Endometrial Cancer Incidence Trends in Europe: Underlying Determinants and Prospects for Prevention

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Abstract

More than one in 20 female cancers in Europe are of the endometrium. Surveillance of incidence rates is imperative given the rapidly changing profile in the prevalence and distribution of the underlying determinants. This study presents an analysis of observed and age-period-cohort–modeled trends in 13 European countries. There were increasing trends among postmenopausal women in many Northern and Western countries. Denmark and possibly France and Switzerland were exceptions, with decreasing trends in postmenopausal women. In premenopausal and perimenopausal women, declines were observed in Northern and Western Europe, most evidently in Denmark, Sweden, and the United Kingdom, affecting consecutive generations born after 1925. These contrast with the increasing trends regardless of menopausal age in some Southern and Eastern European countries, particularly Slovakia and Slovenia. These observations provide evidence of changes in several established risk factors over time and have implications for possible primary prevention strategies. In postmenopausal women, changes in reproductive behavior and prevalence of overweight and obesity may partially account for the observed increases, as well as hormone replacement therapy use in certain countries. Combined oral contraceptive use may be responsible for the declines observed among women aged <55 years. Whereas there are some prospects for chemoprevention in premenopausal women as oral contraceptive use becomes more widespread in Europe, increases in obesity and decreases in fertility imply that endometrial cancer in postmenopausal women will become a more substantial public health problem in the future. (Cancer Epidemiol Biomarkers Prev 2005;14(5):1132–42)

Introduction

Endometrial cancer comprises about 4% of all cancers in women globally and occurs predominantly after the menopause. Some of the highest incidence rates worldwide are found within European populations (1), with rates varying only by a factor of two between countries (2). Cross-sectional incidence rates have been increasing among postmenopausal women in most European populations, whereas mortality rates have been declining, with few exceptions (3). In premenopausal and perimenopausal women, declines have been observed in Northern and Western Europe, most evidently in Denmark, Sweden, and the United Kingdom, affecting consecutive generations born after 1925. These contrast with the increasing trends regardless of menopausal age in some Southern and Eastern European countries, particularly Hungary and the Czech Republic. The epidemiology of endometrial cancer in Western countries is fairly well understood. Family history of endometrial cancer is associated with an increase in risk (4), whereas high parity and late age at last birth is considered to give long-lasting protection (4). The role of obesity as a risk factor in both premenopausal and postmenopausal women is also firmly established (5), whereas there is limited evidence that physical activity has a protective effect (5). Use of combined oral contraceptives (COC) confers a long-lasting protection against endometrial cancer, particularly among long-term users (6). Hormone therapy use for treatment of menopausal symptoms (hormone replacement therapy, HRT) is an important risk factor in countries where their prescription has been common practice in recent decades (4). Risk increases markedly with use of estrogen only and sequential estrogen-progestin HRT, although it may be mitigated by the continuous addition of progestins (7, 8). There is also substantive evidence that smoking is protective (9).

Surveillance of the incidence of endometrial cancer is important from both epidemiologic and public health perspectives. Whereas the rapidly changing profile of the established risk determinants in Europe implies the necessity to monitor endometrial cancer incidence trends, there have been rather few studies published in the last decades. Ewertz and Jensen reported increasing rates between 1943 and 1980 in Denmark, suggesting an increase in estrogen use was responsible among postmenopausal women (10). More recent studies in Sweden (11), East Germany (12), Switzerland (13), and the United Kingdom (14-16) have indicated steady declines in endometrial cancer incidence rates among younger women and in more recent birth cohorts. Most have attributed this phenomenon to the increasing prevalence of COC use (11-15).

This study presents a detailed analysis of age-specific incidence trends of cancer of the corpus uteri across Europe, comparing and contrasting the effects of period of diagnosis and birth cohort in 13 countries. Period effects denote systematic changes in age-specific trends by calendar year, and they often represent artifactual changes in completeness of registration, diagnostic practices, or disease classification (17). They can occur through the introduction of specific environmental factors to which all population members are exposed, regardless of age, for example, following the launch and subsequent uptake of HRT among perimenopausal and postmenopausal women during the 1960s. Cohort effects reflect changes in exposure to risk factors in successive generations. For endometrial cancer, these may include the changing prevalence of COCs among young women, decreasing parity, and a shift towards having children at a later age among more recent birth cohorts.

