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The association between diabetes, comorbidities, body mass index and all-cause and cause-specific mortality among women with endometrial cancer

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HIGHLIGHTS

- Diabetes and co-morbidity were associated with higher EC-specific mortality.
- Diabetes and obesity have a negative impact on non-cancer related mortality.
- Understanding the impact of these factors can help inform women and clinicians.

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ABSTRACT

Objective. Although endometrial cancer (EC) is associated with relatively good survival rates overall, women diagnosed with high-risk subtypes have poor outcomes. We examined the relationship between lifestyle factors and subsequent all-cause, cancer-specific and non-cancer related survival.

Methods. In a cohort of 1359 Australian women diagnosed with incident EC between 2005 and 2007 pre-diagnostic information was collected by interview at recruitment. Clinical and survival information was abstracted from women's medical records, supplemented by linkage to the Australian National Death Index. Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause and cause-specific survival (EC death vs. non-EC death) associated with each exposure, overall and by risk group (low-grade endometrioid vs. high-grade endometrioid and non-endometrioid).

Results. After a median follow-up of 7.1 years, 179 (13%) women had died, with 123 (69%) deaths from EC. As expected, elevated body mass index (BMI), diabetes and the presence of other co-morbidities were associated with a significantly increased risk of all-cause and non-cancer related death. Women with diabetes had higher cancer-specific mortality rates (HR 2.09, 95% CI 1.31–3.35), particularly those who had were not obese (HR 4.13, 95% CI 2.20–7.76). The presence of ≥2 other co-morbidities (excluding diabetes) was also associated with increased risk of cancer-specific mortality (HR 3.09, 95% CI 1.21–7.89). The patterns were generally similar for women with low-grade and high-grade endometrioid/non-endometrioid EC.

Conclusion. Our findings demonstrate the importance of diabetes, other co-morbidities and obesity as negative predictors of mortality among women with EC but that the risks differ for cancer-specific and non-cancer related mortality.

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1. Introduction

Endometrial cancer (EC) is the fourth most commonly diagnosed cancer among women in highly developed countries [1]. EC incidence rates exceed those of other gynaecological cancers and have increased rapidly over the last decade [2]. Overall 5-year survival is 82% [3] but survival varies substantially by tumour cell type and grade. In particular, high grade ECs, predominately serous and clear cell carcinomas, augurs a worse outcome than the more commonly occurring low-grade, endometrioid ECs [4]. Furthermore, while endometrial cancer-specific deaths are frequent in the subset of women with high-grade, poor prognosis ECs [5], many women with low-grade endometrioid EC do not die from their cancer but from cardiovascular or cerebrovascular disease.

Obesity is one of the strongest risk factors for the development of EC, particularly the low-grade endometrioid subtype, but has been inconsistently associated with survival following a diagnosis of EC. Some previous studies report no association between a higher body mass index (BMI) and all-cause mortality in women with EC [6,7], whereas others report an increased risk [8,9]. Similarly, a higher BMI has been associated with endometrial cancer-specific mortality in some studies [8,10,11], while others have reported no association [12,13]. Diabetes is common among women with EC and may contribute to their higher all-cause mortality [12,14,15], however few studies have assessed the association between diabetes and risk of dying from EC and the results are conflicting [11,16–19]. Other factors including smoking [20] and the use of common nonsteroidal anti-inflammatory drugs like aspirin [21–24] and also statins [23,25] have been investigated in relation to risk of dying from EC, however findings have been inconclusive. Furthermore, given the low prevalence of the more aggressive subtypes of EC, few studies have been able to examine these associations separately by tumour subtype. Since obesity and diabetes are strongly associated with low-grade endometrioid ECs, which have inherently better survival than high risk histological subtypes, failure to control for tumour subgroup introduces substantial confounding.

The aim of this study was to describe the association between lifestyle factors and survival following a diagnosis of EC. We considered women with different risk groups (low-grade endometrioid vs. high-grade endometrioid/non-endometrioid) separately and examined deaths from all-causes, cancer-specific and deaths due to non-cancer causes.

