CI=1.10-2.51). Additionally, this study reported an inverse dose-response relationship between increasing BMI and reduced survival (OR_{per 10% BMI}=1.09, 95% CI=1.03-1.16) for women living with endometrial cancer.⁹⁹

In more recent studies, the literature regarding the association between BMI and overall survival remains mixed. Seventeen studies assessed the association with BMI at or prior to endometrial cancer diagnosis and overall survival,^{5,41,64,65,67,70,74,76,78-81,83,84,87,88,94} fourteen of which observed a null associations between BMI and survival.^{41,65,67,70,74,76,78-81,83,84,87,88} Of note, several of these estimates were derived from studies with small samples (n <250).^{70,74,80,87} However, Benedetti Panici et al.⁶⁴ did observe a twofold decrease in overall survival for

endometrial cancer survivors over the age of 65 years who were ≥ 30 kg/m² compared to < 30 kg/m². Results from the Australian National Endometrial Cancer Study also suggested that endometrial cancer survivors with a pre-diagnosis BMI > 35 kg/m² had a reduced overall survival compared to survivors with a BMI within the recommended range (18.5-24.9 kg/m²).⁵ Additionally, a dose-response relationship per five kg/m² increase in pre-diagnosis BMI with reduced overall survival was observed in that study.⁵ The association with overall survival for endometrial cancer survivors did not differ by post-diagnosis BMI in the Women's Health Initiative⁶² while the NIH-AARP Diet and Health Study observed a dose-response relationship (p-trend =0.02) for increased post-diagnosis BMI and decreased overall survival.⁶¹

When endometrial cancer was stratified by histologic type, Kristensen et al.⁹⁴ observed that underweight (at diagnosis BMI < 18.5 kg/m²) women living with Type I as well as Type II endometrial cancer had reduced survival relative to their normal weight (18.5-24.9 kg/m²) counterparts. The authors reported no difference in overall survival among Type I endometrial cancer survivors living with Class I (30-34.9 kg/m²), II (35-39.9 kg/m²) or III (> 40 kg/m²) obesity.⁹⁴ However, women living with Type II endometrial cancer were estimated to have reduced overall survival with increasing levels of obesity.⁹⁴ In a second study that stratified the study population by endometrial cancer type, no significant relationship between overall survival and continuous BMI was observed.⁷⁸

2.2.1.2. Endometrial Cancer-Specific Survival

The majority of studies that examined the association between obesity and endometrial cancer-specific survival^{5,38,42,55,59,60,64-66,71,75,77,79,84,85,88,89,91} have been conducted in an American context. Both categorical and continuous results from the Women's Health Initiative⁵⁹ and NIH-

AARP Study⁶⁰ suggest that increased pre-diagnosis BMI is negatively associated with endometrial cancer-specific survival. Specifically, endometrial cancer survivors living with Class I (30-34.9 kg/m²) or II/III (> 35 kg/m²) obesity had 2.06 (95% CI=1.01-4.2) and 2.23 (95% CI=1.09-4.54, p-trend =0.02) times the hazard of endometrial cancer-specific death compared to survivors with a BMI < 25 kg/m², respectively.⁵⁹ Moreover, the five-year and ten-year endometrial cancer-specific survival decreased with greater pre-diagnosis BMI in the NIH–AARP Study (five-year: p-trend =0.04, ten-year: p-trend =0.02).⁶⁰ Bjorge et al.,³⁸ Calle et al.⁶⁶ and Felix et al.⁷¹ also noted that elevated BMI was associated with decreased endometrial cancer-specific survival. In particular, Calle and colleagues⁶⁶ observed that, in comparison to survivors with a BMI of 18.5-24.9 kg/m², survivors living with a BMI of 25.0–29.9 kg/m² (HR=1.50, 95% CI=1.26–1.78) 30.0–34.9 kg/m² (HR=2.53, 95% CI=2.02–3.18), 35.0–39.9 kg/m² (HR=2.77, 95% CI=1.83–4.18) and ≥ 40.0 kg/m² (HR=6.25, 95% CI=3.75–10.42, p-trend <0.01) had reduced endometrial cancer-specific survival in the Cancer Prevention Study II. Conversely, Felix et al.⁷¹ noted that Type I but not Type II survivors living with obesity had worse endometrial cancer-specific survival compared to normal weight survivors (18.5–24.9 kg/m², p-trend <0.01).

In contrast, the Australian National Endometrial Cancer Study⁵ reported better endometrial cancer-specific survival was noted for those with a BMI of 25-29.9 kg/m² relative to normal weight survivors (18.5-24.9 kg/m²), even though no differences in endometrial cancer-specific survival was observed in this cohort for those with Class I (30-34.9 kg/m²) or II/III (> 35 kg/m²) obesity. Van Arsdale et al.⁹¹ also reported improved endometrial cancer-specific survival among endometrial cancer survivors with Class II (35-39.9 kg/m²) obesity compared to normal weight (18.5-24.9 kg/m²) survivors.⁹¹ However, when stratified by endometrial cancer type, this

association was only observed among women living with Type II endometrial cancer.⁹¹ Nine additional studies that assessed the association between pre/at-diagnosis BMI and endometrial cancer-specific survival failed to observe a statistically significant relationship.^{42,55,64,65,75,84,85,88,89} Univariate analyses and small sample sizes may have contributed to the null results seen in some of these studies.^{64,75,77}

2.2.1.3. Recurrence

The association between BMI and endometrial cancer recurrence was investigated by fifteen studies.^{63,67-69,72,74-76,78,82-84,86,90,92} In a French Multicenter Study, Canlorbe et al.⁶⁸ assessed the relationship between BMI and recurrence according to the European Society of Medical Oncology (ESMO) risk groups. The authors reported that in the high-risk group (n=51), endometrial cancer survivors with a BMI ≥ 35 kg/m² had worse disease-free survival compared to survivors with a BMI < 35 kg/m² (HR=12.5, 95% CI=3.1-51.3). No association was observed in the low and intermediate ESMO risk groups.⁶⁸ Moreover, none of the other studies that assessed the association between BMI and endometrial cancer recurrence observed a statistically significant relationship in the main^{63,67,75,76,82-84,90,92} or stratified analyses by endometrial cancer type,^{69,78} tumour histological subtype,⁷² or cancer stage.^{72,74,86}

2.2.2. Hyperglycemia and Diabetes

2.2.2.1. Overall Survival

Two studies previously assessed the association between pre-diagnosis blood glucose levels and overall survival among endometrial cancer survivors, reporting no statistically significant associations.^{70,80} Seventeen studies^{5,40-42,76,78-80,88,94,95,100-102,105,106,109} additionally

investigated the relationship between pre-/at-diagnosis diabetes and overall survival among women living with endometrial cancer. Six of these studies reported that endometrial cancer survivors with pre-diagnosis diabetes had between a 1.3- and 2.9-fold decrease in overall survival compared to survivors without diabetes.^{5,40-42,101,105} Olson et al.⁹⁵ and Ruterbusch et al.⁸⁸ also reported similar estimates for White endometrial cancer survivors, while only Olson et al.⁹⁵ observed a statically significant association among Black endometrial cancer survivors.

In the Health Surveys in North-Trondelag (HUNT) study, diabetes was assessed within strata of BMI ($< 25 \text{ kg/m}^2$, $\geq 25 \text{ kg/m}^2$).⁷⁹ Among participants with a BMI $< 25 \text{ kg/m}^2$, diabetes was associated with worse overall survival, while the association was not statistically significant for participants with a BMI $\geq 25 \text{ kg/m}^2$.⁷⁹ Four^{76,80,100,109} additional studies observed no association between pre/at-diagnosis diabetes and overall survival among endometrial cancer survivors. Moreover, in the Echantillon Généraliste de Bénéficiaires database, Larouzeé and colleagues¹⁰⁶ noted that survivors with diabetes had improved three-year survival compared to those without diabetes.

Two studies stratified the overall survival estimates by endometrial cancer type and an additional study was comprised of only Type II endometrial cancer survivors.^{78,94,102} Ko and colleagues⁷⁸ reported that diabetes among women living with Type I endometrial cancer was associated with a twofold decrease in overall survival while no association was observed in the Danish Gynecological Cancer Database.⁹⁴ Neither study observed a relationship between diabetes and overall survival among Type II endometrial cancer survivors.^{78,94} However, Burghau et al.¹⁰² observed a negative association between having a history of diabetes and overall survival amongst 108 uterine sarcomas and malignant mixed Mullerian tumour survivors (HR=2.81, 95% CI=1.13-6.98).

2.2.2.2. Endometrial Cancer-Specific Survival

Seventeen studies to date have focused on the relationship between diabetes and endometrial cancer-specific survival,^{5,40,42,55,71,75,77,79,84,88,91,95,103-105,107,108} while a single article has investigated this association with blood glucose concentrations specifically.³⁸ Neither the association between quintile of fasting blood glucose levels (mmol/L) or continuous glucose Z-score with endometrial cancer-specific survival in the Me-Can project reached statistical significance in the fully adjusted analyses.³⁸

In the Cancer Prevention Study-II, Campbell and colleagues¹⁰³ noted endometrial cancer survivors with diabetes had 1.33 (95% CI=1.08-1.65) times the hazard of endometrial cancer-specific death compared to survivors without diabetes. Ranc et al.¹⁰⁸ also observed decrease endometrial cancer-specific survival among Danish endometrial cancer survivors with diabetes (HR=1.32, 95% CI=1.14-1.52). Reports from four additional studies found survivors with diabetes experienced between a twofold and threefold decrease in endometrial cancer-specific survival compared to survivors without diabetes.^{5,79,104,105} Five studies^{40,42,75,77,84} observed no association between diabetes and endometrial cancer-specific survival, although three^{42,75,77} of these studies had limited number of participants with diabetes or endometrial cancer-specific deaths.

Six studies assessed the association with diabetes and endometrial cancer-specific survival in stratified analysis.^{55,71,88,91,95,107} In the SEER-Medicare database, reduced endometrial cancer-specific survival was observed among White cancer survivors with diabetes^{95,107} while there was insufficient evidence that Black endometrial cancer survivors with diabetes compared to those without diabetes had decreased endometrial cancer-specific survival.⁹⁵ Diabetes was not

associated with endometrial cancer-specific survival in White or Black survivors in the Henry Ford Health System tumour registry, yet the number of individuals with known diabetes status in this study was limited (diabetes, White: n=81, Black: n=78).⁸⁸ Decreased endometrial cancer-specific survival was noted for Type I but not Type II endometrial cancer survivors with diabetes,⁹¹ whereas null associations were observed for analysis stratified by histological subtype⁷¹ and cancer stage.⁵⁵

2.2.2.3. Recurrence

Six studies assessed the association between diabetes and endometrial cancer recurrence.^{75,76,78,84,90,100} Ko et al.⁷⁸ noted increased disease-free survival among Type I (HR=1.55, 95% CI=1.08-2.20) but not Type II endometrial cancer survivors with diabetes.⁷⁸ Conversely, four other studies^{75,76,84,100} observed insufficient evidence of an association between diabetes status and disease-free survival. Moreover, the odds of site-specific recurrence did not differ by diabetes status for endometrial cancer survivors treated at the Helsinki University Hospital, Finland.⁹⁰

2.2.3. Hypertension

2.2.3.1. Overall Survival

It remains unclear whether or not an association between hypertension and overall survival among endometrial cancer survivors exists. A 1.5- to 1.8-fold decrease in overall survival for endometrial cancer survivors with hypertension compared to those without this condition has been noted in two studies.^{41,101} However, six additional studies failed to observe either crude^{80,111} or adjusted^{40,63,70,110} associations between hypertension and overall survival in

this population. Furthermore, in stratified analyses, two studies^{88,95} reported no associations with hypertension and survival among White endometrial cancer survivors, while one study⁸⁸ observed improved overall survival with hypertension among Black endometrial cancer survivors. Hypertension was also associated with worse overall survival among Type II but not Type I endometrial cancer survivors in the Danish Gynecological Cancer Database.⁹⁴ A second study of 57 women with uterine carcinosarcomas (i.e. Type II) also observed a relationship between hypertension and reduced overall survival (HR=3.51, 95% CI=1.03-11.90).⁴³

2.2.3.2. Endometrial Cancer-Specific Survival

Bjorge et al.³⁸ failed to observe a relationship between continuous blood pressure Z-score, quintile of SBP, or quintile of DBP with endometrial cancer-specific survival, although there was some evidence of a linear trend for increasing quintile of DBP (p-trend <0.01).³⁸ Amongst studies that assessed the relations between endometrial cancer-specific survival and dichotomous hypertension diagnoses, six studies^{75,77,84} reported null associations including three that failed to observe statistically significant estimates in cancer type,⁹¹ cancer stage,⁵⁵ and race⁹⁵ stratified analyses. Only Ruterbusch et al.⁸⁸ reported a significant relationship between hypertension diagnosis and endometrial cancer-specific survival in which both White and Black endometrial cancer survivors with hypertension had improved cancer-specific survival.

2.2.3.3. Recurrence

Three studies^{63,75,84} have assessed the association between hypertension and endometrial cancer recurrence. Two of these studies did not observe a difference in disease-free survival between normotensive and hypertensive endometrial cancer survivors.^{75,84} In contrary, Akbayir

et al.⁶³ reported a protective association between hypertension and endometrial cancer recurrence among 194 endometrial cancer survivors in Turkey.⁶³

2.2.4. Dyslipidemia

2.2.4.1. Overall Survival

Dyslipidemia generally refers to elevated blood triglycerides, total cholesterol, low density lipoprotein cholesterol (LDL) and/or reduced HDL cholesterol levels.³⁹ While elevated blood triglycerides and reduced HDL cholesterol levels are specifically included in the metabolic syndrome criteria, only one study⁷⁰ has investigated the associations between triglycerides and total cholesterol with survival outcomes among endometrial cancer survivors, reporting no statistically significant associations.

2.2.4.2. Endometrial Cancer-Specific Survival

Limited evidence is available for the association between triglycerides and HDL cholesterol with endometrial cancer-specific survival. Three studies reported null associations between hypercholesterolemia,^{38,84} dyslipidemia⁵⁵ as well as hypertriglyceridemia^{38,55} with endometrial cancer-specific survival. Conversely, Van Arsdale et al.⁹¹ reported a null association between hyperlipidemia and endometrial cancer-specific survival among women living with Type I endometrial cancer but improved endometrial cancer-specific survival for Type II endometrial cancer survivors.