References

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Materials and Methods

Incidence Data. The incidence and population data sets were extracted from the EUROCRIN software package and database (18) according to registry, the 5-year periods of diagnoses available, and for ten 5-year age groups (30-34, 35-39, ..., 75-79). The inclusion requirement was compilation in each of the last three volumes (VI-VIII) of Cancer Incidence in Five Continents (19-21), an indicator of consistent quality of data with time, given the editorial process involves a detailed assessment of comparability, completeness, and validity of incidence data. For the 13 countries, the span of registry data available varied from 15 to 45 years (Table I, columns A-C). In France, Italy, Switzerland, and Spain, a number of regional registries were aggregated to obtain an estimate of the national incidence. The varying span of data available from these regional registries required an aggregation of the data sets that maximized the registration period and the number of registries represented in each country. The countries are presented by European area (Northern, Eastern, Southern, and Western) according to the United Nations classification.

Statistical Analysis. We present the observed incidence rates by birth cohort and period of diagnosis for each of the 13 countries. Whereas the graphical display may outline the complexity of the disease trends and indicate particular relationships with period and cohort, we fitted the age-period-cohort model (APC) to the trends to aid our understanding of the temporal patterns and formally assess alternative descriptions of the data (22) Assuming the incidence rates were constant within the 5-year age classes $a = 1, 2, \ldots, A$ and 5-year periods of diagnosis $P = 1, 2, \ldots, P$, the APC (22-24) model was fitted in Stata (25), with the rates in each country described by a likelihood for the observations that is proportional to a Poisson likelihood for counts, with the log of the person-years at risk specified as an offset:

$$ \log(\lambda(a, p)) = \alpha_a + \beta_p + \gamma_c $$

Birth cohorts were derived from period and age such that $c = p - a$ for $c = 1, 2, \ldots, C$ with $C = A + P - 1$. The variables $\alpha_a, \beta_p,$ and $\gamma_c$ refer to the fixed effects of age group $a$, period $p$, and birth cohort $c$, respectively.

The APC model cannot estimate the individual linear components of the age, period, and cohort effects due to their linear interdependence. We used the method of Holford (22), partitioning the age, period, and cohort effects in terms of their linear and curvature elements. Specification of the assumed "true" slope for age, period, or cohort leads to unique estimates of the other two slopes. We present two possible sets of age, period, and cohort trends, circumventing the nonidentifiability issue by assuming that:

(i) the steady-state (period and cohort adjusted) age-specific incidence curve for endometrial cancer in each population reflects the sensitivity of the target organ to unopposed estrogens. Moolgavkar (26) suggested the possibility of a generalized age curve and a rather stable risk in women ages >60 years possibly due to their low levels of ancillary estrogens. Such an age curve was fixed for each country by choosing the age slopes $\alpha_i$, for which point estimates at ages 65 to 70, 70 to 74, and 75 to 79 would be reasonably flat (i.e., by selecting the estimate of $\alpha_i$ for which $\alpha_i - \alpha_i - 2 = 0$)

(ii) the cohort effects predominate the trends. Fixing the linear slope of the period effects to zero ($\beta_1 = 0$) allows the cohort slope to take up the entire net drift, the identifiable sum of the period and cohort slopes $\beta_1 + \gamma_1$ while still allowing for nonlinear period effects. The latter assumption implies that risk of endometrial cancer over time is mediated only by a changing distribution and prevalence of the known and putative risk factors in successive generations.

On adding together the linear and curvature components, the individual categories of each effect are obtained. The $a$th age effect can be expressed as $\alpha_a = (a - (A + 1) / 2) \times \lambda_1 + \varphi_a$ with $\varphi_a$ representing the departures from the linear trend. $\beta_1$ and $\gamma_1$, the slopes for period and cohort, can be defined in the same way.

