Differential trends in the rising incidence of endometrial cancer by type: data from a UK population-based registry from 1994 to 2006

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BACKGROUND: Endometrial cancer is the most common gynaecological cancer in the western world, the incidence increasing in the United Kingdom by over 40% since 1993. Two types of endometrial cancer exist – oestrogen-dependent type 1 with good prognosis and non-oestrogen-dependent type 2 with poor prognosis. The histopathological distribution of the increase in endometrial cancer is unknown. This study investigates the observed incidence trends of the two types, the age, stage, and socioeconomic distribution of this increase and survival outcome.

METHODS: Data were analysed from 6867 women with endometrial cancer registered between 1994 and 2006, at a UK population-based cancer registry.

RESULTS: Increased endometrial cancer incidence is confined to type 1 cancers with a significant increase in age standardised incidence rate (ASR) from 12.0 per 100 000 (confidence interval (CI) 10.7–13.2) in 1994 to 16.3 per 100 000 (CI 14.9–17.7), P < 0.001 in 2006, while ASR of type 2 cancer changed from 2.5 per 100 000 (CI 2.0–3.1) in 1994 to 2.2 per 100 000 (CI 1.7–2.7) in 2006, which was not statistically significant P > 0.05. Increase in type 1 cancer is most marked in age groups 60–69 years (P < 0.001) and 70–79 years (P < 0.001) and distributed equally among socioeconomic quintiles. While outcome for type 1 cancer has improved, 1-year survival in type 2 cancer is unchanged from 73.1% in 1994 to 74.3%, P = 0.089 and 5-year survival decreased from 55.1% to 40.9%, P = 0.001.

CONCLUSION: Increased incidence in endometrial cancer is confined to type 1 cancers, seen most in the 60–79 age groups and across all socioeconomic quintiles. Survival in type 2 cancer has decreased significantly. Urgent research is needed to investigate prevention strategies in type 1 and improve therapy in type 2 cancers.

British Journal of Cancer (2011) 104, 1505–1510. doi:10.1038/bjc.2011.68 www.bjcancer.com
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Keywords: endometrial cancer; histology; incidence; type 1; type 2; deprivation

Endometrial cancer is now the most common cancer of the female genital tract in the western world, with an estimated worldwide incidence of 287 000 and 74 000 deaths from endometrial cancer in 2008 (Ferlay et al, 2010). Endometrial cancer has increased by over 40% in the United Kingdom since 1993, to 7536 cases in 2007 and 1741 deaths in 2008 (http://info.cancerresearchuk.org/cancerstats/types/uterus/). While the incidence and mortality rates of several other cancers have plateaued or decreased in the last decade the incidence of endometrial cancer has been rising throughout Europe (Jemal et al, 2008). This increase has been attributed to increasing obesity, life expectancy, and adjuvant Tamoxifen use for breast cancer (Bray et al, 2005).

Endometrial cancer can be classified into two distinct groups – type 1 and type 2 based on histology, which differ in molecular as well as in clinical and histopathology profiles (Bokhman, 1983). Type 1 endometrial cancer is oestrogen-driven, of endometrioid histology, arises in the background of endometrial hyperplasia, is strongly linked to obesity, occurs predominantly in pre and perimenopausal women and is associated with good prognosis (> 90% 5-year survival rate) (Doll et al, 2008). Type 2 is non-oestrogen dependent, non-endometrioid, with higher grade histologies, specifically uterine papillary serous carcinomas (UPSCs) and clear-cell carcinomas, more aggressive, and carries an adverse prognosis (Amant et al, 2006; Mendivil et al, 2009). Although type 2 cancers contribute only 10% of endometrial cancer incidence, they cause 50% of recurrence and deaths from endometrial cancer with a low 5-year, all stage, overall survival rate of 35% (Singh et al, 2008; Bansal et al, 2009). Type 2 cancers typically arise in an atrophic endometrial background, and often have deep myometrial penetration and demonstrate lymph node spread. They usually occur at an older age, ~ 5–10 years later than type 1 tumours. In addition, type 1 endometrial carcinomas are characterised by mutations in PTEN, PIK3CA, KRAS, and β-catenin, along with microsatellite instability; type 2 endometrial carcinomas are characterised by genetic alterations in p53, HER-2/neu, p16, and E-cadherin (Llobet et al, 2009).