2.2.4.3. Recurrence

Only Matuso et al.⁸⁴ reported the association between dyslipidemia and endometrial cancer recurrence. The authors observed 94 recurrences among 665 endometrial cancer survivors treated at the Los Angeles County Medical Center, USA.⁸⁴ Approximately 25% of the survivors had hypercholesterolemia at the time of diagnosis, although no association between hypercholesterolemia and disease-free survival was noted in the univariable analysis (HR=1.04, 95% CI=0.66–1.64).⁸⁴

2.3. Literature Summary

Overall, there is some epidemiologic evidence that metabolic syndrome is associated with increased overall^{56,57} and endometrial cancer-specific survival.^{38,55} This literature has largely relied on self-reported cardiometabolic conditions and proxy metabolic syndrome component criteria. To date, the majority of studies have focused on the associations between pre- or at-diagnosis BMI and diabetes with survival outcomes among endometrial cancer survivors. Given that BMI does not differentiate between fat-free mass and fat mass, this measurement does not fully capture the complex physiology of excess body fat associated with cardiometabolic risk.^{14,112} Waist circumference is a strong indicator of visceral adiposity that has been positively associated with cardiometabolic disease and may better reflect the pathophysiology of excess body fatness.¹¹² Moreover, literature regarding the associations between hypertension, elevated triglycerides and cholesterol with recurrence and survival outcomes among endometrial cancer survivors remains sparse. Therefore, additional studies are needed to improve understanding regarding the associations between metabolic syndrome and its components with cancer recurrence and survival outcomes among endometrial cancer survivors.

CHAPTER THREE: METHODS

3.1. Study Design and Population

A prospective cohort of endometrial cancer survivors diagnosed between 2002 and 2006 who participated in a population-based case-control study in Alberta, Canada were followed until March 2019 for recurrence and survival outcomes.¹¹³ Survivors with histologically confirmed, invasive endometrial cancer were originally identified by the Alberta Cancer Registry, which has a case ascertainment rate of $\geq 95\%$.¹¹⁴ Women who were residents of Alberta, English speaking, between 30 and 80 years of age, able to complete an interview and diet history questionnaire, and had no prior history of cancer except non-melanoma skin cancer were eligible to participate. A total of 1,090 cases were identified and 900 cases met the abovementioned study inclusion criteria. Permission to contact cases from their referring physician was obtained for 808 women. Of those, 249 (30.8%) declined to participate, seven (0.9%) could not be contacted and three had complex atypical hyperplasia rather than endometrial cancer.¹¹³ A total of 549 endometrial cancer survivors were included in the original cancer case-control study. Nine additional participants were excluded from the cohort follow-up due to unsatisfactory baseline interviews (n=7), cancer misclassification (n=1) and being diagnosed with an ineligible endometrial cancer sub-type (neuroendocrine endometrial cancer, n=1). The remaining 540 participants were included in this analysis.

Ethical approval for the study was obtained from the Health Research Ethics Board of Alberta– Cancer Committee (Alberta Cancer Board), the Conjoint Health Research Ethics Board (University of Calgary) and the Health Research Ethics Board (University of Alberta). All participants provided informed, written consent at baseline that included the follow-up for this cohort study.

3.2. Data Collection

3.2.1. Participant Characteristics

Participants' demographic information, medical and medication use history, reproductive history, family history of cancer, and lifetime smoking habits were collected via an interviewer-administered questionnaire. Dietary caloric intake and lifetime alcohol consumption as well as lifetime physical activity participation were measured with the Canadian Diet Health Questionnaire-I and the Lifetime Total Physical Activity Questionnaire, respectively.^{115,116} Interviews occurred on average 22 weeks (± 11.5 weeks) following endometrial cancer diagnosis, 72% of interviews were completed within six months and 96% of participants completed the interview within 12 months of diagnosis. Interviewers were located in Calgary and Edmonton, Alberta and had extensive training in cognitive interviewing methods.¹¹⁷ These methods have been shown to improve participants' long-term recall.¹¹⁷ Detailed interviewer and coding manuals, as well as periodic monitoring of the interviews and regular meetings were in place for quality assurance purposes. Interview data were directly entered by the study staff into laptop computers using Blaise version 7 software (BLAISE®, Westat Corporation).

3.2.2. Anthropometric Measurements

All anthropometric measurements were taken at the time of the interview in the participants' homes. Direct measurements of the participants' height, waist and hip circumferences were taken to the first decimal point (cm) using a Lufkin measuring tape. Waists and hips were defined as the widest part of the abdomen and buttocks, respectively. Participants'

weight (kg) was measured using a digital scale. All measurements were taken in multiple and an average of the measurements were used.

3.2.3. Fasting Blood Draws

Blood draws were taken after a minimum eight-hour fast at any participating clinic in the Calgary, Capital, Chinook or Palliser Health Care Regions. Participants enrolled in the study prior to hysterectomy had additional blood samples collected just prior to their surgery (pre-surgical n=235). For participants enrolled after hysterectomy, fasting blood draws were completed at a separate laboratory clinic visit four to six weeks following surgery (post-surgical n=286). All participants had two 7-ml Vacutainer tubes containing ethylenediaminetetraacetic acid (EDTA; for plasma samples) and one 5-ml tube without additive (for serum samples) drawn. Blood samples were labelled with study IDs, date and time of the draw and transported on ice to the specimen biorepository at the Tom Baker Cancer Centre in Calgary, Alberta. Participants' samples were split between two ultra-low temperature (-80 °C) freezers for storage to safeguard against sample loss in the event of a malfunction.

Laboratory assays were conducted between February 2008 and July 2009 in Dr. David WC Lau's laboratory at the University of Calgary by a technician blinded to the case-control status of the samples. Blood samples were analysed in batches with a 2:1 ratio of control to case samples based on the date of blood collection. Additionally, each batch included four quality assurance specimens: 1) a randomly selected case sample from the batch, 2) a randomly selected control sample from the batch, 3) a pooled case-control sample, and 4) a pooled sample of clinical serum specimen from women with a similar age range as the participants. The analyses of relevant biomarkers for the metabolic syndrome were performed in duplicate with

colorimetric or absorbance-based assays (enzyme linked immunosorbent assay: ELISA) specific to the biomarker. The analyses of glucose (10009582; BioAssay Systems), triglycerides (10010303; BioAssay Systems), and HDL cholesterol (K614; Bio-Assay Systems) were completed with serum samples for all participants except three for whom serum samples were unavailable and plasma was used instead. The mean intra- and inter-batch coefficients of variation for fasting glucose were 3.7% and 4.6%, for triglycerides were 1.9% and 3.5%, and for HDL cholesterol were 4.3% and 5.5%, respectively.

3.2.4. Medical Chart Abstraction and Vital Status Assessment

Clinical information including date of diagnosis, cancer histology and stage, primary and adjuvant treatment(s) received, cancer recurrence and occurrence of a new primary cancer diagnosis were abstracted from medical charts between 2006 and 2019 by the Alberta Cancer Registry trained Health Record Technicians. Overall tumour, lymph node, metastasis (TNM) stage was coded according to the American Joint Committee on Cancer guidelines.¹¹⁸ Cancer grade was categorized by the FIGO standards and was assessed by the study pathologist Dr. Anthony Magliocco. Additional cancer characteristics including myometrial or vascular invasion, lymph nodes involvement, presence of distant metastasis and site were available for 510 participants with tissue samples. The Alberta Cancer Registry obtained vital status and underlying cause of death data through regular record linkages with Vital Statistics Alberta and Statistics Canada during study follow-up. Vital status information for participants who died in provinces other than Alberta was obtained by periodic data linkages between provincial cancer registries and the Canadian Mortality Database. Additionally, for participants who left Alberta

with unknown vital status, the date of leaving the province was considered the end of follow-up. Vital status was followed until death or March 20, 2019, whichever occurred first.

3.3. Data Analysis

3.3.1. Variable Definitions

Metabolic syndrome was defined with the harmonized definition using country- and sex-specific waist circumference criteria.⁴⁶ An alternate hypertension criterion was used since direct blood pressure measurements were not available from the original case-control study.

Participants who self-reported hypertension and/or hypertension medication use within one year of endometrial cancer diagnosis met this alternate criterion. Participants with partially missing data (n=27) who still met three or more metabolic syndrome components criteria were classified as having metabolic syndrome (n=7). Moreover, the number of metabolic syndrome components were grouped as zero or one, two or three, and four or five. Participants with incomplete metabolic syndrome data were assigned the lowest possible number of metabolic syndrome components based on the available data.

The medication alternative harmonized metabolic syndrome definition was also assessed. In this alternative definition, participants taking medication for diabetes or triglycerides within a year of diagnosis were also considered to meet the fasting blood glucose and blood triglycerides criteria, respectively. Specifically, participants with fasting blood glucose levels ≥ 100 mg/dL or taking medication for diabetes (e.g. acarbose, acetohexamide, chlorpropamide, gliclazide, glyburide, insulin, metformin hydrochloride, tolbutamide) within a year of the diagnosis date met the alternate glucose criterion. Women who took medication for gestational diabetes that did not persist after the end of pregnancy (n=2) were excluded from this alternative criterion. Moreover,

survivors with blood triglycerides ≥ 150 mg/dL or using medication intended to lower LDL/Triglycerides (e.g. atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, gemfibrozil) within a year of the reference date met the blood triglycerides criterion. Since the year of hypertriglyceridemia diagnosis was not recoded, the year of high cholesterol diagnosis and duration of medication use was used as a proxy.

Endometrial cancer tumour and treatment characteristics were categorized into overall TNM stage (I, II, III/IV), FIGO grade (I/II, III, unknown/non-applicable) and primary cancer treatment(s). Women with incomplete overall cancer stage (n=8) were coded as stage I based on available lymph node inclusion and metastatic information. FIGO tumour grade I/II were those with less than 50% solid growth pattern, while grade III tumours had more than 50% solid growth pattern. Tumours not classically graded (i.e. those within polyps, carcinosarcomas etc.) were coded as non-applicable while endometrial cancer survivors without tissue review (i.e. did not provide consent or did not have hysterectomy) had unknown tumour grade. Non-applicable and unknown tumour grades were combined and treated as a separate category to grade I/II and III. Participants were categorized by the type of primary cancer treatment(s) received: 1) hysterectomy at baseline, 2) hysterectomy and completed chemotherapy, 3) hysterectomy and completed radiation therapy, 4) hysterectomy and at least two types of adjuvant treatments (chemotherapy, radiation and/or hormone therapy), and 5) missing treatment. Of note, no participants received hormone therapy without also receiving chemotherapy or radiation therapy. Missing treatment was defined as any primary treatment (hysterectomy, chemotherapy, radiation or hormonal therapy) not received because of health complications, participants refusing treatment or participants not completing treatment. A new primary cancer was considered any

metachronous new primary cancer recoded by the Alberta Cancer Registry six or more months following initial endometrial cancer diagnosis.

Participants baseline demographic and medical history information were defined as follows: baseline age (years), measured BMI (continuous; kg/m²), marital status (married/common law, other), race (White, non-White), highest education attained (\leq high school, non-university certificate, university degree), residency (rural, urban), parity (null, one-two, \geq two pregnancies \geq 20 weeks gestation), menopausal status (pre- or peri-menopausal, post-menopausal), hormone treatment status (ever, never), first degree family history of uterine (Not otherwise specified (NOS)) or colorectal cancer (yes, no/missing), lifetime recreational physical activity (metabolic-equivalent task [MET]-hours/week/year), lifetime alcohol consumption (grams/year), dietary caloric intake (total daily food energy intake (kcal) excluding implausible values (i.e. $<$ 600 kcal or $>$ 5000 kcal)), smoking status (ever, never: smoked 100 cigarettes in their life), smoking pack years for current and ex-smokers was defined as: (number of cigarettes smoked daily)*(duration of smoking in years)/ 20, and the number of major comorbidities diagnosed before endometrial cancer diagnosis (zero, one, \geq two of any of the following: angina pectoris, pulmonary embolism, myocardial infarction, stroke, thrombosis). Type II diabetes, high cholesterol, hypertension or other free text comorbidity responses were not included in the variable created for the number of major comorbidities.

Cancer recurrence was considered as any primary site recurrence or progression, lymph node recurrence or metastasis of the primary cancer noted in the participants medical record. Deaths attributable to endometrial or uterine (NOS) cancer based on the International Classification of Diseases for Oncology, Third Edition (C54-C55) were categorized as endometrial cancer-specific deaths.¹¹ Survival time was calculated as the time from the initial

diagnosis of endometrial cancer until death or March 20, 2019, whichever occurred first. The endpoints for disease-free survival, overall survival and endometrial cancer-specific survival were the first recurrence or death from any cause, death from any cause and death attributable to endometrial cancer, respectively. The time to recurrence was defined as the time from initial endometrial cancer diagnosis to the date of first recurrence, all other events were censored.

3.3.2. Statistical Analyses

Descriptive statistics were used to assess the distribution and/or proportion of metabolic syndrome, metabolic syndrome components, covariates and outcome events. Dietary caloric intake and race information were not included in multivariable analysis because of the reduction to the analytical sample size due to missing/implausible information (n=489) and a nearly homogeneous sample, respectively. Cox proportional hazards regression models were used to estimate multivariable-adjusted HR and 95% CI for the associations between metabolic syndrome (yes, no), the number of metabolic syndrome components (zero-one, two-three, four-five) and individual metabolic syndrome components with disease-free survival, overall survival and recurrence outcomes. Fine and Gray competing risk models were used for the endometrial cancer-specific survival outcome. The proportional hazards assumption was evaluated with visual and statistical assessments of Schoenfeld residuals and Wald-tests for the interaction of the exposure variable and time in the Cox models and Fine and Gray models, respectively. Models that did not satisfy the proportional hazards assumption were further assessed in an exploratory five- and ten-year restricted time analyses.

The individual metabolic syndrome components tested were: waist circumference (≥ 88 cm, per five cm), fasting blood glucose levels (≥ 100 mg/dL, per five mg/dL), blood triglycerides

(≥ 150 mg/dL, per five mg/dL), HDL cholesterol (< 50 mg/dL, per five mg/dL), and self-reported hypertension (yes, no). Continuous exposures were centered at dichotomous cut-points. Endometrial cancer stage, grade, primary cancer treatment(s), baseline age (years) and non-linear age (age²) variables were forced into the model based on *a priori* biological plausibility. Additionally, disease-free survival models were adjusted for the time to first new primary cancer, overall survival models were adjusted for the time to first recurrence/new primary cancer, and endometrial cancer-specific survival models were adjusted for the time to first recurrence. Finally, all metabolic syndrome component models were mutually adjusted for the other metabolic syndrome risk factors.