In presenting the model variables, the period and cohort effects were reparameterized to rate ratios with reference

| Table 1. Populations included in the analysis (columns A-E), recent rate (column F), and APC model fit (columns G-J) |
|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| A       | B       | C       | D       | E       | F       | G       | H       | I       | J       |
| European area | Country | Period* | Incidence | Person-years | ASR | APC model | Residual deviance | df | P |       |
| Northern | Denmark | 1979-1998 (4) | 535 | 1.5 | 31.8 | APC | 14.0 | 16 | 0.60 |
|          | Estonia | 1971-2000 (6) | 170 | 0.4 | 34.1 | APC | 43.7 | 32 | 0.08 |
|          | Finland | 1955-1999 (9) | 605 | 1.6 | 35.9 | APC | 116.8 | 56 | <0.01 |
|          | Norway | 1953-1997 (9) | 416 | 1.2 | 33.1 | APC | 67.3 | 56 | 0.14 |
|          | Sweden | 1964-1998 (7) | 1087 | 2.6 | 37.3 | APC | 76.0 | 40 | <0.01 |
|          | United Kingdom | 1978-1997 (4) | 3765 | 15.5 | 22.8 | APC | 37.1 | 16 | <0.01 |
| Eastern | Czech Republic | 1985-1999 (3) | 1496 | 3.0 | 44.9 | APC | 11.7 | 8 | 0.16 |
|          | Slovakia | 1968-1997 (6) | 601 | 1.5 | 41.9 | APC | 56.5 | 32 | <0.01 |
| Southern | Italy | 1983-1997 (3) | 520 | 1.3 | 30.3 | AP | 29.3 | 18 | 0.04 |
|          | Slovenia | 1985-1999 (3) | 246 | 0.6 | 38.2 | AD | 16.5 | 19 | 0.26 |
|          | Spain | 1983-1997 (3) | 285 | 0.7 | 29.4 | AD | 5.0 | 9 | 0.83 |
| Western | France | 1978-1997 (4) | 311 | 0.8 | 27.8 | A | 34.5 | 30 | 0.26 |
|          | Switzerland | 1983-1997 (3) | 291 | 0.7 | 32.7 | AD | 22.5 | 19 | 0.26 |

NOTE: Abbreviations: A, age; AD, age + drift; AC, age + drift + cohort; AP, age + drift + period; APC, age + drift + period + cohort.

*Data available according to period of diagnosis, value in parentheses represent number of 5-year periods available in the analysis.

†Truncated annual number of cases and person-years (per million) obtained from most recent 5-year period.

‡Refers to the most parsimonious final model providing a good fit.

To determine the goodness-of-fit, the deviance was compared with the chi-squared distribution on the degrees of freedom (df) determined by the model. $P < 0.05$ indicates the full APC model does not yield an adequate fit.

Aggregation of England, Scotland.

Aggregation of Florence, Varese Province, Parma Province, Ragusa Province, Turin.

Aggregation of Catalonia, Tarragona; Granada, Murcia, Navarra, Zaragoza.

Aggregation of Basel, Geneva, Neuchatel, St. Gall-Appenzell, Vaud, Zurich.
points $P - 1$ and $A + P - 6$, respectively. These variables thus described the risk of cancer of the corpus uteri in a given generation or period of diagnosis, relative to a reference category that was dependent on the particular time period analyzed in each country. The reference midpoints varied from 1990 to 1993 for period and from 1938 to 1941 for birth cohort.

APC models were also fitted in substrata according to menopausal status (ages 30-54 and 55-79 years). However, the generated models did not substantially alter the results obtained for the ages 30 to 79 years, in terms of the significance of individual effects, the overall fit of the hierarchical models, or the interpretation of the variables. We thus present the results solely based on incidence data covering both premenopausal and postmenopausal age groups. It should be noted that due to a paucity of relevant data either by country, age, or over time, the person-years at risk in these analyses remain unadjusted for hysterectomy status.

Discussion

Our study has shown there are distinct patterns in the age-specific trends of cancer of the corpus uteri. A general profile emerged of increasing risk in postmenopausal women (ages >55 years), and decreasing or stable trends in premenopausal and perimenopausal women (ages 50-54 years), particularly in Northern and Western countries. The most consistent declines in these regions were observed in women ages 45 to 54 years in France (Fig. 1). These trends can be considered similar to those observed in Denmark. The suggestion of increases in younger generations in France (Fig. 2) cannot be confirmed or refuted, given the degree of randomness underlying these trends.
Figure 1. Age-specific incidence rates of cancer of the corpus uteri by calendar period and birth cohort in 13 countries by European area, women ages 30 to 79 years. Age-specific rates on the cohort scale are identified by the midyear of the quinquenniums.
Figure 1. Continued
short-term future patterns of risk, these are unfortunately only interpretable in a few countries where sufficient numbers of cases are available. Additionally, the narrow span of period data for a number of countries (only three periods of incidence were available in five countries) made interpretation of the corresponding trends in these populations difficult.

