CHAPTER 4

Trends in Incidence Rates of Breast, Cervix Uteri, Ovary and Corpus Uteri Cancers in Thiruvananthapuram

In this chapter, various analytical approaches employed in the present thesis to estimate trends in incidence rates of breast, cervix uteri, ovary and corpus uteri cancers are provided (Section 4.1). Section 4.2 to 4.4 provide estimates of trends in incidence rates of the above four cancers in Thiruvananthapuram. In Section 4.5, the advantages and limitations of the data are discussed and in Section 4.6, trends in incidence and mortality rates of the above four cancers published worldwide are provided.

4.1. Introduction
Initially estimated annual percentage change using relative difference between the two time periods (earliest and latest) using age-standardized incidence rate of the above four cancers. Then annual percent changes in incidence rates of cancers were
estimated by means of a linear regression analysis through the maximum likelihood procedure for each time period 1991 to 2010. Further, long-term trends in incidence rates (1991-2010) of the above four cancers were analyzed using joinpoint regression model. This model was used to identify points where a statistically significant change over time in linear slope of the trend occurred. This method describes changes in data trends by connecting several different line segments on a log scale at ‘joinpoints’. In joinpoint analysis, the best-fitting points where the rate changes significantly (increase or decrease) are chosen. Analysis starts with the minimum number of joinpoints (i.e. 0 joinpoint, representing a straight line) and tests whether one or more points are statistically significant and should be added to the model (up to four joinpoints). Tests of significance use a Monte Carlo permutation method. In addition, an annual percent change (APC) in incidence rates for each line segment and the corresponding 95% confidence interval were estimated. The APC is tested to determine whether a difference exist from the null hypothesis of no change (0%). In the final model, each joinpoint indicates a statistically significant change in trend, and an APC is computed for each of those trends by means of generalized linear models assuming a Poisson distribution. Significant changes include changes in direction or in the rate of increase or decrease (Kim et al., 2000). Joinpoint analyses were performed using the ‘Joinpoint’ software from the Surveillance Research Program of the US National Cancer Institute (2003).

Average Annual Percent Change (AAPC), a summary measure of the trend over a pre-specified fixed interval is finally estimated. It is computed as a weighted average of the APC's from the joinpoint model, with the weights equal to the length of the APC interval. AAPC is derived by estimating the underlying joinpoint model that best fits the data. Estimated annual percent change in incidence rates (rates that change at a constant percentage every year linearly on a log scale) and average annual percent change via joint point regression model for the above four cancers are compared and these estimates are used for projection of cancer.
4.2. Percent change

During the 20 year period, 1991-2010, breast, ovary and corpus uteri cancers rose substantially in Thiruvananthapuram. The rates increased to 96%, 94% and 125% for breast, ovary and corpus uteri cancers respectively and cervix uteri cancer is decreased to 18% from the period 1991-1995 to 2006-2010 (Table 4.2.1).

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>107</td>
<td>20.5</td>
<td>210</td>
<td>35.2</td>
<td>95.56</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>63</td>
<td>12.0</td>
<td>51</td>
<td>8.6</td>
<td>-18.05</td>
</tr>
<tr>
<td>Ovary</td>
<td>22</td>
<td>4.2</td>
<td>43</td>
<td>7.1</td>
<td>94.11</td>
</tr>
<tr>
<td>Corpus uteri</td>
<td>14</td>
<td>2.7</td>
<td>32</td>
<td>5.4</td>
<td>124.59</td>
</tr>
</tbody>
</table>