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Received 27 October 2010; revised 21 January 2011; accepted 1 February 2011
Although the increase in incidence in endometrial cancer is well recognised, the distribution of this increase across the two types of endometrial cancer is not known. This information has vital implications for health policy and the development of targeted therapies in endometrial cancer. Understanding the trends in incidence of endometrial cancer and socioeconomic distributions may help inform strategies to improve early diagnosis and therapy and target healthcare resource efficiently.

In this study, we present an analysis of the observed incidence trends of the two major types of endometrial cancer in the West Midlands area of the United Kingdom from 1994 to 2006. We sought evidence of a differential increase between type 1 and type 2 cancers over this time period, and whether or not this varied with socioeconomic distribution. We also explored age and stage distribution of endometrial cancers over this time period and survival outcome based on histology type and socioeconomic deprivation.

METHODS

Population details

Analysis was performed of prospective data collated on all newly diagnosed endometrial cancer patients registered between 1994 and 2006 at the West Midlands Cancer Intelligence Unit (WMCIU). Registration of a cancer diagnosis usually occurs within 3 months of diagnosis, though registration of all clinical information can take longer. All analysis involving patient identifiable data was conducted on fully complete cases in house by the researchers employed by the WMCIU who are authorized to access these confidential data. The data were then tabulated for use within the paper. The WMCIU houses a population-based cancer registry serving the 5.4 million residents in the West Midlands region of the United Kingdom. All neoplasms of invasive, in situ, uncertain or unknown behaviour are recorded on the WMCIU’s central database. The WMCIU aims to register each case from a range of data sources to ensure the most accurate information possible – full coding of a cancer case may involve data from hospital patient information systems, pathology reports, medical records departments, radiotherapy systems, hospices, other cancer registries, general practices, private hospitals, cancer screening programmes, nursing homes, and death certificates.

Histology

The registry records data on the histology of the cancer as determined by the pathologist issuing the registry occurrence at the time of diagnosis of cancer. These histology reports were categorised into the International Statistical Classification of Diseases and Related Health Problems, 10th Edition, Volume 1 (World Health Organisation) (ICD-10) code C54 = malignant neoplasm of corpus uteri and code C55 = malignant neoplasm of uterus, part unspecified. Specific histopathological tumour types were classified in accordance with the International Statistical Classification of Diseases and Related Health Problems, 10th Edition, Volume 3 (World Health Organisation), referring to the morphology of the cancer site by the same international classification. These morphologies were then further grouped into type 1 and type 2 endometrial cancers by the specialist histopathologist in gynaecological cancer on the team (RG). The WMCIU researchers then applied the appropriate type, based on the groupings produced, to the actual cases included within the study so that the analysis could be carried out.

Type 1 included common indolent types of endometrial adenocarcinoma, which were coded as grades 1–3 endometrioid, mucinous, or adenocarcinoma. Type 2 encompassed the more uncommon and highly aggressive types of uterine cancer. These included those coded as serous, clear-cell, carcinosarcoma or malignant mixed mullerian tumour. Uterine sarcomas and other types of endometrial cancers that are distinct from the above two subtypes were excluded from analysis (Table 1).