The modeled component involved an APC analysis. Such an undertaking results in difficulties at the analysis, presentation, and interpretation stages (27). In this article, we have sought to present one set of trends for which an element of biological plausibility is preserved. The nonidentifiability problem was circumvented by fixing the underlying age structure via the long-standing consideration that endometrial cancer is a consequence of the physiologic action of unopposed estrogens that increase the cell proliferation, opposed by progestins which instigate differentiation to a secretory state (7, 28). As a comparison, a second set of age, period, and cohort trends were obtained on simply assuming an overall period slope of 0 (29), whereby the changing distribution and prevalence of the component causes are presumed to show up mainly as generational influences in each country, with the nonspecific linear trend (drift) attributable to birth cohort only. In this formulation, nonlinear period effects are also considered. The estimates presented in Fig. 2 must clearly be interpreted with considerable caution, given our inability to quantify the slopes for period and cohort. Nevertheless, our estimates are based on two plausible assumptions that serve to aid interpretation of the observed rates in Fig. 1.

These difficulties notwithstanding, the trends provide clues to changing distribution of the primary risk factors, including use of exogenous estrogens, reproductive factors, overweight and obesity, and smoking, and the potential for successful preventative strategies aimed at the population level in Europe. Below, we compare our results with previous preventative strategies aimed at the population level in Europe. Below, we compare our results with previous preventative strategies aimed at the population level in Europe.

**Trends in Postmenopausal Women.** The rising trends in women ages ≥55 years, as observed in many Northern and Western European countries, imply both period and birth cohort influences are in operation. Possible underlying mechanisms include temporal changes in reproductive behavior and in the prevalence of overweight and obesity. Early age at menarche has been consistently described as a risk factor for endometrial cancer (4). During the last 150 years, age at menarche has declined at a rate of about 2 to 3 months per decade (30). Completed family size has declined among female cohorts born during the 20th century in most European countries (31). The most substantial decreases occurred following the post-war “baby boom;” the peak in total fertility rates in the early to mid-1960s was followed by declines in successive generations born after the mid-1930s (32). Nulliparity decreased in most European countries for cohorts born from 1930 to 1945 (32). In England and Wales, where data are available for a longer period, the decline in nulliparity began for cohorts born since 1910 (15). A recent study indicated that reproductive patterns may account for about half of the cases of endometrial cancer in Sweden in women diagnosed from 1961 to 2002 (33), although the importance of reproductive behavior on risk has been shown to decrease at older ages (34).

The use of HRT has been common in the Nordic countries and Western Europe, first during the 1960s as estrogens without added progestins, and from the mid-1970s, as a succession of preparations combining estrogens and progestins either sequentially, cyclically, or continuously (8). Several studies confirmed a strong association between use of estrogens without progestins and endometrial cancer risk (4), and a few studies also showed that the addition of progestins sequentially or cyclically to estrogens increases risk too (35, 36). Risk increases with duration of HRT use and remains increased some years after cessation (8, 37, 38).

Part of the increase in risk of endometrial cancer among postmenopausal women may be related to the use of HRT in the European regions where use has been widespread (i.e., in Northern and Western Europe; ref. 39). There are uniform increases in rates with time in Finland, Norway, Sweden, and the United Kingdom, and to a much lesser extent, in Estonia. In Finland and Norway, the cohort-specific increases in endometrial cancer began in women born towards the end of the 19th century, for which exogenous estrogens are an unlikely explanation; these women were ages >65 years when HRT was first introduced. Women born from 1910 onwards would have in theory the possibility of having been exposed to HRT. Indeed the main acceleration in risk among postmenopausal women in Sweden is seen after 1910 and coincides with the market introduction in the mid-1960s, and peak of sales in the mid-1970s (11). The decreases in sales of estrogens without added progestins for treatment of menopausal symptoms
of “ever users” of hormonal contraceptives was about 40% for women born in the 1930s (51) compared with ~70% in birth cohorts of 1940s and 80% to 90% for those born in the 1950s (15). In other European countries, the prevalence of use of COCs has varied, being quite high in Northern and Western Europe, to less common in Southern and Eastern Europe before the 1980s (39).

