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The unrecognized burden of cardiovascular risk factors in women newly diagnosed with endometrial cancer: A prospective case control study

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HIGHLIGHTS

- CVD risk was measured in a prospective study of 150 EC patients and 746 controls.
- EC patients had significantly more CVD risk factors than other women.
- Most CVD risk factors were either unrecognized or inadequately treated.
- EC patients had a significantly higher 10-year risk of CVD (QRISK2) than controls.
- Identifying and treating CVD risk factors could improve outcomes for EC survivors.

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ABSTRACT

Background. Cardiovascular disease is a major cause of death in endometrial cancer survivors. The aim of this study was to determine whether women newly diagnosed with endometrial cancer have a higher prevalence of cardiovascular risk factors than the general population.

Methods. The prevalence of adequately treated and unrecognized/inadequately treated cardiovascular risk factors and the corresponding 10-year cardiovascular risk by QRISK2 score was measured in 150 consecutive women undergoing primary treatment for endometrioid endometrial cancer in the North West of England, and 746 age and ethnicity-matched control women from the Health Survey for England 2014.

Results. Women with endometrial cancer had higher proportions of obesity (BMI ≥ 30 60.7% vs. 32.4%, $p < 0.0001$) and a preponderance of unrecognized and inadequately treated cardiovascular risk factors. Compared with controls, endometrial cancer cases had a higher prevalence of incident hyperglycemia (57.2% vs. 11.5%, $p < 0.0001$), total: HDL cholesterol ratio > 4.5 (26.7% vs. 13.7%, $p < 0.0001$), and were more likely to have three or more cardiovascular risk factors (22% vs. 6%, $p < 0.0001$). This equates to a higher 10-year cardiovascular risk (median QRISK2 score 12.6% vs. 8.8%, $p < 0.0001$). Optimization of risk factors would have a greater impact on absolute cardiovascular disease risk for cases than controls (QRISK2 score reduction 1.8% vs. 0.7%).

Conclusions. Women undergoing primary treatment for endometrial cancer have a higher prevalence of cardiovascular risk factors than women without the disease. Early identification and treatment of these risk factors could improve outcomes for endometrial cancer survivors.

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1. Introduction

Endometrial cancer, the fourth most common female malignancy, affects over 9000 women each year in the UK and its incidence is rising, such that by 2030 it is estimated that there will be an additional 3600 new cases diagnosed every year in England and Wales alone [1–3]. Similar trends have been reported in other countries, for example in the

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USA, where 60,000 women are diagnosed annually and endometrial cancer is set to overtake lung and colorectal cancer to become the third most common female malignancy [4,5]. Endometrioid endometrial cancer accounts for 80% of cases and its early presentation with postmenopausal bleeding means that the majority of women are diagnosed with disease confined to the uterus, making it amenable to curative surgical resection [6]. More women than ever are thus surviving a diagnosis of endometrial cancer, with 79% and 77.5% of women expected to live at least five and 10 years respectively following diagnosis [7].

Despite this, women with a history of endometrial cancer have a higher mortality rate than the general population, particularly if diagnosed at a young age [8]. Rather than dying of their endometrial cancer, however, cardiovascular deaths predominate in those with early stage disease and this becomes more pronounced the longer women survive their cancer diagnosis. Overall, the risk of death from myocardial infarction and stroke is estimated to be two-fold higher than the risk of death from endometrial cancer and nearly nine-fold higher than that of women from the general population [8,9].

This is not surprising given that endometrial cancer and cardiovascular disease share the common risk factors of obesity and diabetes [10]. Obesity is the strongest risk factor for endometrial cancer, driving carcinogenesis through unopposed estrogen excess, hyperinsulinemia and insulin resistance [2,11,12]. Women with diabetes have a two-fold higher risk of endometrial cancer compared with non-diabetic women, even after adjustment for body mass index (BMI), suggesting an independent relationship between the two conditions.

Yet screening for, and optimization of, cardiovascular risk factors is not routinely undertaken in endometrial cancer survivors. Indeed, the true prevalence of hypercholesterolemia, hypertension and hyperglycemia in women with endometrial cancer is unknown. Previous estimates have been based on established diagnoses of cardiovascular risk factors, which may underestimate the true prevalence of conditions that are often asymptomatic [13–15]. This makes it difficult to estimate the benefit to be gained from introducing a program of routine testing and treatment of cardiovascular risk factors in endometrial cancer survivors.