Social deprivation

The Indices of Multiple Deprivation 2004 (IMD 2004) is a deprivation index at the small area level, created by the British Department for Communities and Local Government. Commissioned and published by the Department for Communities and Local Government, the Indices of Deprivation 2004 are based upon a mix of 2001 national census data and 2001 administrative data sources. These have been updated with more recent (2005) administrative data sources from Government Departments and have been published as Indices of Deprivation 2007 (Department for Communities and Local Government TElODoL). IMD 2004 is made up of seven distinct dimensions of deprivation called domain indices, which relate to deprivation in income, employment, health and disability, education skills and training deprivation, barriers to housing and services, living environment deprivation, and crime. The deprivation score of the area where the individual lives is assumed to be characteristic of the deprivation experienced by all individuals living there. Scores are calculated at small geographical areas (lower super output areas (LSOA), each containing ~1500 people), but there may still be some variation in deprivation within each LSOA which is not captured in this analysis. All LSOAs in England were ranked according to their deprivation (measured by the 2004 income domain score) and divided into five equal groups (quintiles). The top 20% was defined as the ‘most affluent population of England’. All LSOAs in the West Midlands that were within the scores for the ‘most affluent population of England’ were defined as ‘the most affluent population’ in the West Midlands, and conversely LSOAs that were within the scores for ‘the least affluent population of England’ were defined as the ‘least affluent population’ in the West Midlands. Each cancer registration is routinely assigned a deprivation score and quintile by the WMCIU based upon the diagnosis postcode/address information received for each case. The data for this study therefore already contain the deprivation index. Because of the possibility of ‘mathematical coupling’ whereby the relationship between IMD 2004 and markers of health can be predicated by including the health domain of IMD 2004, this analysis focuses only on the income domain of IMD 2004 where 1 = the most deprived and 5 = the least deprived (Archie, 1981; SIGN, 2002).

Statistical analysis

Age standardised incidence rates (ASRs) were calculated via the direct method. Age standardisation was conducted using the standard European population throughout; all figures are based on a female population. To assess the statistical significance of the results, 95% confidence intervals (CIs) were also calculated for the ASRs using the Poisson distribution (Breslow NEaDNE, 1987). Relative survival analysis was performed to all cancers.

Relative survival is defined as the observed survival in the patient group divided by the expected survival of the general population, matched by age, sex, and calendar year (Dickman et al, 2004). Relative survival was calculated in STATA (v.11) (StataCorp LP, College Station, TX, USA) using the str programme which calculates relative survival estimates using the Ederer II method (Evaluation Section NCI, 1959; http://www.pauldickman.com/survival/strs.pdf). National life tables were obtained from the Cancer Research UK Cancer Survival Group at the London School of Hygiene and Tropical Medicine. One- and five-year relative survival was calculated using 5-year rolling averages.

The incidence of endometrial cancer, its two subtypes, and the relative proportions were tested with Pearson’s correlation with
A total of 7465 women with endometrial cancer were registered at the WMCIU during 1994–2006. We excluded 598 cases that did not conform to either type 1 or type 2 histology, giving a final total of 6867 cases. Of these, 5903 were classified as type 1 and 964 as type 2 endometrial cancers as per histology classified in Table 1. Less than 2% of endometrial cancers analysed as type 1 or type 2 were death certificate only (DCO) registrations. These cases have been included for the purpose of calculating incidence rates as they represent real cases and so trends in incidence of these endometrial cancers were analysed. Given that DCOs represent <2% of cases, they have been removed from the survival analysis due to insufficient information regarding the duration of disease and the possible bias this could introduce to the analysis. This is a widely used approach applied in other studies of cancer survival (De Angelis et al, 2009; Coleman et al, 2011). An overall increase in the ASR of endometrial cancer was observed over the time period, from 16.1 per 100 000 population (CI 14.6–17.5) in 1994 to 19.6 per 100 000 population (CI 18.1–21.1) in 2006. Analysis by type of endometrial cancer revealed a marked differential trend in incidence by type. The ASRs of type 1 cancers showed a highly significant linear increase from 12.0 per 100 000 (CI 10.7–13.2) in 1994 to 16.3 (CI 14.9–17.7) in 2006, \( r = 0.94, P < 0.001 \). However, the ASR of type 2 cancers remained static; 2.5 per 100 000 (CI 2.0–3.1) in 1993 compared with 2.2 per 100 000 (CI 1.7–2.7) in 2006, \( r = -0.15, P = 0.633 \). This is represented graphically in Figure 1.