All other potential confounding variables were included in preliminary models and removed sequentially via backwards elimination. Only variables that meaningfully changed the estimate of the association of interest remained in the models. A change greater than roughly ten percent was generally considered meaningful. The number of major comorbidities (zero, one, \geq two) was included in metabolic syndrome models for disease-free and overall survival outcomes while continuous BMI (kg/m²) was included in all multivariable-adjusted models. There was insufficient evidence that lifetime alcohol consumption, marital status, hormone treatment status, parity, menopausal status, smoking pack years, highest education attained, residency, or first-degree family history of uterine (NOS) or colorectal cancer confounded the associations of interest. Nor was there evidence that fasting blood insulin levels (pM/ml) confounded the associations in fasting blood glucose models.

Potential modification of the associations between metabolic syndrome and its components with overall and disease-free survival by BMI (kg/m²) and lifetime recreational physical activity (MET-hours/week/year) were assessed with Wald-tests in hierarchically well-

formulated models. Associations with statistically significant effect modification were presented by median groups.

Sample size for this analysis was predetermined by the number of available cases; hence, the final analytical sample included participants with complete metabolic syndrome data (n=520) and complete metabolic syndrome component data (n=513). Statistical significance was set at five percent and all analyses were performed using Stata software version 15.1 (StataCorp LLC, College Station, TX).

CHAPTER FOUR: RESULTS

This chapter includes the manuscript from this thesis which addresses the relationship between the harmonized metabolic syndrome criteria and its components with disease-free survival, overall survival, endometrial cancer-specific survival and recurrence among endometrial cancer survivors from the Alberta Endometrial Cancer Cohort Study.

The citation for the manuscript is:

Kokts-Porietis RL, McNeil J, Nelson GS, Courneya KS, Cook LS, Friedenreich CM. Prospective Cohort Study of Metabolic Syndrome and Endometrial Cancer Survival. *Gynecol Oncol*. 2020. <https://doi.org/10.1016/j.ygyno.2020.06.488>

4.1. Prospective Cohort Study of Metabolic Syndrome and Endometrial Cancer Survival

4.1.1. Abstract

Objective: Comorbidities are known to increase endometrial cancer risk, but the separate and combined impact of these risk factors on endometrial cancer survival remains unclear. This study aimed to determine the associations between metabolic syndrome and its components with disease-free survival, overall survival, endometrial cancer-specific survival and recurrence among endometrial cancer survivors.

Methods: Cases from a population-based case-control study who were diagnosed with primary endometrial cancer between 2002 and 2006 in Alberta, Canada were followed until death or March 20, 2019. Baseline in-person interviews, direct anthropometric measurements and fasting blood samples were used to assess metabolic syndrome (presence of ≥ 3 of the following: waist circumference ≥ 88 cm, fasting blood glucose ≥ 100 mg/dL, triglycerides ≥ 150 mg/dL, high-density lipoprotein cholesterol < 50 mg/dL and self-reported hypertension). Cox proportional hazards regression and Fine and Gray competing risk models were used to estimate multivariate-adjusted hazard ratios (95% CI) for these associations.

Results: Among 540 endometrial cancer survivors, 325 had metabolic syndrome at diagnosis and 132 had a recurrence and/or died during the median 14.2 years of follow-up (range: 0.3-16.5 years). In multivariable analyses, being diagnosed with metabolic syndrome (HR=1.98, 95% CI=1.07-3.67) and having an elevated waist circumference (≥ 88 cm; HR=2.12, 95% CI=1.18-3.80; HR_{per 5 cm}=1.21, 95% CI=1.07-1.36) were associated with worse overall survival. Additionally, increasing waist circumference (per 5 cm) was also associated worse with disease-free survival (HR_{per 5 cm}=1.11, 95% CI=1.00-1.24).

Conclusion: The metabolic syndrome, in particular central adiposity, were associated with worse overall and disease-free survival in endometrial cancer survivors.

Keywords: Endometrial Cancer, Survival, Metabolic Syndrome, Co-morbidities

4.1.2. Introduction

Endometrial cancer is the sixth most frequently diagnosed cancer among women worldwide.¹ In 2018, the International Agency for Research on Cancer (IARC) estimated that 382,069 new cases of endometrial cancer and 89,929 endometrial cancer-specific deaths occurred globally¹ with the highest rates occurring in North America and Central and Eastern Europe.^{1,9} Between 2005 and 2015, uterine cancer mortality rates increased 2.0% annually in Canada and 1.9% annually between 2011 and 2015 in the USA, making endometrial cancer one of the few cancer types with both increasing incidence and mortality rates.^{11,12}

Obesity and diabetes have been previously identified as major risk factors for endometrial cancer, whereas physical activity is thought to reduce endometrial cancer risk.^{9,36,39} These risk factors may also be associated with endometrial cancer recurrence and mortality.^{5,41,99} Specifically, obesity is an established risk factor for endometrial cancer survival, with convincing biological plausibility through metabolic disruptions, hormonal and growth factor imbalances, unopposed estrogens released by adipose tissue¹⁴ and chronic inflammation that prompts tumour growth.^{9,14-16} Furthermore, among cancer survivors, obesity has been associated with reduced responses to standard treatments, higher rates of metastatic disease and poorer prognoses compared to normal weight individuals.¹⁶ Diabetes and hypertension may also increase cancer-specific mortality and all-cause mortality in this population.^{5,40-42,94} However, the combined impact of these comorbidities on endometrial cancer survival outcomes remains unclear.

Metabolic syndrome is defined as the clustering of cardiovascular and metabolic disease risk factors including central adiposity, hypertension, hyperglycemia, elevated triglycerides and low high-density lipoprotein (HDL) cholesterol.⁴⁶ Women with metabolic syndrome are

estimated to have a roughly twofold elevation in endometrial cancer risk compared to those without.^{3,4,39,52,58,119} Despite biological plausibility that metabolic syndrome may also be associated with endometrial cancer recurrence and survival,^{14,54} limited information on survival outcomes currently exists. Therefore, the objective of the current study was to determine the association between metabolic syndrome and its components, defined by harmonized criteria⁴⁶ with disease-free survival, overall survival, endometrial cancer-specific survival and recurrence among endometrial cancer survivors.

4.1.3. Methods

4.1.3.1. Study Design

The Alberta Endometrial Cancer Cohort Study is a follow-up of women diagnosed with histologically confirmed, invasive, primary endometrial cancer between 2002 and 2006 who participated in a population-based case-control study in Alberta, Canada.¹¹³ Full details of the case-control study have been previously reported.^{58,113} Briefly, 549 (61.0%) cases identified through the Alberta Cancer Registry who were residents of Alberta, English speaking, between 30-80 years of age, able to complete an interview and diet history questionnaire, and had no prior history of cancer except non-melanoma skin cancer, were included. Nine participants were excluded from this analysis due to unsatisfactory baseline interviews (n=7), cancer misclassification (n=1) and being diagnosed with an ineligible endometrial cancer sub-type (*neuroendocrine* endometrial cancer; n=1). The remaining 540 participants (60.0%) were included in this study. Ethical approval for the study was obtained from the Alberta Cancer Board, the Conjoint Health Research Ethics Board (University of Calgary) and the Health

Research Ethics Board (University of Alberta). All participants provided informed, written consent.

4.1.3.2. Data Collection

Participant's demographic information, menstrual and reproductive history, hormone use history, medical history, medication use information, family history of cancer, and lifetime smoking habits were collected via an interviewer-administered questionnaire following endometrial cancer diagnosis (mean 22 ± 11.5 weeks).¹¹³ Lifetime alcohol consumption and lifetime physical activity participation were measured with the Canadian Diet Health Questionnaire-I and the Lifetime Total Physical Activity Questionnaire (LTPAQ), respectively.^{115,116} At the time of the interviews, standardized anthropometric measurements including the participant's height, weight and waist circumferences were taken in triplicate and the average was recorded as the final measurement.¹¹³ Participants fasted for at least eight hours before blood samples were collected either pre-hysterectomy or four-six weeks post-hysterectomy if blood could not be drawn pre-surgery (pre-surgical n=235; post-surgical n=286). Blood samples were processed into blood fractions (serum, plasma, red blood cells, and buffy coat), frozen at -80°C within 24 hours of collection and stored in biorepository at the Tom Baker Cancer Centre, Calgary, Alberta.¹²⁰

4.1.3.3. Follow-up and Outcome Ascertainment

Clinical information including date of diagnosis, cancer histology and stage, primary and adjuvant treatment(s) received, cancer recurrence and occurrence of a new primary cancer diagnosis were abstracted from medical charts by the Alberta Cancer Registry trained Health

Record Technicians. Overall stage (tumour, lymph node, metastasis (TNM)) was coded according to the American Joint Committee on Cancer guidelines.¹¹⁸ Women with incomplete overall cancer TNM stage (n=8) were coded based on available lymph node inclusion and metastatic information. Cancer grade (International Federation of Gynecology and Obstetrics) and tumour histology (endometrioid, mixed cell, serous, clear cell, mucinous adenocarcinoma, carcinosarcoma, adenosarcoma and other) were additionally available via tissue samples, as previously described.¹²⁰ Vital status and underlying cause of death data were provided by Vital Statistics Alberta and Statistics Canada, respectively. Vital status information from participants who died in provinces other than Alberta were obtained from data linkages between provincial cancer registries.

For the purpose of this analysis, cancer recurrence was considered as any primary site recurrence or progression, lymph node recurrence or metastasis of the primary cancer noted in the medical record. Deaths that were attributable to endometrial or uterine (NOS) cancer were categorized as endometrial cancer-specific deaths. Survival time was calculated as the time from the initial diagnosis of endometrial cancer until death or March 20, 2019, whichever occurred first. Disease-free survival was defined as the time from diagnosis to the first recurrence or death from any cause, while overall survival was the time from diagnosis until the time of death from any cause.

4.1.3.4. Statistical Analyses

Metabolic syndrome was categorized with the harmonized definition using country- and sex-specific waist circumference criteria.⁴⁶ Participants with three or more of the following risk factors were classified as having metabolic syndrome: waist circumference ≥ 88 cm, fasting

blood glucose levels ≥ 100 mg/dL, blood triglycerides ≥ 150 mg/dL, HDL cholesterol < 50 mg/dL, or self-reported hypertension and/or hypertension medication use within one year of endometrial cancer diagnosis. The alternate hypertension criterion was used as direct blood pressure measurements were not available from the original case-control study.^{46,58} Twenty-seven participants were missing one or more metabolic syndrome components (missing: waist circumference n=4; fasting blood glucose levels n=20; blood triglycerides n=23; HDL cholesterol n=20). Participants with partial missing data who still met three or more metabolic syndrome components criteria were classified as having metabolic syndrome (n=7).

Cox proportional hazards regression models were used to estimate multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for the associations between metabolic syndrome (yes, no), the number of metabolic syndrome components (0-1, 2-3, 4-5) and individual metabolic syndrome components with disease-free survival, overall survival and recurrence outcomes. Fine and Gray competing risk models were used for the endometrial cancer-specific survival outcome. The individual metabolic syndrome components tested were: waist circumference (≥ 88 cm, per 5 cm), fasting blood glucose levels (≥ 100 mg/dL, per 5 mg/dL), blood triglycerides (≥ 150 mg/dL, per 5 mg/dL), HDL cholesterol (< 50 mg/dL, per 5 mg/dL), and self-reported hypertension (yes, no). Continuous exposures were centred at dichotomous cut-points. All models were hierarchically well-formulated and adjusted for endometrial cancer stage (I, II, III/IV), grade (I/II, III, unknown/non-applicable), primary cancer treatment(s) (hysterectomy, hysterectomy/chemotherapy, hysterectomy/radiation, hysterectomy/chemotherapy/radiation and/or hormone therapy, missing treatment), baseline age (years) and non-linear age (age²) based on *a priori* biological plausibility. Additionally, disease-free survival models were adjusted for the time to first new primary cancer, overall survival models were

adjusted for the time to first recurrence/new primary cancer, and endometrial cancer-specific survival models were adjusted for the time to first recurrence. Moreover, all metabolic syndrome component models were mutually adjusted for the other metabolic syndrome risk factors.

Additional confounding variables were identified via backwards elimination. Continuous BMI (kg/m^2) was included in all multivariable-adjusted models while there was only evidence that the number of major comorbidities (0, 1, ≥ 2 of any of the following: angina pectoris, pulmonary embolism, myocardial infarction, stroke, thrombosis) confounded the association between metabolic syndrome with disease-free and overall survival. There was insufficient evidence that lifetime alcohol consumption (grams/year), marital status (married/common law, other), hormone replacement treatment status (ever, never), parity (null, 1-2, ≥ 2) menopausal status (pre or peri-menopausal, post-menopausal), smoking pack years defined as: (number of cigarettes smoked daily)*(duration of smoking in years)/ 20, highest education attained (\leq high school, non-university certificate, university degree), residency (rural, urban) or first degree family history of uterine (NOS) or colorectal cancer (yes, no/missing) confounded the associations of interest. Nor was there evidence that fasting blood insulin levels ($\mu\text{M}/\text{ml}$) confound associations in fasting blood glucose models.

Potential modification of the association between metabolic syndrome and its components with overall and disease-free survival by BMI (kg/m^2) and lifetime recreational physical activity (metabolic-equivalent task [MET]-hours/week/year) were assessed with Wald-tests. Associations with statistically significant effect modification are presented by median groups.

The proportional hazards assumption was evaluated with visual and statistical assessments of Schoenfeld residuals and Wald-tests for the interaction of the exposure variable

and time in the Cox models and Fine and Gray models, respectively. Results are not presented for the analyses that did not satisfy the proportional hazards assumption. Sample size for this analysis was predetermined by the number of available cases; hence, the final analytical sample included participants with complete metabolic syndrome data (n=520) and complete metabolic syndrome component data (n=513; **Figure 2**). All analyses were performed using Stata software version 15.1 (StataCorp LLC. College Station, TX).

4.1.4. Results

Among the 540 endometrial cancer survivors, 325 (60.2%) had metabolic syndrome at the time of endometrial cancer diagnosis and 132 had a recurrence and/or died during the median 14.2 years of follow-up (range: 0.3-16.5 years). Specifically, there were 73 recurrences, 50 endometrial cancer-specific deaths and 111 overall deaths during follow-up. Most participants were diagnosed with endometrioid histology (81.5%), low stage and grade endometrial cancer (Stage I: 77.8%; Grade I: 53.3%), had hysterectomy as part of primary treatment (97.6%) and a mean age of 59.1 (SD 9.3) years (**Table 3**).

In the multivariable-adjusted analyses, a statistically significant association between metabolic syndrome and worse overall survival (HR=1.98, 95% CI=1.07-3.67) was observed (**Table 4**). The association with metabolic syndrome and endometrial cancer-specific survival did not reach statistical significance (HR=1.80, 95% CI=0.75-4.33). Likewise, there was insufficient evidence of associations between metabolic syndrome with disease-free survival or endometrial cancer recurrence in these analyses (**Table 4**).