In the current study, we asked whether women newly diagnosed with endometrial cancer have a higher prevalence of known and unrecognized cardiovascular risk factors than the general female population. Using the QRISK2 score, a widely-used UK-based validated cardiovascular risk calculator [16], we estimated the 10-year risk of cardiovascular disease in the two groups and calculated the likely benefit to be derived from optimization of modifiable risk factors.

2. Methods

2.1. Study design

This was a prospective case-control study performed between 2016 and 2017 in the North West of England.

2.2. Research ethics

The study was approved by the West of Scotland Research Ethics Committee (reference 16/WS/0040) and was prospectively registered on the NIHR Clinical Research Network Portfolio.

2.3. Selection of cases and data collection

We recruited consecutive patients with newly diagnosed endometrioid endometrial cancer referred for primary treatment by hysterectomy, who provided written, informed consent to participate in the study. A detailed medical history was obtained through interview and checked against medical records regarding known diagnoses of diabetes, pre-diabetic hyperglycemia, hypertension, hypercholesterolemia and cardiovascular disease, defined as a previous myocardial infarction, angina, coronary artery bypass graft, stroke or transient ischemic attack.

Current medications used for the aforementioned conditions were also considered evidence of a prior diagnosis. Smoking status categorised women as never smokers, ex-smokers or current smokers and the number of cigarettes smoked per day was recorded.

Anthropometric measurements were recorded in a standard fashion; height was determined using a stadiometer and performed barefooted and weight measured using electronic scales after removal of bulky clothing. BMI was calculated using the formula weight (kg)/height (m)². Venepuncture was performed after an overnight fast of at least six hours duration and blood sent to the Clinical Biochemistry Department of the Manchester University NHS Foundation Trust for routine analysis. Determination of glycosylated hemoglobin (HbA1C) was undertaken using high performance liquid chromatography whilst total and high density lipoprotein (HDL) cholesterol levels were measured using an enzymatic colorimetric method, all according to standard operating procedures. Measurement of blood pressure was performed at rest in a seated position using a calibrated, automated sphygmomanometer.

2.4. Selection of controls and data collection

Each endometrial cancer case was matched for age (± 5 years), female sex and ethnicity to five participants in the Health Survey for England (HSE) 2014, the details of which have been previously published [17]. In brief, the survey is performed annually and collects information on the general health of 8000 adults randomly selected by postcode from across England using standardised questionnaires. Participants are representative of the general population, with each region proportionally sampled in a similar age distribution to the wider UK population [17]. In particular, the prevalence of overweight and obese individuals are equivalent to whole population estimates (HSE 58% vs. National Statistics 58%) [17,18]. Individual level data is made freely available through the NHS Digital website. Information on previous medical history, in particular a prior diagnosis of cardiovascular disease, hypertension and diabetes, and drug history is available. Weight and height measurements and fasted serum levels of total and HDL cholesterol and HbA1C are measured in a comparable way to that of cases and recorded on line. Limited information was available in the Health Survey for England on cancer status, in particular a prior history of endometrial cancer, and participants were therefore not excluded on this basis.

2.5. Outcome definitions

New diagnoses of non-diabetic hyperglycemia and type 2 diabetes were defined as an HbA1C between 42 and 48 mmol/mol and >48 mmol/mol, respectively, in a woman not previously diagnosed with these conditions. The HbA1C values used are in accordance with recommendations from the World Health Organisation [WHO, [19]].

A new diagnosis of hypercholesterolemia was defined as a total:HDL cholesterol ratio >4.5 in a woman not previously prescribed treatment with statins [20]. Inadequately treated hypercholesterolemia was defined as a total:HDL cholesterol ratio >4.5 in a woman already taking statin therapy.

Newly diagnosed hypertension was defined as a systolic blood pressure of >140 mm Hg in a person not previously known to have a physician-obtained diagnosis of hypertension, or taking antihypertensive therapy [16]. Inadequately treated hypertension was the persistence of a systolic blood pressure greater than this threshold in someone already taking antihypertensive medication.

2.6. QRISK2 score

The QRISK2 score was calculated using the validated 2016 version of the online calculator available at <https://www.qrisk.org/2016/>. QRISK2 derives cardiovascular disease risk estimates based on prospective

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