The overall distribution of our cases among the socioeconomic quintiles was roughly similar with the exception of the smaller proportion of cases overall that were diagnosed in the most
affluent quintile (Table 2; quintiles 1–5 with 1 being most deprived and 5 being least deprived). Analysis of the increase in type 1 endometrial cancer by socioeconomic distribution revealed that this increase in incidence rates was evenly distributed among all socioeconomic quintiles. There was a strong relationship between the rates of increase in groups 1 and 2 vs groups 4 and 5, \( r = 0.74, P = 0.004 \). Figure 2 represents an analysis of type 1 cancer incidence comparing groups 1 and 2 with groups 4 and 5. When analysing the distribution of all cases by age, the largest proportion of cases fell in the 60–69 age group, which accounted for 31% of all cases. The 0–59 group was the second largest, although in over 99% of cases, the age at diagnosis was in the 30–59 age group (Table 3). To investigate the impact of increased life expectancy on type 1 cancer we analysed the ASRs in age groups 0–59, 60–69, 70–79, and over 80 years. An increase in type 1 endometrial cancer was seen in age groups 0–59 years: \( r = 0.707, P = 0.007 \); 60–69 years: \( r = 0.861, P < 0.001 \); and 70–79 years: \( r = 0.838, P < 0.001 \) over the study period, while the age standardised incidence in the over 80 years remained static; 80+ years: \( r = 0.24, P = 0.418 \) (Figure 3).

Over the study period, there was an overall improvement in 1-year and 5-year relative survival rates for all morphologies combined (types 1 and 2 and all other morphologies) of endometrial cancer. One-year survival improved from 85.6% in time period 1994–1998 to 90.3% by 2003–2007, and 5-year survival from 73.2% in 1994–1998 to 75.8% in 1999–2003, \( r = 0.86, P = 0.001 \). This improvement was limited to type 1 cancer, with 1-year survival improving from 89.1% in 1994–1998 to 94.7% by 2003–2007, \( r = 0.94, P < 0.001 \). Five-year survival in type 1 cancer increased slightly from 78.7% to 82.4%, \( r = 0.33, P = 0.950 \), but the difference was not statistically significant. Specifically, outcome for type 2 cancers demonstrated a deterioration over time, with 1-year relative survival unchanged from 73.1% in 1994 to 74.3%, \( r = -0.56, P = 0.089 \) and 5-year relative survival decreasing from 55.1% to 40.9%, \( r = -0.98, P = 0.001 \) over the study period (Figure 4).

We investigated survival by individual deprivation quintile and by separate subtype, however, due to small numbers, the data were found to lack robustness and so have not been presented. To investigate the deprivation gap in relative survival for endometrial cancer we therefore combined all morphologies (type 1, type 2 and all other morphologies). One-year survival rates for endometrial cancer showed no impact as a result of deprivation, 2003–2007 data, groups 1 and 2 showed 90.5% (CI 88.4–92.2%) while groups 4 and 5 showed 90.0% (CI 87.9–91.7%) relative survival rates. However, analysis of 5-year survival in women diagnosed from time periods 1994 to 2003, demonstrated a significant improvement in relative survival in more affluent groups 4–5, from 74.8% to 78.5%, \( r = 0.66, P = 0.036 \), while survival was not significantly better, 69.8–72.4%, \( r = 0.66, P = 0.151 \) in less affluent groups 1–2, over the study period. The difference in survival between groups 1–2 and 4–5 was not significant, \( r = 0.27, P = 0.6 \). Type 1 cancer was more frequently diagnosed at an earlier stage, 69% at stages 1–2 and 4–5 vs 59% at stages 1–2 and 4–5, respectively, and stage at diagnosis was significantly related to socioeconomic distribution. Confidence intervals for both graphs overlap at each time point.