For the individual components of metabolic syndrome, waist circumference (≥ 88 cm) was associated with statistically significantly worse overall survival (HR=2.12, 95% CI=1.18-

3.80) but not disease-free survival (HR=1.66, 95% CI=0.98-2.79), endometrial cancer-specific survival (HR=2.14, 95% CI=0.73-6.31) or recurrence (HR=1.21, 95% CI=0.58-2.52). Positive linear dose-response relationships were observed per 5 cm increase in waist circumference with overall survival (HR_{per 5 cm}=1.21, 95% CI=1.07-1.36) and disease-free survival (HR_{per 5 cm}=1.11, 95% CI=1.00-1.24) in the multivariable-adjusted models.

Lifetime recreational physical activity prior to diagnosis (MET-hours/week/year) significantly modified (p-value<0.05) the associations between metabolic syndrome, waist circumference (per 5 cm), HDL cholesterol (per 5 mg/dL) and hypertension with overall survival as well as the association between HDL cholesterol (per 5 mg/dL) and disease-free survival in the multivariable-adjusted models. Specifically, among endometrial cancer survivors with lower lifetime recreational physical activity (<9.7 MET-hours/week/year), those with metabolic syndrome had worse overall survival (HR=2.45, 95% CI=1.19-5.05) compared to participants without the syndrome. No association with metabolic syndrome and overall survival was observed amongst survivors with higher recreational physical activity (for ≥9.7 MET-hours/week/year, HR=0.88, 95% CI=0.46-1.69). Increasing waist circumference was associated with worse overall survival for women with lower (HR_{per 5 cm}=1.30, 95% CI=1.13-1.49), as well as higher (HR_{per 5 cm}=1.16, 95% CI=1.02-1.32) lifetime recreational physical activity. Improved overall survival (HR_{per 5 mg/dL}=0.85, 95% CI=0.76-0.96) and disease-free survival (HR_{per 5 mg/dL}=0.85, 95% CI=0.76-0.94) was observed for greater HDL cholesterol levels (per 5 mg/dL) among women with lower physical activity. Lastly, hypertension was associated with worse overall survival (HR=1.80, 95% CI=1.02-3.18) among endometrial cancer survivors with lower lifetime recreational physical activity.

Finally, the models assessing the number of metabolic syndrome components and fasting blood glucose did not satisfy the proportional hazard assumption and are therefore not reported.

4.1.5. Discussion

In the current study, endometrial cancer survivors with metabolic syndrome had approximately a twofold decrease in overall survival compared to study participants who did not have this syndrome. Our findings also suggest that metabolic syndrome may be associated with worse endometrial cancer-specific survival although the association was not statistically significant in the multivariable-adjusted model. There was insufficient evidence of an association between metabolic syndrome and disease-free survival or endometrial cancer recurrence in the present study. Finally, of the individual metabolic syndrome components, only waist circumference was observed to be associated with survival outcomes.

To our knowledge, this investigation is the first study among endometrial cancer survivors to use a standardized definition of metabolic syndrome to test its association with survival outcomes as well as the first conducted in a North American context. Our findings are generally consistent with prior literature that observed worse overall and endometrial cancer-specific survival with metabolic syndrome among endometrial cancer survivors. Ni and colleagues⁵⁶ used a study-specific definition of metabolic syndrome (presence of \geq three of the following components: history of Type 2 diabetes, medically-treated hypertension, diagnosed or treated hyperlipidemia and either waist circumference \geq 80 cm or BMI \geq 28 kg/m²) to assess the association with all-cause mortality among histologically confirmed endometrial cancer cases (n=385; n=64 deaths) in China. The authors noted that endometrial cancer survivors with the study-specific metabolic syndrome had 6.65 (95% CI=1.93-47.79) times the hazard of all-cause

mortality compared to those without metabolic syndrome.⁵⁶ The same study-specific metabolic syndrome definition used by Ni et al.,⁵⁶ was also associated with worse overall survival among 139 Chinese non-endometrioid uterine cancer patients.⁵⁷ Within the Metabolic Syndrome and Cancer Project (Me-Can), metabolic syndrome was associated with 1.56 (95% CI=1.32-1.84) times the hazard of uterine cancer-specific mortality per one-unit increment of composite metabolic syndrome Z-score.³⁸

In the current study, women with a waist circumference above 88 cm had approximately half the overall survival compared to women with a waist circumference below 88 cm. Furthermore, for every additional 5 cm increase in waist circumference above 88 cm, women were estimated to have a 21% decrease in overall survival and an 11% decrease in disease-free survival. Our findings also suggest that greater waist circumference may also be associated with worse disease-free survival, endometrial cancer-specific survival and recurrence although these associations were attenuated by BMI. Previous research has shown that both waist circumference and BMI are positively correlated with estrogen levels in endometrial cancer survivors, unopposed estrogens released by adipose tissue is a known risk factor of endometrial cancer tumour proliferation.^{14,121} The underlying mechanism of pathogenesis via adipose tissue and elevated estrogen concentrations may partially explain why the associations between waist circumference with disease-free survival, endometrial cancer-specific survival and recurrence were attenuated by BMI. However, waist circumference is a strong indicator of central adiposity which has been positively associated with additional biological mechanisms related to hyperglycemia, dyslipidemia, hyperinsulinemia and systemic inflammation that may also drive tumour pathogenesis.¹⁴ Previous findings from the Nurses' Health Study observed that women had a 34% (95% CI=23%–39%) increase in all-cause mortality and a 18% (95% CI=9%–28%)

increase in obesity-related (colon cancer, breast cancer, pancreatic cancer, uterine, ovarian, and kidney cancer) cancer mortality per ~10 cm increase in waist circumference in multivariable adjusted models including adjustments for BMI.¹²²

To our knowledge, the present study is the first to assess whether lifetime physical activity prior to diagnosis impacts the relationship between metabolic syndrome at diagnosis and its components with survival outcomes among endometrial cancer survivors. Our findings suggest that women with greater lifetime recreational physical activity participation do not experience the same harmful associations between metabolic syndrome, waist circumference, and hypertension with overall survival compared to those with lower amounts of lifetime physical activity participation. A protective association was also observed with increasing HDL cholesterol and survival outcomes amongst women with lower lifetime physical activity participation. These findings add to current literature that suggests cancer survivors with greater physical activity participation experience better survival, although specific estimates among endometrial cancer survivors are limited.^{19,123} Arem and colleagues previously reported an association between pre-diagnosis recreational moderate-to-vigorous-intensity physical activity and lower overall 5-year mortality, but not 10-year mortality, endometrial cancer-specific mortality or all-cause mortality in the Women's Health Initiative⁵⁹ and the National Institutes of Health- American Association of Retired Persons (NIH–AARP) Diet and Health Study.⁶⁰

This study has several key strengths, including a substantial study follow-up time of nearly 17 years. Participants were representative of the larger endometrial cancer survivor population living in Alberta since cases were originally identified through the Alberta Cancer Registry which has a $\geq 95\%$ case ascertainment rate¹¹⁴ of histologically confirmed, endometrial cancer cases. Additionally, data linkage with national and provincial registries ensured that

comprehensive vital status data were captured. Direct measurements of most of the metabolic syndrome components, particularly the anthropometric measures and blood assays, were assessed in multiple to provide valid and reliable data. Finally, covariates were extensively measured during the in-person interviews and interviewers were trained with cognitive interview methods.

Some limitations must be acknowledged in the current study. Primarily, the small sample size and limited number of events may have hindered the ability of the current study to observe statistically significant associations. Particularly the estimates of endometrial cancer-specific survival and recurrence should be interpreted with caution because of the small number of events in the dichotomized analyses. Larger studies are thus needed to confirm and contribute to our findings. Moreover, some results could not be presented because the proportional hazard assumptions were violated. The metabolic syndrome was only assessed at the time of cancer diagnosis and may not represent an individual's health status for the entire follow-up period. Consequently, the prevalence of metabolic syndrome may have been underestimated in this cohort. However, previous findings from the Atherosclerosis Risk in Communities Study suggest that, for the majority of individuals (76%), the severity of metabolic syndrome increases over time.¹²⁴ Moreover, medical treatment of individual risk factors failed to reduce the severity of metabolic syndrome during the follow-up period in the Atherosclerosis Risk in Communities Study.¹²⁴ Therefore, women in the current study likely did not have improved metabolic health status during follow-up if they had metabolic syndrome or some of its components at baseline. Finally, given that the study participants represent a largely homogenous group of White (93.9%), well educated (67.2% \geq high school education), endometrial cancer survivors living in

Alberta, the current findings may not be generalizable to all populations including racial-ethnic minority populations in Canada.

Given that endometrial cancer mortality rates are currently rising^{11,12} and women living with endometrial cancer have greater amounts of diagnosed, undiagnosed or undertreated cardiometabolic risk factors compared to the general population,⁶ identifying opportunities to intervene is becoming increasingly important. In this study, the results suggest that the association between metabolic syndrome and endometrial cancer survival is largely explained by central adiposity. Moreover, endometrial cancer survivors with greater lifetime recreational physical activity had improved survival despite metabolic syndrome risk factors compared to those with lower lifetime physical activity. Additional research is needed to confirm these results and improve our understanding of the role of physical activity and other lifestyle factors in modifying the metabolic syndrome and survival associations among endometrial cancer survivors.

4.1.6. Declarations

Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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Author Contribution

Renée L. Kokts-Porietis: Conceptualization, Methodology, Formal analysis, Writing - Original Draft, Writing - Review & Editing. **Jessica McNeil:** Conceptualization, Writing - Review & Editing, Supervision. **Gregg Nelson:** Conceptualization, Writing - Review & Editing, Supervision. **Kerry S. Courneya:** Conceptualization, Methodology, Funding acquisition, Investigation, Project administration, Writing - Review & Editing. **Linda S. Cook:** Conceptualization, Methodology, Funding acquisition, Investigation, Project administration, Writing - Review & Editing. **Christine M. Friedenreich:** Conceptualization, Methodology, Investigation, Data Curation, Funding acquisition, Writing - Review & Editing, Supervision.

4.1.7. Tables and Figures

Table 3. Participant Characteristics of the Alberta Endometrial Cancer Cohort by Vital Status, Alberta, Canada (N=540)

Characteristics (Mean (SD); N (%))	All (n=540)	Alive (n=429)	Disease-Free Survival (n=132)	Overall Deaths (n=111)	Cancer-Specific Deaths (n=50)
Age at diagnosis (years)	59.1 (9.3)	57.6 (8.8)	63.5 (9.8)	64.9 (9.2)	62.7 (7.7)
Highest Education					
High school diploma	177 (32.8)	134 (31.2)	50 (37.9)	43 (38.7)	15 (30.0)
Non-university certificate	249 (46.1)	198 (46.2)	61 (46.2)	51 (46.0)	26 (52.0)
University degree	114 (21.1)	97 (22.6)	21 (15.9)	17 (15.3)	9 (18.0)
Married/common-law	372 (68.9)	300 (69.9)	84 (63.6)	72 (64.9)	30 (60.0)
White	507 (93.9)	401 (93.5)	123 (93.2)	106 (95.5)	46 (92.0)
Urban residence	363 (67.2)	300 (69.9)	77 (58.3)	63 (56.8)	32 (64.0)
Parity					
0	111 (20.6)	91 (21.2)	23 (18.70)	20 (18.0)	8 (16.0)
1-2	248 (45.9)	208 (48.5)	45 (36.59)	40 (36.0)	21 (42.0)
>2	181 (33.5)	130 (30.3)	55 (44.72)	51 (46.0)	21 (42.0)
Post-Menopausal	415 (76.9)	312 (72.7)	116 (87.9)	103 (92.8)	45 (90.0)
Histology					
Endometrioid	440 (81.5)	366 (85.3)	91 (68.9)	74 (66.7)	28 (56.0)
Non-Endometrioid	100 (18.5)	63 (14.7)	41 (31.1)	37 (33.3)	22 (44.0)
Overall AJCC stage					
I	428 (79.3)	362 (84.4)	78 (59.1)	66 (59.5)	17 (34.0)
II	69 (12.8)	49 (11.4)	25 (18.9)	20 (18.0)	11 (22.0)
III/IV	43 (8.0)	18 (4.2)	29 (22.0)	25 (22.5)	22 (44.0)
FIGO Grade					
I	288 (53.3)	250 (58.3)	47 (35.6)	38 (34.2)	10 (20.0)
II	125 (23.2)	102 (23.8)	27 (20.5)	23 (20.7)	11 (22.0)
III	73 (13.5)	41 (9.6)	36 (27.3)	32 (28.8)	18 (36.0)
Not Reported/Missing	54 (10.0)	36 (8.4)	22 (16.7)	18 (12.2)	11 (22.0)
Primary treatment					
Hysterectomy	527 (97.6)	422 (98.4)	120 (90.9)	105 (94.6)	46 (92.0)
Chemotherapy	45 (8.3)	26 (6.1)	20 (15.2)	19 (17.1)	17 (34.0)
Hormone therapy	6 (1.1)	6 (1.4)	2 (1.5)	0 (0)	0 (0)

Radiation therapy	168 (31.1)	124 (28.9)	52 (39.4)	44 (39.6)	21 (42.0)
Not Received	33 (6.1)	16 (3.7)	25 (18.9)	17 (15.3)	12 (24.0)
New Primary Cancer	92 (17.0)	63 (14.7)	33 (25.0)	29 (26.1)	2 (4.0)
Family History of Uterine or Colorectal Cancer	88 (16.3)	64 (14.9)	27 (20.5)	24 (21.6)	12 (24.0)
BMI (kg/m ²)	32.3 (7.9)	32.1 (17.1)	33.2 (17.6)	33.0 (9.1)	33.3 (17.6)
Smoker (Ever)	271 (50.2)	218 (50.8)	62 (47.0)	53 (47.8)	19 (38.0)
Lifetime recreational PA (Mets-hours/week/year)	12.1 (9.2)	12.5 (9.6)	11.2 (8.9)	10.5 (7.5)	10.6 (7.3)
Metabolic Syndrome	325 (60.2)	248 (57.8)	87 (65.9)	77 (69.4)	37 (74.0)
Metabolic Syndrome Components					
0-1	81 (15.0)	68 (15.9)	15 (11.4)	13 (11.7)	5 (10.0)
2	114 (21.1)	98 (22.8)	23 (17.4)	16 (14.4)	6 (12.0)
3	147 (27.2)	117 (27.3)	32 (24.2)	30 (27.0)	18 (36.0)
4	130 (24.1)	95 (22.1)	41 (31.1)	35 (31.5)	14 (28.0)
5	48 (8.9)	36 (8.4)	14 (10.6)	12 (10.8)	5 (10.0)
Waist Circumference (cm)	98.0 (18.8)	97.4 (18.2)	100.6 (20.1)	100.5 (20.9)	99.1 (22.5)
Fasting Glucose (mg/dL)	122.6 (43.4)	123.2 (44.1)	120.1 (38.7)	120.4 (40.4)	118.3 (38.5)
Triglycerides (mg/dL)	146.8 (97.9)	143.8 (97.5)	161.6 (102.7)	158.2 (98.7)	154.6 (87.8)
HDL Cholesterol (mg/dL)	37.3 (12.7)	37.9 (12.4)	34.9 (13.7)	35.2 (13.8)	36.3 (13.9)
Hypertension (self-reported)	186 (34.4)	133 (31.0)	57 (43.2)	53 (47.8)	22 (44.0)

^aAJCC: American Joint Committee on Cancer, FIGO: International Federation of Gynecology and Obstetrics, BMI: body mass index (kg/m²), PA: Physical Activity, HDL: High-Density Lipoprotein.