2. Methods

2.1. Study population

This study included women with EC who participated in a population-based case-control study: the Australian National Endometrial Cancer Study. The full details of the study have been reported elsewhere [26]. Briefly, 2231 women aged 18–79 years, newly diagnosed with EC between 2005 and 2007, identified through major treatment centres and state-based cancer registries across Australia were invited to participate and, of these, 1497 (67%) agreed to take part. Women were eligible for the current analyses if they had completed the baseline study questionnaire (N = 1399). We excluded thirty women with synchronous endometrial and ovarian cancers, seven women with cancers of unknown stage, and three women who did not have any primary treatment; the remaining 1359 women were included in this analysis. The study was approved by the Human Research Ethics Committees at the QIMR Berghofer Institute of Medical Research and all participating institutions, and all women provided informed consent.

2.2. Exposure assessment

Detailed pre-diagnostic sociodemographic and lifestyle information was collected using a standard questionnaire that was administered by telephone interview when women were recruited into the study. Women were classified according to their exposure status one year prior to reference date (one year before cancer diagnosis for cases, or 1 year ago for controls). Exposures of interest included age, height and weight (used to calculate BMI categories 18.5–24.9, 25–29.9, 30–34.9, ≥35 kg/m^2), smoking status (never/ex, current), any diabetes (no, yes [type 1 n = 2 and type 2 n = 182]), number of other major comorbidities (including angina/heart attack, heart failure, deep vein thrombosis, stroke, autoimmune diseases, lung disease, kidney disease, liver disease, previous cancer, other conditions including multiple sclerosis/Parkinson's disease) (0, 1, 2+), physical activity (active - strenuous or moderate exercise ≥1 week, inactive - strenuous and moderate exercise both <1 week). Women were asked how often (on average over the last 5 years) they had taken aspirin (never, occasionally, ≤1 week, ≥2 week, daily low dose) and/or nonsteroidal anti-inflammatory drugs (NSAIDS) (never, occasionally, ≤1 week, ≥2 week). Detailed information regarding diabetic treatment was not available in our study.

2.3. Covariates, follow-up and mortality ascertainment

Clinical data, including tumour cell type, stage and grade at diagnosis were abstracted from the women's medical and pathology records by trained research nurses. Stage was coded according to the International Federation for Gynecology and Obstetrics 2009 criteria. Final tumour cell type/grade categories included low-grade endometrioid EC (grades 1 and 2) and high-grade endometrioid and non-endometrioid EC (endometrioid grade 3, serous, clear cell and endometrioid mixed with serous/clear cell and carcinosarcoma). Treatment data including information about surgery and adjuvant treatment was also abstracted from the medical records. Almost all the women (97%) had surgery (hysterectomy) and oophorectomy as part of their primary treatment.

Information about vital status and cause of death from obtained from the medical records and to supplement these data, we linked the cohort to the Australian National Death Index which utilised probabilistic record linkage software to identify likely matches based on full name, date of birth, date of last contact, and, if applicable, and state of residence at the time of death. Follow-up information was available through 31 December 2013. For the purposes of our analyses we categorised the 123 deaths that had EC as the underlying cause of death as cancer-specific deaths and the remaining 56 deaths as non-cancer related. We had cause of death information for 48 of the 56 women who died from non-cancer related causes. Of these, 18 (38%) had diseases of the circulatory system recorded as the 'underlying' or an 'other causes of death'.

Survival time was calculated from the date primary treatment commenced to study exit due to death or censoring (women not identified as having died were censored on 31 December 2013). We used the date treatment commenced rather than date of diagnosis to calculate survival time because of the variable time interval between diagnosis of EC (usually on dilation and curettage) and start of treatment. Survival models were left truncated at the date of interview/recruitment if this was after the date that primary treatment commenced because women had to survive to this point to be eligible.

2.4. Statistical analysis

The all-cause and cause-specific hazards were modelled using Cox proportional hazards regression. This provides a direct measure of the association between our exposures of interest with a single cause of death (either cancer-specific death or non-cancer related death), treating any competing events as censored at the time they occurred [27]. Fine and Gray models [27] that provide the cumulative incidence of each event while simultaneously considering the competing risk of the other outcome gave essentially the same results, therefore we only present HRs from Cox models, consistent with a recent paper by

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