4.3 Estimated annual percent change via joinpoint regression model

There was a steep increase in breast cancer incidence rates in Thiruvananthapuram from 1991 to 2000, then slightly increased till 2010 (Figure 4.3.1). Hence two different joinpoints were used and estimated the annual percent change (EAPC) according to the two segments such as 1991-2000, 2001-2010. The corresponding EAPCs were 6.8%, 1.6% per year in the respective segments. The EAPCs were statistically significant. Widely scattered values are observed for corpus uteri and ovarian cancers due to the small number of cases. However, similar to breast cancer, increased incidence rates were observed for ovary and corpus uteri cancers in Thiruvananthapuram. From Figures 4.3.3 and 4.3.4, it was observed that the increase was almost linear. Hence only one joinpoint was used and the corresponding estimated the annual percent changes were 3.7%, 6.6%, per year for ovary and corpus uteri cancer respectively. The EAPCs were statistically significant. In contrast to the above cancers, cervix uteri cancer incidence rates were decreasing and from Figure 4.3.2, it was observed that the decrease was linear. Thus only one joinpoint was used. The corresponding EAPC was 2.2% (Table 4.3.1).
Table 4.3.1. Estimated annual percentage change in age-standardized rates identified via joinpoint regression: Breast, cervix uteri, ovary and corpus uteri cancers in Thiruvananthapuram Taluk (1991-2010)

<table>
<thead>
<tr>
<th>Site</th>
<th>Segment</th>
<th>EAPC (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>i</td>
<td>1991-2000</td>
<td>6.8*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.8, 9.8</td>
</tr>
<tr>
<td></td>
<td>ii</td>
<td>2001-2010</td>
<td>1.6*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-0.5, 3.7</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>1991-2010</td>
<td>-2.2*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-3.2, -1.2</td>
</tr>
<tr>
<td>Ovary</td>
<td>1991-2010</td>
<td>3.7*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.8, 5.6</td>
</tr>
<tr>
<td>Corpus uteri</td>
<td>1991-2010</td>
<td>6.6*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.4, 12.2</td>
</tr>
</tbody>
</table>

*significant at 5% level

Figure 4.3.1. Estimated annual percentage change via joinpoint regression of age-standardized rates of breast cancer in Thiruvananthapuram Taluk (1991-2010)

Figure 4.3.2. Estimated annual percentage change via joinpoint regression of age-standardized rates of Cervix uteri cancer in Thiruvananthapuram Taluk (1991-2010)
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Figure 4.3.3. Estimated annual percentage change via joinpoint regression of age-standardized rates of ovarian cancer Thiruvananthapuram Taluk (1991-2010)

Figure 4.3.4. Estimated annual percentage change via joinpoint regression of age-standardized rates of Corpus uteri cancer Thiruvananthapuram Taluk (1991-2010)

4.4. Average annual percent change

Overall increasing trends were observed for the cancer sites such as breast, ovary and corpus uteri and decreasing trend for cervix uteri during the period 1991-2010. The average annual percent changes (AAPC) were 1.6%, 3.7%, 6.6% and -2.2% for breast, ovary, corpus uteri and respectively. All the changes were statistically significant (Table 4.4.1).
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Table 4.4.1. Average annual percentage change (AAPC) identified via joinpoint regression of the age-standardized rates of breast, cervix uteri, ovary and corpus uteri cancers in Thiruvananthapuram Taluk (1991-2010)

<table>
<thead>
<tr>
<th>Site</th>
<th>AAPC (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>1.6*</td>
<td>-0.5, 3.7</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>-2.2*</td>
<td>-3.2, -1.2</td>
</tr>
<tr>
<td>Ovary</td>
<td>3.7*</td>
<td>1.8, 5.6</td>
</tr>
<tr>
<td>Corpus uteri</td>
<td>6.6*</td>
<td>1.4, 12.2</td>
</tr>
</tbody>
</table>

*significant at 5% level

4.5. Discussion

To assess trends in incidence rates of cancer, three different methods such as percent change, annual percent change using linear regression model and average annual percent change via joint point regression model. The variations in incidence rates of breast, cervix uteri, corpus uteri and ovarian cancers during the period 1991-2010 were obtained. Based on the incidence rates during the 20-year (1991-2010) period, it was observed that the estimated annual percent change (EAPC) was 3.8% (p<0.05) (assuming linearity). However, it was observed that the rates were not increased monotonically for breast cancer and thus strictly an assumption of linear increase may be biased. Considering two joinpoints, the average annual percent change (AAPC) for breast cancer incidence rate was 1.3% (p<0.05). Similarly the EAPC and AAPC were -2.2% and -2.2% for cervix cancer, 3.3% and 2.9% for ovarian cancer and 6.7% and 2.9% for corpus uteri cancer respectively.