^bWomen with incomplete TMN stage (n=8) were categorized as Stage I.

Table 4. Disease-Free Survival, Overall Survival, Endometrial Cancer-Specific Survival and Recurrence Outcomes for Endometrial Cancer Survivors in the Alberta Endometrial Cancer Cohort, Alberta, Canada (N=520)

	Disease-Free Survival (n=125/520)		Overall Survival (n=106/520)		Endometrial Cancer- Specific Survival (n=48/520)		Recurrence (n=69/520)	
	Events /Cases	Multivariable HR (95% CI)	Events /Cases	Multivariable HR (95% CI)	Events /Cases	Multivariable HR (95% CI)	Events /Cases	Multivariable HR (95% CI)
Metabolic Syndrome								
No	38/195	1.00	29/195	1.00	11/195	1.00	22/195	1.00
Yes	87/325	1.05 (0.68-1.63)	77/325	1.98 (1.07-3.67)	37/325	1.80 (0.75-4.33)	47/325	0.77 (0.43-1.38)
Waist Circumference (cm)								
<88	32/168	1.00	28/168	1.00	13/168	1.00	18/168	1.00
≥88	90/345	1.66 (0.98-2.79)	75/345	2.12 (1.18-3.80)	34/345	2.14 (0.73-6.31)	50/345	1.21 (0.58-2.52)
Per 5 cm increase		1.11 (1.00-1.24)		1.21 (1.07-1.36)		1.09 (0.91-1.31)		1.04 (0.90-1.21)
Fasting Glucose (mg/dL)								
<100	44/177	1.00	38/177	1.00	17/177	1.00	25/177	1.00
≥100	78/336	NR	65/336	NR	30/336	0.65 (0.33-1.31)	42/336	0.77 (0.46-1.30)
Per 5 mg/dL increase		0.98 (0.95-1.00)		0.98 (0.96-1.01)		NR		0.98 (0.95-1.01)
Triglycerides (mg/dL)								
<150	69/331	1.00	58/331	1.00	24/331	1.00	38/331	1.00
≥150	53/182	1.35 (0.90-2.02)	45/182	1.32 (0.83-2.10)	23/182	1.26 (0.56-2.86)	30/182	1.08 (0.61-1.89)
Per 5 mg/dL increase		1.01 (1.00-1.01)		1.00 (0.99-1.01)		1.00 (0.98-1.01)		1.00 (0.98-1.01)
HDL Cholesterol (mg/dL)								
≥50	16/73	1.00	14/73	1.00	7/73	1.00	9/73	1.00
<50	106/440	0.61 (0.34-1.08)	89/440	0.55 (0.29-1.03)	40/440	0.31 (0.12-0.82)	59/440	0.63 (0.29-1.34)
Per 5 mg/dL increase		0.94 (0.87-1.02)		0.96 (0.88-1.04)		1.01 (0.85-1.21)		0.95 (0.85-1.06)
Hypertension								
No	70/339	1.00	54/339	1.00	26/339	1.00	44/339	1.00
Yes	52/174	0.90 (0.60-1.34)	49/174	1.18 (0.77-1.81)	21/174	1.01 (0.85-1.21)	24/174	0.55 (0.31-1.00)

^aHazard Ratios (HR), Confidence Interval (CI), Not Reported (NR), Component models (n=513).

^bMultivariable models adjusted for stage (I/missing, II, III/IV), grade (I/II, III, missing), primary treatment(s) (hysterectomy, hysterectomy/chemotherapy, hysterectomy/radiation, hysterectomy/chemotherapy/ radiation and/or hormone therapy, missing treatment), baseline age (years), non-linear age (age²) and continuous BMI (kg/m²). Disease-free survival model additionally adjusted for time to first new primary cancer; Overall survival additionally adjusted for time to first new primary cancer/recurrence; Endometrial cancer-specific survival additionally adjusted for time to first recurrence.

^cAll models for metabolic syndrome components were mutually adjusted for the other components.

^dDisease-free survival and overall survival metabolic syndrome multivariable models were additionally adjusted for number of major comorbidities (0, 1, ≥ 2).

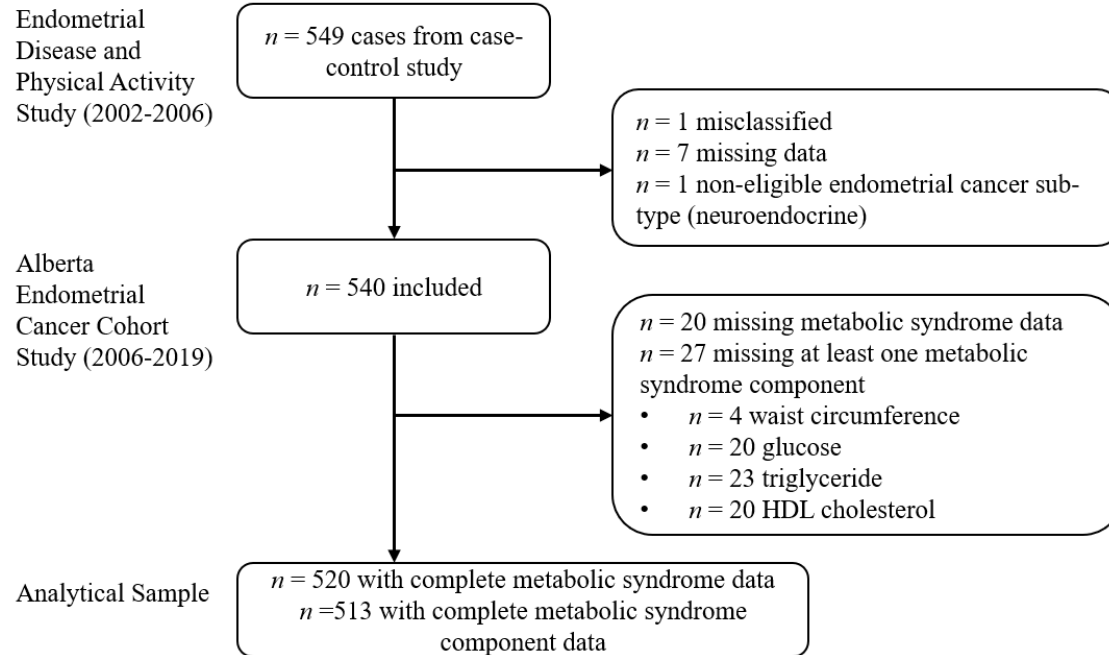


Figure 2. Participant Flowchart for the Alberta Endometrial Cancer Cohort, Alberta, Canada

4.2. Supplementary Results

The results for the medication alternative metabolic syndrome definition analysis and exploratory five- and ten-year restricted analyses for models in the Prospective Cohort Study of Metabolic Syndrome and Endometrial Cancer Survival manuscript (**Section 4.1.4**) that did not satisfy the proportional hazards assumption are provided in the sections below.

4.2.1. Medication Alternative Metabolic Syndrome Analysis

In this analysis, 33 study participants used diabetes medication within a year of their endometrial cancer diagnosis date. Of these, 28 participants also had fasting blood glucose levels ≥ 100 mg/dL and thus already met the blood glucose criterion regardless of their medication use. Consequently, only five additional participants met the alternative blood glucose criterion in addition to the 340 participants with fasting blood glucose levels ≥ 100 mg/dL ($n=345$). Likewise, 22 participants who used triglyceride medication within a year of diagnosis met the alternate triglyceride criterion (triglyceride ≥ 150 mg/dL $n=183$, total $n=205$). With the proxy fasting blood glucose and blood triglycerides criterion included in the medication alternative metabolic syndrome definition, 330 (63.2%) of 521 participants were categorized as having metabolic syndrome at the time of endometrial cancer diagnosis, rather than 325 of 520 participants in the primary analysis. Use of the medication alternative metabolic syndrome criteria instead of the primary harmonized criteria changed six study participants' metabolic syndrome status. However, since all six participants were alive and had not experienced cancer recurrences at the end of follow-up, the number of events that occurred by metabolic syndrome status was the same for both metabolic syndrome definitions. For example, regardless of which

metabolic syndrome criteria were used, 77 and 29 overall deaths occurred among endometrial cancer survivors with and without metabolic syndrome, respectively.

As mentioned above (**Section 4.1.4.**), harmonized metabolic syndrome was associated with worse overall survival but not disease-free survival, endometrial cancer-specific survival or the time to endometrial cancer recurrence. In comparison, no associations between the medication alternative metabolic syndrome criteria and survival outcomes were observed in multivariable-adjusted analyses (**Table 5**).

Table 5. Disease-Free Survival, Overall Survival, Endometrial Cancer-Specific Survival and Recurrence Outcomes for Endometrial Cancer Survivors with the Medication Alternate Metabolic Syndrome Definition in the Alberta Endometrial Cancer Cohort, Alberta, Canada (N=521)

	Disease-Free Survival (n=125/521)		Overall Survival (n=106/521)		Endometrial Cancer-Specific Survival (n=48/521)		Recurrence (n=69/521)	
	Events /Cases	Multivariable HR (95% CI)	Events /Cases	Multivariable HR (95% CI)	Events /Cases	Multivariable HR (95% CI)	Events /Cases	Multivariable HR (95% CI)
Alternative Metabolic Syndrome								
No	38/191	1.00	29/191	1.00	11/191	1.00	22/191	1.00
Yes	87/330	0.98 (0.63-1.52)	77/330	1.35 (0.83-2.20)	37/330	1.75 (0.72-4.25)	47/330	0.74 (0.41-1.33)

^aHazard Ratios (HR), Confidence Interval (CI).

^bMultivariable models adjusted for stage (I/missing, II, III/IV), grade (I/II, III, missing), primary treatment(s) (hysterectomy, hysterectomy/chemotherapy, hysterectomy/radiation, hysterectomy/chemotherapy/ radiation and/or hormone therapy, missing treatment), baseline age (years), non-linear age (age²) and continuous BMI (kg/m²). Disease-free survival model additionally adjusted for time to first new primary cancer and number of major comorbidities (zero, one, ≥ two). Overall survival additionally adjusted for time to first new primary cancer/recurrence and number of major comorbidities (zero, one, ≥ two). Endometrial cancer-specific survival additionally adjusted for time to first recurrence.

4.2.2. Five- and Ten-Year Restricted Analyses

Provided that the models assessing the number of metabolic syndrome components with disease-free, overall and endometrial cancer-specific survival did not satisfy the proportional hazards assumption in the primary analyses (**Section 4.1.4.**), they were further assessed in exploratory five- and ten-year restricted analyses. The association between ten-year endometrial

cancer-specific survival and the number of metabolic syndrome components did not meet the proportional hazards assumption and was therefore not reported (**Table 6**). There was insufficient evidence of an association between the number of metabolic syndrome components with five-year disease-free survival, overall survival or endometrial cancer-specific survival in multivariable analyses. In the ten-year multivariable analysis, null associations were noted for the relationship between the number of metabolic syndrome components and disease-free survival, whereas participants with four or five metabolic syndrome components had increased ten-year overall survival compared to those with zero or one components (**Table 6**).

Table 6. Five- and Ten-Year Disease-Free Survival, Overall Survival and Endometrial Cancer-Specific Survival Outcomes for Endometrial Cancer Survivors by Number of Metabolic Syndrome Components in the Alberta Endometrial Cancer Cohort, Alberta, Canada (N=520)

	Disease-Free Survival		Overall Survival		Endometrial Cancer-Specific Survival	
	Events/ Cases	Multivariable HR (95% CI)	Events/ Cases	Multivariable HR (95% CI)	Events/ Cases	Multivariable HR (95% CI)
Five Years						
Metabolic Syndrome Components						
0-1	8/81	1.00	3/81	1.00	2/81	1.00
2-3	28/261	0.55 (0.23-1.32)	20/261	1.10 (0.30-4.00)	16/261	1.48 (0.43-5.13)
4-5	28/178	0.64 (0.25-1.65)	17/178	0.74 (0.18-3.03)	15/178	1.26 (0.28-5.70)
P for Trend		0.69		0.41		0.99
Ten Years						
Metabolic Syndrome Components						
0-1	12/81	1.00	11/81	1.00	5/81	1.00
2-3	44/261	0.71 (0.35-1.42)	34/261	0.63 (0.30-1.34)	23/261	NR
4-5	33/178	0.62 (0.29-1.32)	23/178	0.40 (0.17-0.95)	17/178	NR
P for Trend		0.25		0.03		NR

^aHazard Ratios (HR), Confidence Interval (CI), Not Reported (NR).

^bMultivariable models adjusted for stage (I/missing, II, III/IV), grade (I/II, III, missing), primary treatment(s) (hysterectomy, hysterectomy/chemotherapy, hysterectomy/radiation, hysterectomy/chemotherapy/ radiation and/or hormone therapy, missing treatment), baseline age (years), non-linear age (age²) and continuous BMI (kg/m²). Disease-free survival model additionally adjusted for time to first new primary cancer. Overall survival additionally adjusted for time to first new primary cancer/recurrence. Endometrial cancer-specific survival additionally adjusted for time to first recurrence.