**Table 2** Socioeconomic distribution of endometrial cancers diagnosed in the West Midlands, 1994–2006

| Deprivation quintile  | Proportion (%) |
|-----------------------|----------------|
| Least affluent         | 21.1           |
| Less affluent          | 20.7           |
| Average               | 20.4           |
| More affluent          | 22.6           |
| Most affluent          | 15.1           |

**Table 3** Age distribution of endometrial cancers diagnosed in the West Midlands, 1994–2006

| Age group (years) | Proportion (%) |
|-------------------|----------------|
| 0–29              | 0.1            |
| 30–34             | 0.3            |
| 35–39             | 0.9            |
| 40–44             | 1.7            |
| 45–49             | 3.8            |
| 50–54             | 8.8            |
| 55–59             | 14.2           |
| 60–64             | 15.2           |
| 65–69             | 15.3           |
| 70–74             | 13.5           |
| 75–79             | 12.0           |
| 80–84             | 7.7            |
| 85+               | 6.3            |

**Figure 2** Analysis of increase in type 1 endometrial cancer rates by socioeconomic distribution. Confidence intervals for both graphs overlap at each time point.

**Figure 3** Analysis of type 1 endometrial cancer incidence by age groups.

**Figure 4** Five-year relative survival of endometrial cancer types 1 and 2.
and 2 vs 43% at stages 1 and 2 for type 2 cancers. However, these data have to be interpreted with caution, as data on stage were incomplete in at least 20% of cases.

DISCUSSION

This study identifies a differential increase in endometrial cancer from 1994 to 2006 based on data from a population-based cancer registry, with a marked increase in oestrogen-dependent type 1 cancers and a static level of type 2 cancers. To our knowledge, this is the first paper to demonstrate this differential increase. Investigation of ASRs in the different age groups revealed an increase across most age groups 0–79 years, most markedly in age groups 60–69 and 70–79 years. Our data demonstrate the likelihood of an enduring type 1 endometrial cancer risk from hyper-oestrogenic states that persists well beyond the perimenopausal time frame. There is a need for research in prevention strategies that can target this persistent risk, for example, long-term prophylaxis with progesterone or the Mirena progesterone coil, particularly in those most at risk.

Increasing body mass index shows a strong linear relationship with endometrial cancer and some postulate that the incidence of endometrial cancer will rise to twice the 2005 rates by 2015 (Bjorge et al, 2007; Reeves et al, 2007; Renehan et al, 2008; Lindemann et al, 2008, 2010). In the affluent developed world, obesity is unequally distributed with greater prevalence in the more deprived socioeconomic groups (Friel et al, 2007). The prevalence of obesity in women has been shown to rise steadily and significantly with increasing area deprivation from 20.1% in the least deprived to 33.1% in the most deprived (http://www.scotpho.org.uk/home/Clinicalrisk-factors/Obesity/obesity_data/obesity_deprivation.asp). Given that obesity is a significant main driver for oestrogen-related endometrial cancers and a static level of type 2 cancers. To our knowledge, this is the first paper to demonstrate this differential increase. Investigation of ASRs in the different age groups revealed an increase across most age groups 0–79 years, most markedly in age groups 60–69 and 70–79 years. Our data demonstrate the likelihood of an enduring type 1 endometrial cancer risk from hyper-oestrogenic states that persists well beyond the perimenopausal time frame. There is a need for research in prevention strategies that can target this persistent risk, for example, long-term prophylaxis with progesterone or the Mirena progesterone coil, particularly in those most at risk.

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The significant deterioration in 5-year survival rates for type 2 cancers, while incidence remains static, may reflect greater awareness of pathologists of these histologies and improved pathological classification. Our findings are consistent with the Surveillance, Epidemiology and End Results database (SEER), United States study of >45 000 women with endometrial cancer, which suggest that there is an increase in mortality which may be related to advanced-stage cancers and high-risk histologies namely UPSC and clear-cell carcinoma (Ueda et al, 2008). A significant deprivation gap in survival exists between the most affluent and the most deprived groups with endometrial cancer of ~4% based on data from England and Wales with survival lagging 2–6% behind Europe (Kitchener, 2008). Our study confirms that recent improvements in 5-year survival are seen mostly in the more affluent groups, showing that more work is needed to overcome this discrepancy.

The strengths of the study are that it is population based, with data subjected to robust quality assurance and, is therefore likely to accurately reflect changes in incidence in a broader population.

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