The data on occurrence of cancers is available since 1991 from the Population-based cancer registry (PBCR) established in the Regional Cancer Centre, Thiruvananthapuram. Although the area and population covered by these registries is small, the present analyses give some idea on the magnitude of breast, cervix uteri, corpus uteri and ovarian cancers in the community.

Reporting APCs for each joinpoint segment provides a complete characterization of the trend over time. The statistical power to determine if an APC is different from 0 is a function of the length of the interval. Thus, a short segment rising at a steep rate may not
be statistically significant. Prior to the development of the joinpoint and AAPC methodology, to characterize a trend over a fixed interval, a single regression line (on a log scale) over the fixed interval was fit, and the slope coefficient was then transformed to an APC. EAPC has two disadvantages over AAPC. First, EAPC assumes linearity of the trend (on a log scale) over the interval, while the AAPC does not. Secondly, the AAPC can be used to characterize a short segment based on a joinpoint model fit over a much longer series. This is especially advantageous for situations when the data are rare or data from a small geographic area. In these cases, because of the variability of the underlying data, the older method estimates an APC with a wide confidence interval.

The absolute number of these cancers is increasing rapidly due to an increase in the size of the population as well as an increase in the proportion of elderly persons due to improved life expectancy. In general trends or change in the rates of cancer may occur from a variety of factors such as initiation of screening programme, completeness and reliability of data, changing profile of risk factors in the population, or as a consequence of better health awareness. The increase in the incidence over time period suggests that there has been an increase in the exposure factors for the development of disease over successive calendar years. Various indices of reliability viz. proportion of microscopic verification of diagnosis; proportion registered by death certificates alone and percentage of deaths have been used in the cancer registry.

Statistically significant increase in EAPC was noted for incidence rates of breast, ovary and corpus uteri cancers. Some of the widespread increase in the incidence of breast, ovary and corpus uteri cancers may be accounted for by the trends, in aspects of reproductive behavior that are known to be associated with the risk of these cancers progressively smaller family size and proportion of never married women, nulliparous women are also at an elevated risk.

The strengths of the analysis arise from the fact that population-based incidence and not mortality trends considered. Incidence rates are more closely related to trends in factors that affect the etiology of the disease, whereas mortality would also be affected by trends in treatment for the disease. Although substantial advances in treatment of these cancers have been a relatively recent phenomenon, there may have been some systematic improvement in prognosis that would make the mortality rate more difficult to interpret within the framework of the etiology of these cancers.
As regards the reliability of data, Thiruvananthapuram cancer registry (TCR) routinely undertake various exercises to ensure that the data they collect and process is of high quality. A high percentage of cases are diagnosed with histological confirmation (more than 90%). A through check of data is done before tabulation by employing various reliability indices. This confirms that the incidence data collected by the TCR is of acceptable standard and an interpretation of the observed trends can be attempted.

Joinpoint regression analysis is the first kind of analysis of trends over time in India. The use of Joinpoint analysis has allowed statistical testing of directions and sizes of trends in incidence rates for female breast and reproductive tract cancers, detecting some significant changes. Accordingly, joinpoint analysis provides a much clearer picture of what is happening during a distinct period in specific terms (identifying the years in which significant changes in trends occurred) than a single summary trend statistic (Kim et al., 2000).

### 4.6. Trends in incidence or mortality rates of breast, cervix uteri, ovary and corpus uteri cancers - worldwide scenario

Time trend analysis of breast, cervix uteri, ovary and corpus uteri cancers published in the literature employing different regression models such as log-linear model, Poisson regression model, Joinpoint regression model etc. are provided in the subsequent session.