The use of hormonal contraceptives may, at least in part, be responsible for the decreases in incidence in several countries. Steadily increasing incidence rates of endometrial cancer in the Czech Republic and Slovakia in Eastern Europe, as well as in Slovenia and Spain in Southern Europe have been observed both in younger and older women. An explanation for the endometrial cancer trends in premenopausal ages may be that women in these regions have failed to benefit from the protective effects of COC due to their unavailability. Fertility has also been on the decline, although more slowly than seen elsewhere in Europe (47).

The declines seen in Sweden are not evident among premenopausal women in Finland and Norway. Furthermore, there is some indication that there are increasing trends in young women in Finland and possibly elsewhere (e.g., France). It is at present difficult to explain such a trend, should it be genuine. In any case, it is too early to conclude whether the observed incidence pattern might project itself into the future, given the underlying random variation arising from small numbers.

The above findings are in broad agreement with previous temporal studies in Europe either at the international level (52), or within individual countries. Declines in incidence have been reported either in terms of cross-sectional declines in younger women or in successive generations of women born after 1920 in Sweden (11), England and Wales (14-16), East Germany (12), and Switzerland (13).

We are not aware of major changes in routine diagnostics for endometrial cancer in Europe that may have affected the results presented. New cases of uterine cancer with subsite unspecified represent a small proportion of all uterine cancers in each of the populations studied and over time (18-21). One possible artifact involves countries where HRT is most prevalent. Women who are users of menopausal hormones are likely to be more intensively investigated, and early precancerous or cancerous lesions more readily detected and reported to the cancer registries as cancers.

Hysterectomy in Europe is not as common a procedure as it is in the United States, where over 30% of postmenopausal women may have undergone hysterectomy (53). Recent evidence suggests that adjustment for hysterectomy affects the magnitude and direction of trends in endometrial cancer (54). We did not take into account hysterectomy rates in our analysis due to a lack of data for different countries in different periods and ages, and the varying prevalence of hysterectomies may have affected the trends. The incidence of hysterectomy has been increasing in Finland (54), Denmark (55), and England and Wales (16), and the unadjusted trends presented here may underestimate the overall time trend and thus the cohort-specific trends. As noted by Ewertz and Jensen (10), the assumption of a decline after the menopause used here to present one set of age, period, and cohort trends may be artificially distorted by a declining number of “susceptibles” (i.e., women who have not had a hysterectomy).

Conclusions

We have observed uniform increases in rates of endometrial cancer incidence among the main risk group, postmenopausal women, in most European countries studied, with Denmark being an important exception. Both calendar period and birth cohort effects seem in operation. The reasons for
Figure 2. Incidence rate ratios of cancer of the corpus uteri by calendar period and birth cohort in 13 countries by European area, women ages 30 to 79 years. Estimates are obtained from the APC model with solid lines referring to assumption that age curve is fixed by choosing the age slope for which $\alpha_A = \alpha_A - 2 = 0$, and dashed lines that the linear slope of the period effects is 0 ($\beta_L = 0$; see Materials and Methods).
Figure 2. Continued
the increases in countries as diverse as Sweden and Slovakia may include a general Europe-wide shift towards declining fertility rates and marked increases in overweight and obesity, although only in Sweden and several other affluent countries can the effects of HRT be responsible for the rising trends. In premenopausal and perimenopausal women, rates are declining in Sweden, Denmark, and the United Kingdom, mostly evidently in successive cohorts born since 1930. The downward trends in young women are presumably the result of increasing use of COCs in these countries, because they became available mainly to cohorts born in the mid-1920s and thereafter. In a number of Southern and Eastern countries (notably Slovakia), trends are increasing regardless of menopausal age, countries for which the lack of availability of COCs has offered little protection to younger women. Prevention of endometrial cancer will possibly be realized in these areas as COC use becomes increasingly widespread. The continuing increases in obesity and decreases in fertility however forewarns that endometrial cancer, as a postmenopausal disease, will become a more important public health problem in Europe in future years.

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Figure 2. Continued


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