Additionally, the proportional hazards assumption was not satisfied in the primary models for fasting blood glucose (≥ 100 mg/dL) with disease-free and overall survival nor the models for continuous fasting blood glucose (per five mg/dL increase) with endometrial cancer-specific survival. Fasting blood glucose (≥ 100 mg/dL) was associated with improved five-year ($HR_{5\text{ year}}=0.51$, 95% CI=0.29-0.90) and ten-year disease-free survival ($HR_{10\text{ year}}=0.51$, 95% CI=0.32-0.80). Participants with elevated fasting blood glucose levels (≥ 100 mg/dL) also had statistically significantly better ten-year ($HR_{10\text{ year}}=0.49$, 95% CI=0.29-0.84), but not five-year, overall survival ($HR_{5\text{ year}}=0.57$, 95% CI=0.28-1.14) compared to those with fasting blood glucose < 100 mg/dL. Moreover, linear dose-response relationships were observed per five mg/dL increase in fasting blood glucose with improved five-year ($HR_{\text{per } 5\text{ mg/dL}}=0.93$, 95% CI=0.88-0.97) and ten-year endometrial cancer-specific survival ($HR_{\text{per } 5\text{ mg/dL}}=0.94$, 95% CI=0.90-0.98) in the multivariable-adjusted models.

4.3. Results Summary

Overall, 325 (60.2%) participants had metabolic syndrome defined by the harmonized criteria at the time of endometrial cancer diagnosis. During the median 14.2 years of follow-up, there were 132 recurrence and/or death events including 73 recurrences, 50 endometrial cancer-specific deaths and 111 overall deaths. Metabolic syndrome was associated with worse overall survival but not disease-free survival, endometrial cancer-specific survival or the time to recurrence when assessed with the harmonized criteria. No associations were observed between the alternate metabolic syndrome criteria and any of the outcomes. Conversely, increased number of metabolic syndrome components was associated with improved ten-year overall survival, but not any five-year survival outcomes or ten-year disease-free survival.

Waist circumference was the only individual component of metabolic syndrome associated with worse overall survival (≥ 88 cm, per five cm) and disease-free survival (per five cm) in the main multivariable-adjusted analyses. Although elevated fasting blood glucose (≥ 100 mg/dL) was associated with improved five-year disease-free survival as well as ten-year disease-free and overall survival. Increasing fasting blood glucose (per five mg/dL) was also associated with better five-year and ten-year endometrial cancer-specific survival.

Lifetime recreational physical activity prior to diagnosis statistically significantly modified associations between metabolic syndrome (harmonized) and its components with overall survival and disease-free survival. Specifically, metabolic syndrome, increasing waist circumference (per five cm), and hypertension were associated with worse overall survival, whereas greater HDL cholesterol levels (per five mg/dL) was related to improved overall and disease-free survival among endometrial cancer survivors with lower lifetime recreational physical activity (< 9.7 MET-hours/week/year). Among survivors with higher lifetime recreational physical activity (≥ 9.7 MET-hours/week/year), only increasing waist circumference (per five cm) was associated with worse overall survival.

CHAPTER FIVE: DISCUSSION

5.1. Overview

The aim of this thesis was to investigate the associations between metabolic syndrome and its components with recurrence and survival outcomes among endometrial cancer survivors. To achieve this aim, an analysis of the Alberta Endometrial Cancer Cohort (n=540) that had data collected shortly after cancer diagnosis on direct measures of anthropometry, biomarkers and self-reported data on important covariates was conducted. The primary analyses of interest in this thesis were the associations between metabolic syndrome (using the harmonized criteria) with disease-free survival, overall survival, endometrial cancer-specific survival and time to recurrence. These associations were also assessed with a medication alternative definition of metabolic syndrome that included alternate fasting glucose and triglyceride medication use indicators. In the second set of analyses, the relationships between the number of metabolic syndrome components as well as each individual metabolic syndrome component with these cancer outcomes were examined. The last set of analyses assessed the associations between metabolic syndrome and its components with disease-free and overall survival by participants' lifetime recreational physical activity level.

5.2. Previous Research on Metabolic Syndrome and Endometrial Cancer Survival

5.2.1. Metabolic Syndrome

In this analysis, an approximate twofold decrease in overall survival was observed for endometrial cancer survivors with metabolic syndrome defined by the harmonized criteria compared to those without this syndrome. It was also noted that metabolic syndrome may be

associated with worse endometrial cancer-specific survival, although this association did not reach statistical significance in the multivariable-adjusted model.

Limited research has been conducted on the associations between metabolic syndrome and survival outcomes among endometrial cancer survivors. Four previous observational epidemiologic studies have examined the relationship between metabolic syndrome and either overall or cancer-specific survival in this population.^{38,55-57} All of these studies were retrospective reviews of cohorts, large databases or medical records.^{38,55-57} To date, no standardized definition of metabolic syndrome has been adopted in this research area. This lack of standardization may be partially explained by the fact that previous studies have often relied on the presence of self-reported comorbid conditions (e.g. diabetes, hypertension, high cholesterol levels and/or high BMI levels) as alternative proxy indicators for metabolic syndrome components. The predominate use of self-reported comorbidities suggests that data on metabolic syndrome components assessed using standardized methods (i.e. anthropometric measures and fasting blood samples) may not be routinely available in these types of retrospective studies.

Two studies conducted by the Department of Gynecologic Oncology at the Zhejiang Cancer Hospital in China observed reduced overall survival among endometrial cancer survivors with the study-specific metabolic syndrome definition (presence of \geq three of the following components: history of Type 2 diabetes, medically-treated hypertension, diagnosed or treated hyperlipidemia and either waist circumference \geq 80 cm or BMI \geq 28 kg/m²), relative to those without this syndrome.^{56,57} Although these studies reported statistically significant results, these findings should be interpreted with caution since the analyses included limited adjustment for known prognostic factors (e.g. participant age, cancer treatment) and the resulting estimates had low precision. While previous research, as well as the current thesis, have consistently reported

poor overall survival among endometrial cancer survivors with metabolic syndrome, additional studies are needed to contribute to this under-studied research topic.

Two prior studies^{38,55} reported statistically significant associations between metabolic syndrome and endometrial cancer-specific survival. Jin and colleagues⁵⁵ included 10,090 endometrial cancer survivors from the SEER-Medicare database, of whom 1,786 later had a cancer-specific death. Medicare claims for metabolic syndrome were associated with worse endometrial cancer-specific survival for stage I/II (HR=1.28, 95% CI=1.09-1.53), but not stage III /IVa (HR=1.18, 95% CI=0.93-1.49) endometrial cancer survivors. Similarly, Bjorge et al.³⁸ reported that metabolic syndrome was associated with 1.56 (95% CI=1.32-1.84) times the hazard of uterine cancer-specific mortality per one-unit increment of composite metabolic syndrome Z-score. The Me-Can project identified women with endometrial cancer based on death records; 129 cancer-specific deaths were included in the project, although only 58% of these study participants had a prior diagnosis of incident endometrial cancer in the cohort.³⁸ Moreover, tumour and treatment characteristics were unknown, and therefore not included in the statistical models.³⁸ In contrast to prior research, the relationship between metabolic syndrome and endometrial cancer-specific survival did not reach statistical significance in this thesis, although this lack of a statistically significant association is likely attributable to the limited number of endometrial cancer specific-events that occurred in the Alberta Endometrial Cancer Cohort.

No known study has assessed the association between metabolic syndrome and recurrence outcomes among endometrial cancer survivors. In the current thesis, there was insufficient evidence of an association between metabolic syndrome and disease-free survival or the time to endometrial cancer recurrence in multivariable-adjusted models. This lack of association might be attributable to the small numbers of recurrences that occurred in the Alberta

Endometrial Cancer Cohort. However, given that the relationship between metabolic syndrome and recurrence may act as an early indicator of poor survival for endometrial cancer survivors, understanding this area of research should be the focus of future studies.

In addition to the assessment of metabolic syndrome with the primary harmonized criteria, this thesis assessed the medication alternative definition that included treatment use indicators for the fasting blood glucose and triglyceride components. Only participants using medication within one year of endometrial cancer diagnosis were included in the alternative medication definition to maintain a consistent time frame with the hypertension criteria. When the medication alternative metabolic syndrome criteria were used, no associations were observed for any of the survival outcomes. The attenuation in the estimates that incorporated the inclusion of medication use as a proxy for high glucose and triglyceride levels compared to the primary metabolic syndrome criteria may be related to the management of these risk factors as a result of taking these medications.

The relationship between the number of metabolic syndrome components and survival outcomes has not been previously investigated. In this thesis, only eleven participants had no metabolic syndrome risk factors, so the reference group included survivors with both zero and one risk factor. The relationship between the number of metabolic syndrome components (zero-one, two-three, four-five) and survival outcomes varied over time in the main analysis. Therefore, exploratory five- and ten-year restricted analyses were conducted. Contrary to the main results in which metabolic syndrome (\geq three components) was associated with poor overall survival, endometrial cancer survivors with four or five, compared to zero or one, metabolic syndrome components had better ten-year overall survival. No associations between the number of metabolic syndrome components and overall survival were seen for five-year

outcomes. It is important to note that these analyses do not account for any potential change in the number of metabolic syndrome components during follow-up and assumes that each metabolic syndrome contributes equally to individuals' health status.

5.2.2. Obesity and Waist Circumference

In this thesis, the results suggest that the association between metabolic syndrome and endometrial cancer survival was largely attributable to the association between waist circumference and survival. Compared to endometrial cancer survivors with a waist circumference < 88 cm, survivors with a waist circumference ≥ 88 cm had a twofold decrease in overall survival. For every five cm increase in waist circumference ≥ 88 cm, endometrial cancer survivors were estimated to have a 11% decrease in disease-free survival and a 21% decrease in overall survival. Although the associations between greater waist circumference (≥ 88 cm) and worse disease-free survival, endometrial cancer-specific survival and recurrence did not reach statistical significance in multivariable models, these findings may still be clinically relevant.

Both waist circumference and BMI have been previously positively correlated with estrogen levels in endometrial cancer survivors.^{14,121} Excess adipose tissue can produce elevated concentrations of estrogens, which in the absence of sufficient progesterone is a known risk factor of endometrial cancer tumour proliferation.^{14,121} The adipose tissue and unopposed estrogen mechanism of pathogenesis may partially explain the attenuation of the associations between waist circumference with disease-free survival, endometrial cancer-specific survival and recurrence in multivariable models that adjusted for BMI. Waist circumference is also a strong indicator of central adiposity which has been positively associated with other biological

mechanisms related to tumour pathogenesis, such as hyperglycemia, dyslipidemia, hyperinsulinemia and systemic inflammation.¹⁴

This thesis is the first known project to directly assess the relationship between measured central adiposity (i.e. waist circumference) and survival outcomes among endometrial cancer survivors. In the general population, the Nurses' Health Study previously reported that for every approximate ten cm increase in waist circumference, women had a 34% (95% CI=23–39%) increase in all-cause mortality and a 18% (95% CI=9–28%) increase in obesity-related (colon cancer, breast cancer, pancreatic cancer, uterine, ovarian, and kidney cancer) cancer mortality in multivariable adjusted models which included adjustments for BMI.¹²²

Most of the previous literature in the endometrial cancer survivor population, including a systematic review and meta-analysis of 18 cohort studies conducted by Secord et al.⁹⁹ has focused on the relationship between BMI and survival outcomes. Secord et al.⁹⁹ noted a dose–response relationship between increasing BMI and reduced survival that reached statistical significance among endometrial cancer survivors with a BMI ≥ 40 kg/m². More recently, elevated BMI has been associated with reduced overall survival and endometrial cancer-specific survival in four^{5,61,64,94} and five studies,^{35,38,59,60,66} respectively. However, two studies have reported findings that Type II endometrial cancer survivors with a BMI above the normal range (18.5-24.9 kg/m²) experience better endometrial cancer-specific survival.^{5,91} This improved survival has become known as the obesity paradox hypothesis, which suggests that obesity may be protective of incidence and mortality for some cancer sites.¹⁴ Yet, several other potential reasons to explain the obesity paradox in cancer patients have been proposed, including residual confounding by age, smoking and physical activity which all impact measures of BMI and survival.¹⁴ Additionally, some have suggested that the obesity paradox is related to reverse

causation proposing that lower body weight at cancer diagnosis may be the result of cancer cachexia rather than health status.¹⁴ Moreover, the association between obesity and less aggressive tumour characteristics may partially explain these results.¹⁴

One study to date has observed a statistically significant association between BMI and endometrial cancer recurrence.⁶⁸ Canlorbe et al.⁶⁸ assessed the relationship between BMI and recurrence according to the ESMO risk groups and only observed an association among endometrial cancer survivors in the ESMO high-risk group. Several studies have failed to observe a statistically significant relationship between BMI with overall survival,^{41,65,67,70,74,76,78-81,83,84,87,88} endometrial cancer-specific survival^{42,55,64,65,75,84,85,88,89} and recurrence.^{63,67,69,72,74-76,78,82-84,86,90,92} Study design and methodical approaches may contribute to some of the null results reported. Of note, many of these estimates were derived from studies with small samples (n <250), low numbers of events and univariate analyses which may have contributed to the null findings reported by some of these studies.^{64,70,74,75,77,80,87}

Although the body of literature has largely focused on the associations between BMI and prognostic outcomes, the current findings are generally consistent with prior research that observed worse overall survival with increasing obesity among endometrial cancer survivors. The current findings also provide some indication that obesity, particularly central adiposity, may be a more relevant risk factor for overall survival than endometrial cancer-specific survival and recurrence outcomes.

5.2.3. Diabetes

There was no evidence of a relationship between fasting blood glucose levels and any of the survival outcomes in the current thesis' primary analysis. Additionally, the proportional

hazards assumption was not satisfied in the main disease-free or overall survival models for fasting blood glucose (≥ 100 mg/dL), nor the endometrial cancer-specific survival models for continuous fasting blood glucose (per five mg/dL increase). In the five- and ten-year restricted analyses, blood glucose (≥ 100 mg/dL) was associated with improved five-year disease-free survival and ten-year disease-free and overall survival. A positive dose-response relationship was also noted for improved five- and ten-year endometrial cancer-specific survival per five mg/dL increase in fasting blood glucose.

Three previous studies have assessed the association between pre-diagnosis blood glucose levels and either overall survival^{70,80} or endometrial cancer-specific survival,³⁸ reporting no statistically significant associations among endometrial cancer survivors. Most of the studies that have explored the relationship between diabetes and overall survival have reported a harmful relationship,^{5,40-42,78,79,88,95,101,102,105} whereas only half of the studies observed worse endometrial cancer-specific survival among endometrial cancer survivors with diabetes.^{5,79,91,95,103-105,107,108} Improved three-year survival was noted in one study¹⁰⁶ for survivors with diabetes compared to those without diabetes. Of the studies that assessed the relationship between diabetes and recurrence outcomes,^{75,76,78,84,90,100} only Ko et al.⁷⁸ noted a statistically significant relationship with reduced disease-free survival. Generally, this literature has been limited by the number of participants with diabetes and the number of events that occurred in each study.^{42,75,77,88}

The results from the primary analyses in this thesis align with the null findings previously reported for the association between fasting blood glucose and prognostic outcomes among endometrial cancer survivors. However, the exploratory five- and ten-year restricted analyses in this study suggested a protective association with survival outcomes.