**Breast cancer**

Breast cancer in the US women have steadily increased for decades. The trends with period increased after 1982, when more aggressive screening began, and the trend is steeper for women older than 40 years. Birth cohort trends have increased steadily and the trends for those older than 50 years have continued to increase (Holford et al., 2006). The continuing increase in incidence in the US from 1975 to 2002 is limited to White women aged 50 and older. Among women of all races and ages, breast cancer mortality rates declined at an average rate of 2.3% per year between 1990 and 2002. Death rates in African American women remain 37% higher than in Whites, despite lower incidence
Early detection of breast cancer in White and Black women followed a similar pattern of significant increase in the early 1980s that continued through 1998 with slight modification in 1987 (Nasseri 2004). The San Francisco Bay Area has a history of high breast cancer incidence rates relative to the rest of the US. For Marin County, where rates are high, women aged 45 to 64 experienced a marked increase in breast cancer rates between 1991 and 1997 (EAPC= 8%, p=0.02), regardless of disease stage or tumor histology (Prehn et al., 2002). Breast cancer mortality rate for US White females dropped 6.8% from 1989 through 1993. A significant decrease in the slope of the mortality trend of approximately 2% per year was observed in every decade of age from 40 to 79 years of age (Chu et al., 1996). Thirty-five year trends in Alaska Native people in the US showed increasing rates in breast cancer. Increasing breast cancer rates among Alaska Natives has greatly contributed to the increasing burden of cancer in women (Day et al., 2007).

South Asians comprise people having origins mainly in India, Pakistan, Bangladesh and Sri Lanka forms a large majority of the Asian population of US. Compared to Asian/Pacific Islander of California, South Asian population experienced more breast cancers with significantly increasing time trends in incidence between 1988-2000 (Jain et al., 2005). In Puerto Rico, breast cancer incidence rate (per 10^5) increased from 15.3 in 1960-1964 to 43.3 in 1985-1989 and corresponding mortality rate increased from 5.7 to 10.6 from two time periods 1960-1964 to 1985-1989 (Nazario et al., 2000).

Incidence trends (1932-1990) of breast cancer by age, sex and birth cohort in Saskatchewan, Canada showed a continuously increasing trend since the 1930s. The trend was age dependent--in general, the 60 years and older age group had greater increases in incidence rates than did younger age groups. The increase in incidence rates in the 45 years and older age group was consistent over time and incidence rates for those younger than 45 years increased until the 1960s, with a decline in trend following the 1960s. Birth cohort was a significant factor in the incidence of breast cancer (Wang and Cao 1996).

Trends in mortality rates from breast cancer over the period 1970-2000 were analyzed for 38 European countries. A favorable pattern in breast cancer mortality in 25 countries of the European Union (EU) was observed after 1989, leading to a fall in overall rates from 21.3/10^5 in 1990 to 18.9 in 2000. The EAPC in the EU was -2.1% between 1995
and 2000. Most northern European countries, including several Scandinavian countries and the UK, but also some central and southern European countries like Germany, Poland, the Czech Republic, Austria, Switzerland, Italy and Spain showed appreciable falls in rates (i.e. between 8 and 19% in the last 5 calendar years). The falls were smaller in France, Greece, Portugal and most eastern European countries. In the Russian Federation, all-age breast cancer mortality increased from 16.1 to 17.3/10^5 (+7.5% over the last 5 calendar years) (Levi et al., 2005).

An accelerated increase in breast cancer incidence rates in Japan during 1959-1997 took place. The effects of period and cohort were statistically significant. The nonlinear effect for cohort indicates an increasing trend, beginning with the cohort in 1888-1897, and the non-linear effect for period showed a clear increase in risk with calendar period. The full model including a linear component showed a steadily upward trend in the cohort effect (Minami et al., 2004). An increasing trend was confirmed for breast cancer mortality in Japan between 1958 and 2004 (Qiu et al., 2009). Trends in breast cancer mortality among first-generation Japanese-Brazilians in the state of São Paulo between 1979 and 2001 were compared with those for Japanese living in Japan and Brazilians living in the state of São Paulo. Increasing trends for breast cancer over the 20 years in all three populations was observed. Standardized mortality ratios from breast cancer in Japanese-Brazilians increased over the last 20 years and intermediate between those for Japanese living in Japan and Brazilians living in the state of São Paulo (Iwasaki et al., 2008).

Time trend analysis showed that breast cancer incidence is increasing significantly in Alexandria, Egypt during 1972 to 2001. Age-incidence correlation showed a high correlation between age group of 40-50 years old and incidence. Highest occurrence of breast cancer is shown in the age category of 45-50 years followed respectively by the age categories of 40-45 years, 50-55 years, 35-40 years and then 55-60 years (Hosny and Elkaffas 2002).

The risk of breast cancer death in Korea was found to increase with age after adjusting for the cohort effect, and it was different from the cross-sectional age curve. Also, breast cancer mortality increased along with the birth cohort (Choi et al., 2006). Breast cancer incidence rates in Korea increased from 14.5 in 1993 to 26.2 per 10^5 in 2002 and age-specific incidences showed peaks among women in their forties. Mortality
Breast cancer mortality rates in Spain increased 2.18% per year during 1977-1991 followed by a significant fall after 1992 (EAPC= -2.67%; 95% CI: -2.97, -2.31). Cohorts born before 1952 showed higher risk of death than those born after this year. Projections showed an increase of mortality among women older than 50 years in the period 2002-2016 (range of increase=10%-40%) (Clèries et al., 2006). Breast cancer incidence in Italy significantly increased (EAPC= +1.7%) and mortality decreased since 1989 (EAPC=-2.0%) (Crocetti et al., 2004). Trends in incidence rates for Maori and non-Maori population in New Zealand were computed from all primary cancers of the breast registered in the National Cancer Registry, 1978-92. The age-specific rates increased sharply from age 20, leveled out at age 45 and slowly increased through 85 years and older. In New Zealand, there were steady, but non-significant, increases in the incidence rates of BC during the period 1978-92 (Armstrong and Borman 1996).

Among women in Shanghai, breast cancer (27.5/10^5 women) was the commonest cancer and over the period (1972-1994), the incidence rate was doubled (Jin et al, 1999). Trends in breast cancer incidence rates using Poisson regression model in Bulgaria from 1981 to 1990 reported significant increase with average annual increases of 1.3% (Valerianova et al., 1994). Trends in breast cancer mortality rates (1985-2002) in Central Serbia increased by 0.35% (p=0.0001) (Markovic-Denic et al., 2006). Among Arab women breast cancer incidence rates increased from 14.1 per 10^5 in 1979-1981 to 42.6 in 2000-2002. Among Jewish women, the rates increased from 71.1 per 10^5 women in 1979-1981 to 103.6 in 2000-2002. Incidence to mortality rate ratio increased for both population groups, but it is still lower among Arab women. Arab women were more likely to be diagnosed at a more advanced stage of the disease (Tarabeia et al., 2007). Trends in breast cancer incidence rates in India (Mumbai, Bangalore, Chennai, Delhi, Bhopal, and Barshi) over a period of 1990 to 2003 reported significant increasing trends in Bhopal, Chennai and Delhi. Bangalore and Mumbai showed no significant changes (Yeole 2008; Takiar and Srivastav 2008).

In summary, an increasing trend in in-situ and early stage breast cancer incidence and a declining trend in breast cancer mortality have been observed in the US and in most of the European countries. Statistical modeling suggested an association between the
rapid increase in the incidence of early stage breast cancer and widespread use of screening mammography. Birth cohort effect indicated that the increase in incidence might be due to changes in risk factor profile. Although some of the differences reflect changing data sources, cancer registry results in developing countries indicated a fairly dramatic increase in rates in recent years. Rapid increases in incidence and mortality of breast cancer have been reported in many low incidence countries such as Ireland, Japan, Korea, Spain, China, India and Arab world. The rise in breast cancer incidence and mortality rates emphasize the need for increasing early detection of breast cancer by improving rates of compliance with screening mammography.