The discrepancies between these different study findings may be partially explained by different criteria used to define diabetes and hyperglycemia in the metabolic syndrome. Compared to the hyperglycemia criteria of metabolic syndrome, which defines fasting blood glucose as ≥ 100 mg/dL, diabetes is generally diagnosed at fasting glucose levels of 126 mg/dL.^{46,125} Additionally, diabetes is characterized by impaired insulin production or reduced cellular response to insulin.¹²⁵ Insulin resistance has been linked to accelerated transformation of androstenedione into estrogen, thus increasing the levels of circulating unopposed estrogen.¹²⁶ Additionally, hyperinsulinemia has been associated with greater invasion of endometrial cancer cells, inhibition of apoptosis of cancer cells, promotion of angiogenesis in tumours and lymph node infiltration, independently of glucose concentrations.¹²⁶ While hyperglycemia has been linked to metabolic reprogramming of tumour cells, tumour inflammation, angiogenesis and inhibition of macrophages function in endometrial cancer survivors, studies conducted in mice models failed to demonstrate a positive association between glucose levels and tumour growth in the absence of hyperinsulinemia.^{14,126} Therefore, this difference in the definition criteria used for hyperglycemia as part of metabolic syndrome and for the diagnosis of diabetes may explain these discrepancies in study findings.

5.2.4. Hypertension

Self-reported hypertension was not associated with any of the prognostic outcomes in this thesis. The literature regarding the association between hypertension and survival among women living with endometrial cancer remains mixed. Only Bjorge et al.³⁸ have examined the association between measured blood pressure and survival outcomes. The authors reported some evidence of a linear trend for increasing quintile of DBP (p-trend <0.01) with decreased survival,

but no relationship between continuous blood pressure, quintile of SBP or DBP with endometrial cancer-specific survival.³⁸

Worse overall survival has been noted for endometrial cancer survivors with hypertension compared to those without.^{41,101} Decreased overall survival with hypertension has been particularly evident among Type II endometrial cancer survivors.^{43,94} However, the majority of this literature has failed to observe either crude^{80,111} or adjusted^{40,63,70,88,95,110} associations between hypertension and overall survival in this population. There has been one study⁸⁸ that reported improved overall survival with hypertension among Black endometrial cancer survivors. Of the seven studies that assessed the association between hypertension and endometrial cancer-specific survival, no studies observed a harmful association, one study⁸⁸ observed a positive association and six studies reported null associations.^{55,75,77,84,91,95} There is limited research^{63,75,84} that has investigated the association between hypertension and endometrial cancer recurrence. Two studies have previously^{75,84} observed null associations and one reported a protective relationship between hypertension and recurrence outcomes.⁶³

While some literature among endometrial cancer survivors supports the notion that hypertension reduces overall survival, there is less evidence of a relationship with endometrial cancer-specific outcomes. The current results add to the body of literature reporting null associations between hypertension with recurrence and survival outcomes.

The potential mechanisms between hypertension and endometrial cancer-specific survival and recurrence are not well understood.¹²⁶ However, it is plausible that the association between hypertension and overall survival among endometrial cancer survival is driven by cardiovascular disease. Felix and colleagues⁴⁵ have previously reported that endometrial cancer survivors in the

Iowa Women's Health Study with hypertension had increased cardiovascular disease mortality compared to normotensive survivors.

5.2.5. Triglycerides and HDL Cholesterol

In this thesis, blood triglycerides and HDL cholesterol were assessed via fasting blood draws at the time of endometrial cancer diagnosis. Based on the metabolic syndrome threshold of 150 mg/dL, blood triglycerides levels were not associated with any prognostic outcomes, nor was there evidence of a linear trend. Nearly all participants (n=440, 81.5%) had blood HDL cholesterol concentrations < 50 mg/dL. Therefore, the protective relationship observed between low HDL cholesterol and improved endometrial-cancer survival is likely an artifact of the data rather than a clinically meaningful result. Moreover, for every additional five mg/dL increase in HDL cholesterol \geq 50 mg/dL, endometrial cancer survivors were estimated to have improved overall and disease-free survival, although these relationships did not reach statistical significance. The linear trend, though also not statistically significant, supports the notion that the protective association seen with endometrial cancer-specific survival was the result of the homogeneous sample rather than biological plausibility.

Previous literature has used multiple variations of dyslipidemia and abnormal blood lipid definitions in the assessment of recurrence and survival outcomes. While the metabolic syndrome criteria specifically assesses blood triglycerides and HDL cholesterol, dyslipidemia generally refers to elevated blood triglycerides, total cholesterol, LDL and/or reduced HDL cholesterol levels.³⁹ No statistically significant associations have been observed between triglyceride and total cholesterol levels with overall survival among endometrial cancer survivors.⁷⁰ Three studies reported null associations between hypercholesterolemia,^{38,84}

dyslipidemia⁵⁵ as well as hypertriglyceridemia^{38,55} with endometrial cancer-specific survival. However, Van Arsdale et al.⁹¹ noted improved endometrial cancer-specific survival for Type II endometrial cancer survivors with hyperlipidemia, but a null association among women living with Type I endometrial cancer. The association between dyslipidemia and endometrial cancer recurrence has been assessed in one study, which failed to observe an association in the univariable analysis.⁸⁴

The null results in this thesis are therefore consistent with previous research. The potential mechanisms by which triglyceride and cholesterol impact endometrial cancer have been largely assessed in terms of cancer incidence. Less is understood about how abnormal blood lipids impact endometrial cancer progression.¹²⁶ It has been suggested that elevated free fatty acids may be related to the progression of endometrial cancer via an estrogen receptor-dependent pathway.¹²⁶ A proposed relationship between HDL metabolism and cellular lipid homeostasis regulation has also been suggested for gynecologic cancer pathogenesis.¹²⁷

5.2.6. Physical Activity Modification

In this analysis, the associations between metabolic syndrome and its components with survival outcomes depended on the participants' lifetime recreational physical activity prior to diagnosis (as assessed in terms of MET-hours/week/year). For endometrial cancer survivors with lower lifetime recreational physical activity (< 9.7 MET-hours/week/year), those with metabolic syndrome had a 2.5-fold decrease in overall survival compared to participants without the syndrome. Conversely, the association between metabolic syndrome and overall survival did not reach statistical significance amongst survivors with higher lifetime recreational physical activity (≥ 9.7 MET-hours/week/year). A harmful relationship between hypertension and overall

survival, as well as protective associations with HDL cholesterol, and overall and disease-free survival were only observed among endometrial cancer survivors with lower recreational physical activity levels. Finally, increasing waist circumference was associated with worse overall survival for both women with lower as well as higher lifetime recreational physical activity, although the association was attenuated among endometrial cancer survivors with greater lifetime recreational physical activity compared to those with lower lifetime physical activity.

No known prior study has examined metabolic syndrome or its components with survival outcomes among endometrial cancer survivors in the context of physical activity. Generally, these findings add to a larger body of literature that suggests cancer survivors with greater physical activity participation experience better survival.¹⁹ Overall cancer survivors with the highest compared to lowest levels of pre-diagnosis physical activity have been reported to have an 18% (95% CI=14-21%) improvement in total cancer-specific survival.¹⁹ However, women living with female reproductive cancers (cervical, endometrial, and ovarian cancers) with the highest versus lowest pre-diagnoses physical activity did not experience a statistically significant difference in overall or cancer-specific survival.¹⁹ Specific survival estimates with physical activity among endometrial cancer survivors are limited.^{19,123} In the NIH–AARP Diet and Health Study, Arem and colleagues⁶⁰ previously reported endometrial cancer survivors with higher pre-diagnosis recreational moderate-to-vigorous-intensity physical activity had better five-year overall survival, but not ten-year overall survival or endometrial specific-survival. The authors also investigated the association between pre-diagnosis physical activity and survival among endometrial cancer survivors in the Women’s Health Initiative, although no associations were observed with overall and endometrial cancer-specific survival outcomes.⁵⁹

Our findings suggest that endometrial cancer survivors with greater lifetime recreational physical activity participation do not experience the same harmful associations between metabolic syndrome, waist circumference, and hypertension with overall survival compared to those with lower amounts of lifetime physical activity participation. The overall survival benefits experienced with greater physical activity is thought to relate to lower levels of obesity and improved cardiorespiratory fitness, therefore reducing cardiac morbidity and mortality.^{128,129} Moreover, physical activity has been reported to improve insulin sensitivity and reduce systemic inflammation, blood pressure and visceral adiposity in the general population.¹³⁰ It is therefore possible that metabolic syndrome and the accompanying pathophysiology (e.g. chronic inflammation) may be less severe in women who regularly participate in physical activity.

5.3. Strengths of Project

The substantial study follow-up time and well-defined study population are key strengths of the current project. Participants were originally identified through the Alberta Cancer Registry, which has a $\geq 95\%$ case ascertainment rate¹¹⁴ of histologically confirmed, endometrial cancer cases and are therefore representative of the larger endometrial cancer survivor population living in Alberta. The median follow-up time was 14.2 years (range: 0.3-16.5 years) which provides an appropriate duration of time for events to occur in this population.¹³¹ Moreover, outcome ascertainment was conducted through data linkage with national and provincial registries which assures that the survival data are comprehensive. Metabolic syndrome exposure data including direct anthropometric measures and blood assays were taken in multiples at the time of endometrial cancer diagnosis and provide valid and reliable data with a clear temporal relationship to the outcomes assessed. Interviewers trained with cognitive interview methods

administered questionnaires at the time of endometrial cancer diagnosis to collect data on potential covariates. Cognitive interviewing data collection methods have been shown to improve participants' long-term recall ability and have been successfully used in a variety of surveys.¹¹⁷

5.4. Limitations

The limitations of this study also need to be considered when assessing these results. The limitations include threats to internal and external validity such as selection bias, misclassification bias, type I and II error, confounding and generalizability.

5.4.1. Internal Validity

Internal validity is the extent to which the observed associations represent the true relationship of interest. The internal validity of a study can be threatened by either random or systematic error. As the name suggests, random error occurs by chance and threatens all studies, although has a greater impact on studies with smaller sample sizes. Systematic error, on the other hand, is caused by defects in the study approach or methods which impact the accuracy of the estimates. Selection bias, measurement bias and confounding are the most common types of systematic error.¹³²

5.4.1.1. Selection Bias

Selection bias results from study design defects and other factors that impact who is included in a study. The current project was composed of endometrial cancer cases from the original population-based case-control study, therefore the inclusion in the current study was

contingent upon participation in the prior study. Of the eligible endometrial cancer cases identified between 2002 and 2006 by the Alberta Cancer Registry, 61% participated in the case-control study. Given that these endometrial cancer survivors self-selected to participate in the project, they represent women who were first and foremost healthy enough to participate and secondly potentially more health conscious than women who refused to participate.

Of the 540 participants who were eligible for this analysis, 27 participants were missing \geq one metabolic syndrome component. Seven of these endometrial cancer survivors still met \geq three metabolic syndrome components criteria and were classified as having metabolic syndrome. Participants missing at least one metabolic syndrome component were not included in the component models and survivors who could not be categorized by metabolic syndrome status were missing from the metabolic syndrome analysis. Incomplete fasting blood assays was the primary reason for partial metabolic syndrome data, and likely occurred at random. Moreover, endometrial cancer survivors included in the component analyses (n=513) were similar in terms of mean age at diagnosis, FIGO grade and BMI to those with incomplete metabolic syndrome data (n=27) (Age n=513: 59.1 ± 9.4 years, n=27: 57.8 ± 8.3 years; Cancer grade n=513: I/II = 76.2%, III = 13.4%, NR = 10.3%, n=27: I/II = 81.5%, III = 14.8%, NR = 3.7%; BMI n=513: 32.1 ± 7.9 kg/m², n=27: 35.8 ± 6.9 kg/m²). Although, endometrial cancer survivors included in the component analyses had slightly fewer stage II tumours (n=513: I = 80.1%, II = 11.9%, III/IV = 8.0%, n=27: I = 63.0%, II = 29.6%, III/IV = 7.4%) and comorbidities (n=513: zero = 88.1%, one = 9.3%, \geq two = 2.5%, n=27: zero = 81.5%, one = 18.5%, \geq two = 0%) than the survivors missing metabolic syndrome data.

5.4.1.2. Misclassification Bias

Misclassification bias results from systematic error in the measurement of the exposure or outcome. The primary aim of the original population case-control study was to address the association between physical activity and endometrial cancer risk, while the association with metabolic syndrome was a later addition to this research program. Given that the original funding and participants' measurements were obtained in the case-control study prior to the addition of metabolic syndrome, not all metabolic syndrome components were fully captured. While the majority of the metabolic syndrome components were available from direct measurements (i.e. waist circumference, fasting blood glucose, triglycerides, HDL cholesterol), blood pressure was not assessed. Data on self-reported hypertension diagnosis and/or antihypertensive medication use were proxy measures in the metabolic syndrome criteria, meaning that participants with undiagnosed hypertension would have been misclassified as normotensive. Endometrial cancer survivors have been reported to have more diagnosed and undiagnosed hypertension compared to women in the general population.⁶ Since all participants were equally likely to have undiagnosed hypertension, this misclassification is non-differential in nature. Therefore, underdiagnosed and unreported hypertension in the current project may have attenuated the estimates of associations with hypertension and potentially metabolic syndrome.

Moreover, the artificial categorization of metabolic syndrome components and subsequent classification of metabolic syndrome relies heavily on threshold values which can result in the loss of information. This categorization could have contributed to the unexpected protective associations observed in the HDL cholesterol and fasting blood glucose analyses. For instance, participants with fasting blood glucose levels of 101 mg/dL and 126 mg/dL were both categorized as meeting the blood glucose criteria despite the fact that participants with blood

glucose levels of 126 mg/dL would be considered diabetic while participants with fasting blood glucose levels of 101 mg/dL have a nearly normal fasting blood glucose concentration. One possible explanation for the protective association observed in the five- and ten-year restricted glucose analyses is that the threshold of 100 mg/dL was too low as a cut-off point to represent two meaningfully distinct groups in these analyses. Therefore, the comparison and reference groups would be more similar than anticipated. However, the practice of categorization has long been accepted in the health field to facilitate real-world decisions and treatments, and the use of these cut-off points have been previously validated as being associated with increased disease risk.¹³²⁻¹³⁵

Metabolic syndrome was only assessed at the time of cancer diagnosis and may not represent participants' health status for the entire follow-up period. Previous findings from the Atherosclerosis Risk in Communities Study suggest that most individuals (76%) experienced increased severity of metabolic syndrome over time and medical treatment of the individual risk factors was ineffective at reducing the severity.¹²⁴ Therefore, the burden of metabolic syndrome among endometrial cancer survivors in the current study may have been underestimated since participants who did not have metabolic syndrome at baseline may have developed it during the follow-up period. This change over time would lead to the exposed and non-exposed groups being more similar and the estimates would be skewed towards the null.

5.4.1.3. Power, Precision, and Residual Confounding

Statistical power is the probability of detecting an association when that relationship truly exists. If a study is underpowered, the probability of failing to observe an association when in

truth the relationship exists, committing a type II error, increases. Statistical power is impacted by the study's sample size, magnitude of effect and the level of statistical significance that is set. Increasing sample size is the most common method used to improve statistical power and will increase the precision of the estimates as reflected in the width of the confidence intervals. Statistical significance was set at five percent in the current thesis, therefore the probability of observing a statistically significant association by chance, type I error, was five percent. As the number of statistical tests performed increases, so does the chance that the observed results are the product of type I error.¹³²

Due to the small sample size and limited number of events, the current study was likely underpowered to observe statistically significant associations and therefore at risk of type II error. This risk of type II error is particularly relevant for the endometrial cancer-specific survival and recurrence results, which should be interpreted with caution because of the small number of events in the categorical analyses. The lower precision of the estimates reflected in the wide confidence intervals are indicative of underpowered analyses. Specifically, the association between HDL cholesterol and endometrial-cancer specific survival is likely an erroneous result and an artifact of the limited number of events in the reference group.

Many associations were assessed in this thesis because of the number of metabolic syndrome components and number of outcomes considered. While it is possible that some associations were the result of type I error, the consistency across outcomes and analyses would suggest that the results were not as a result of chance. Moreover, a basic biological plausibility model was determined *a priori* and included in all analyses to reduce the number of analyses performed.

Confounding is the intermixing of an additional factor in the association of interest. Confounding variables are characterized as independent risk factors for the outcome, associated with the exposure and not on the causal pathway between exposure and outcome.¹³² Possible confounding factors were assessed using backwards elimination and based on *a priori* biological plausibility and existing literature. This method is considered an effective way of assessing potential confounding factors. However, it is possible that unmeasured factors may have resulted in residual confounding in the present analyses.

5.4.2. External Validity

The extent to which the results of one study can be generalized beyond its original context to the larger population represents a study's external validity. This type of validity is contingent upon the study first being deemed internally valid. Results from studies with samples defined by rigorous inclusion criteria may not be generalizable to the broader population. In the current thesis, there were no restrictions on demographic characteristic except age, in which all women between 30 and 80 years of age were eligible. Provided that the vast majority of women at risk of developing endometrial cancer are within this age range, this eligibility criteria is not likely a limiting factor.³ Although not inclusion criteria, the study participants represent a predominantly White (93.9%) and well educated (67.2% \geq high school education) group of endometrial cancer survivors living in Alberta. Due to the homogenous study population, the potential impact of race and ethnic background could not be assessed in this thesis. Future research should address this gap by including racially diverse endometrial cancer survivors in the assessment of metabolic syndrome with survival outcomes. Therefore, the current findings may be most applicable to White endometrial cancer survivors who have access to similar cancer

treatments as the survivors in the Alberta Endometrial Cancer Cohort did. However, given the similarity between endometrial cancer and other obesity-linked cancers, these results may be relevant to the broader cancer survivor population.

5.5. Future Directions

This thesis, along with the available literature, suggest that endometrial cancer survivors with metabolic syndrome experience both reduced endometrial cancer-specific survival and overall survival.^{38,55-57} However, the key factors of the associations between metabolic syndrome and prognostic outcomes in endometrial cancer survivors are still debated. While this thesis and most previous research^{38,39} suggests that the association is primarily related to obesity and central adiposity, not all studies support this hypothesized biological link.⁵⁵ Additional research is needed to understand the biological mechanism associated with metabolic syndrome and survival outcomes. Moreover, studies to date have been conducted with the assumption that all metabolic syndrome components contribute equally to endometrial cancer survival. Future studies should aim to determine the critical risk factors within the metabolic syndrome and assess the assumption that all metabolic syndrome components contribute equally to cancer prognosis. Furthermore, future research should aim to assess metabolic syndrome at multiple time points during study follow-up with objective measurements.

Provided that endometrial cancer survivors have greater amounts of cardiometabolic risk factors that may or may not be diagnosed or treated compared to the general population,⁶ and that endometrial cancer mortality rates are currently rising,¹¹ identifying opportunities to intervene in this population is becoming increasingly important. This thesis provides some evidence that the associations with metabolic syndrome and its components were attenuated

among endometrial cancer survivors with greater lifetime recreational physical activity compared to those with lower physical activity levels before cancer diagnosis. Lifestyle interventions that target weight management, healthy diets and physical activity have been proposed as means to address the growing burden of chronic conditions among endometrial cancer survivors and improve survival outcomes.^{6,51} The impact of lifestyle interventions on recurrence and survival outcomes among gynecological cancer survivors remains unclear.¹³⁶ Moreover, it has been suggested that cancer diagnosis represents a time in which individuals are more receptive to the adoption of lifestyle changes.¹³⁷ Results from the Survivors of Uterine CanCer Empowered by Exercise and Healthy Diet (SUCCEED) trial suggest that after a six-month lifestyle intervention, endometrial cancer survivors were able to lose and maintain weight loss successfully at one year follow-up with diet and physical activity.¹³⁸ Future survival analyses from the SUCCEED trial¹³⁸ and additional studies that assess metabolic syndrome and its components are needed to improve our understanding of the role physical activity and other lifestyle factors play in the association between metabolic syndrome and endometrial cancer survivors' prognosis.

5.6. Conclusion

This thesis improves our understanding of the associations between metabolic syndrome and its components with cancer recurrence and survival outcomes among endometrial cancer survivors. Endometrial cancer survivors with metabolic syndrome had reduced overall survival compared to those without this syndrome. Moreover, the results suggest that the association between metabolic syndrome and endometrial cancer survival is largely explained by central adiposity. It also illustrated that endometrial cancer survivors with greater lifetime recreational physical activity before diagnosis had improved survival despite metabolic syndrome risk factors

compared to those with lower lifetime recreational activity levels. This thesis provides some additional evidence needed to develop and assess interventions in endometrial cancer survivors targeting early indicators of cardiovascular and metabolic disease, such as metabolic syndrome, with the ultimate aim of improving endometrial cancer survival.

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APPENDIX A

Literature Review Search Strategies

EMBASE (Ovid) databases 1990-March 19, 2020

1. uterus cancer/
2. endometrium tumor/
3. endometrium cancer/
4. (endometr* adj4 canc*).tw,kw.
5. (endometr* adj4 carcinom*).tw,kw.
6. (uter* adj4 canc*).tw,kw.
7. (uter* adj4 neopla*).tw,kw.
8. (endometr* adj4 neopla*).tw,kw.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. vital statistics/
11. mortality/
12. survival rate/
13. disease free survival/
14. survival analysis/
15. progression free survival/
16. tumor recurrence/
17. recurrent disease/
18. cancer mortality/
19. "cancer survival"/
20. Cause of Death/
21. Surviv*.tw,kw.
22. mortal*.tw,kw.
23. fatal.tw,kw.
24. Death.tw,kw.
25. Overall surviv*.tw,kw.
26. vital statist*.tw,kw.
27. (surviv* adj4 analys*).tw,kw.
28. (Neoplas* adj4 Recurren*).tw,kw.
29. (canc* adj4 Recurren*).tw,kw.
30. Recurren*.tw,kw.
31. (mort* adj4 endomet*).tw,kw.
32. (Cause adj4 Death).tw,kw.
33. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34. 9 and 33
35. "metabolic syndrome".tw,kw.
36. obesity/

37. "disorders of lipid and lipoprotein metabolism"/
38. metabolic syndrome x/
39. body mass/
40. morphometry/
41. anthropometry/
42. adipose tissue/
43. BMI.tw,kw.
44. Obes*.tw,kw.
45. Body mass index.tw,kw.
46. diabetes mellitus/
47. diabet*.tw,kw.
48. high density lipoprotein cholesterol/
49. dyslipidemia/
50. triacylglycerol/
51. glucose level/ or glucose blood level/
52. hypertension/ or elevated blood pressure/
53. hypertension.tw,kw.
54. HDL.tw,kw.
55. waist circumference/
56. Waist circumference.tw,kw.
57. triglycerid*.tw,kw.
58. cholester*.tw,kw.
59. "blood press*".tw,kw.
60. 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59
61. 34 and 60
62. limit 61 to yr="1990 -Current"

MEDLINE (Ovid) databases 1990-March 19, 2020

1. uterus cancer/
2. Endometrial Neoplasms/
3. (endometr* adj4 canc*).tw,kf.
4. (endometr* adj4 carcinom*).tw,kf.
5. (uter* adj4 canc*).tw,kf.
6. (uter* adj4 neopla*).tw,kf.
7. (endometr* adj4 neopla*).tw,kf.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. vital statistics/
10. mortality/
11. survival rate/

12. disease-free survival/
13. progression-free survival/
14. survival analysis/
15. Neoplasm Recurrence, Local/
16. Recurrence/
17. Endometrial Neoplasms/mo [Mortality]
18. Cause of Death/
19. Surviv*.tw,kf.
20. morta*.tw,kf.
21. Fatal.tw,kf.
22. Death.tw,kf.
23. Overall surviv*.tw,kf.
24. vital statist*.tw,kf.
25. (surviv* adj4 rate).tw,kf.
26. (surviv* adj4 analys*).tw,kf.
27. (canc* adj4 Recurren*).tw,kf.
28. Recurren*.tw,kf.
29. (mort* adj4 endomet*).tw,kf.
30. (Cause adj4 Death).tw,kf.
31. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32. 8 and 31
33. "metabolic syndrome".tw,kf.
34. metabolic syndrome/ or metabolic diseases/
35. glucose metabolism disorders/
36. diabetes mellitus/
37. hyperglycemia/
38. hyperinsulinism/
39. insulin resistance/
40. lipid metabolism disorders/
41. dyslipidemias/
42. obesity/
43. "body weights and measures"/
44. body mass index/
45. anthropometry/
46. Adipose Tissue/
47. Body mass index.tw,kf.
48. BMI.tw,kf.
49. Obes*.tw,kf.
50. Waist circumference.tw,kf.
51. diabet*.tw,kf.

52. cholesterol/ or cholesterol, hdl/ or lipoproteins, hdl/
53. HDL.tw,kf.
54. waist circumference/
55. Dyslipidemias/
56. diabetes mellitus, type 2/ or hyperglycemia/ or hyperinsulinism/
57. hypertension.tw,kf.
58. Hypertension/
59. triglycerid*.tw,kf.
60. "blood press*".tw,kf.
61. 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60
62. 32 and 61
63. limit 62 to yr="1990 - 2020"

APPENDIX B

Letter of Permission

I, Christine Friedenreich on June 25, 2020 grant permission to include the below mentioned manuscript in Renee Kokts-Porietis Masters Thesis “A Prospective Cohort Study of Metabolic Syndrome and Endometrial Cancer Survival.”

Citation of manuscript included in thesis:

Kokts-Porietis RL, McNeil J, Nelson GS, Courneya KS, Cook LS, Friedenreich CM. Prospective Cohort Study of Metabolic Syndrome and Endometrial Cancer Survival. **Gynecologic Oncology**, *in press*.

This thesis will be added to the institutional repository at the University of Calgary and the Library and Archives Canada.

University of Calgary Theses Repository – The Vault <http://theses.ucalgary.ca/>
Library and Archives Canada <http://collectionsCanada.gc.ca/obj/s4/f2/frm-nl59-2-e.pdf>

Letter of Permission

I, Gregg Nelson _____, on June 25, 2020 grant permission to include the below mentioned manuscript in Renee Kokts-Porietis Masters Thesis “A Prospective Cohort Study of Metabolic Syndrome and Endometrial Cancer Survival.”

Citation of manuscript included in thesis:

Kokts-Porietis RL, McNeil J, Nelson GS, Courneya KS, Cook LS, Friedenreich CM. Prospective Cohort Study of Metabolic Syndrome and Endometrial Cancer Survival. **Gynecologic Oncology**, *in press*.

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Library and Archives Canada <http://collectionsCanada.gc.ca/obj/s4/f2/frm-nl59-2-e.pdf>

Letter of Permission

I, Linda S. Cook, on June 25, 2020 grant permission to include the below mentioned manuscript in Renee Kokts-Porietis Masters Thesis “A Prospective Cohort Study of Metabolic Syndrome and Endometrial Cancer Survival.”

Citation of manuscript included in thesis:

Kokts-Porietis RL, McNeil J, Nelson GS, Courneya KS, Cook LS, Friedenreich CM. Prospective Cohort Study of Metabolic Syndrome and Endometrial Cancer Survival. **Gynecologic Oncology**, *in press*.

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Library and Archives Canada <http://collectionsCanada.gc.ca/obj/s4/f2/frm-nl59-2-e.pdf>

Letter of Permission

I, Jessica McNeil, on June 25 2020 grant permission to include the below mentioned manuscript in Renee Kokts-Porietis Masters Thesis “A Prospective Cohort Study of Metabolic Syndrome and Endometrial Cancer Survival.”

Citation of manuscript included in thesis:

Kokts-Porietis RL, McNeil J, Nelson GS, Courneya KS, Cook LS, Friedenreich CM. Prospective Cohort Study of Metabolic Syndrome and Endometrial Cancer Survival. **Gynecologic Oncology**, *in press*.

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Library and Archives Canada <http://collectionscanada.gc.ca/obj/s4/f2/frm-nl59-2-e.pdf>

Letter of Permission

I __Kerry Courneya_____, on June _26___ 2020 grant permission to include the below mentioned manuscript in Renee Kokts-Porietis Masters Thesis “A Prospective Cohort Study of Metabolic Syndrome and Endometrial Cancer Survival.”

Citation of manuscript included in thesis:

Kokts-Porietis RL, McNeil J, Nelson GS, Courneya KS, Cook LS, Friedenreich CM. Prospective Cohort Study of Metabolic Syndrome and Endometrial Cancer Survival. **Gynecologic Oncology**, *in press*.

This thesis will be added to the institutional repository at the University of Calgary and the Library and Archives Canada.

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Library and Archives Canada <http://collectionscanada.gc.ca/obj/s4/f2/frm-nl59-2-e.pdf>