**Cervix cancer**

There have been substantial declines in cervix cancer incidence and mortality, most clearly observed in Western countries where there are well-developed screening programs. Declines are evident in some developing countries also. Although some of the differences reflect changing data sources, cancer registry results indicated a fairly dramatic decline in rates. As a result of these trends, cervix cancer has ceded its place as the leading cancer in developing countries to breast cancer; only in sub-Saharan Africa, Central America, south central Asia, and Melanesia is now the main cancer-affecting women (Ferlay et al., 2008).

A significant decline during the period 1973-1991 in incidence of squamous cell carcinoma (SCC) of the cervix was noted in the American populations (except for US Hispanic), Australia, the non-Maori women of New Zealand, northern and Western Europe (except Italy and Spain, where the rates remain stable) and Asian populations (except Malay women of Singapore, who have stable rates). An increasing trend, mainly restricted to younger women, was found for Slovakia, Jewish women born in Israel and the United Kingdom. In Slovenia, the increasing trend was observed for all age groups (Vizcaino et al., 2000).

There was a significant increase in the incidence of cervical adenocarcinomas (AC) in women born in the mid-1930s and in successive cohorts thereafter in some populations in the United States (whites and Hispanic women), Australia, New Zealand
(non-Maori), England, Scotland, Denmark, Slovenia, Slovakia and Japan (Osaka) and among Chinese women in Singapore, with a general decline in the incidence in women born in earlier periods. In Sweden and Slovenia there is an increasing trend and a decrease in incidence was apparent in Finland, France and Italy (Vizcaino 1998).

Cervix cancer death rates for US-born women decreased uniformly in all regions in the US and mortality rates have increased among foreign-born women in the US, and have influenced overall mortality trends (Seeff and McKenna, 2003). Incidence rates among Alaska Native women using data obtained from the Alaska Native Tumor Registry, in Anchorage, Alaska were compared with the incidence rates for US Whites SEER data. Incidence rates among Alaska Natives are similar to US White rates (Day et al., 2007).

Among black and white women in the US during 1976-2000, the overall incidence of SCC of cervix declined over time, and majority of tumors are detected as in situ and localized carcinomas and in young women. The incidence of in situ SCC increased sharply in the early 1990s. Incidence rates of adeno carcinoma (AC) of in situ cervix increased, especially among young women. In black women, invasive AC incidence rose linearly with age (Wang et al., 2004). Incidence rates of overall cervix cancer and SCC specifically declined among US women with less than 30 years old during 1973-1999, with estimated EAPC of -0.94% (95% CI: -1.47%, -0.41%) and -1.10% (95% CI: -1.59%, -0.62%), respectively. Rates of AC increased (2.90%; 95% CI: 1.34%, 4.49%), though trends have been stable since 1990 (Chan et al., 2003).

In Argentina, declining trends were observed for cervix cancer mostly between the 1960s and the 1980s (Munoz et al., 1998). Contrary to the declining trend, increasing trend was observed in Rio Grande do Sul, Brazil. Standardized mortality ratios in Rio Grande do Sul from 1979 to 1998 revealed a positive linear trend of 0.17, and the mean annual mortality rate was 7.58 per 10^5 women (Kalakun et al., 2005).

Incidence rates (per 10^5 women) of SCC of the cervix in the Canadian provinces of Ontario, Saskatchewan, and British Columbia decreased from 11.1 in 1970-72 to 5.3 in 1994-96, while the rate for cervical AC increased from 1.1 to 1.5 over the same period. Mortality rate declined from 7.9 per 10^5 women in 1953-55 to 1.9 in 1995-97. Age-specific mortality rates in 1953-72 were different from those in 1973-97; younger women experienced larger reductions in mortality during the earlier period while older women benefited to a greater extent during the latter period (Liu et al., 2001). In Ontario, Canada
opportunistic cervical cancer screening has been accompanied by significantly decreased rates of SCC since at least 1981. Conversely, the incidence of AC rose by 3.1% per year (95% CI: 1.6%, 4.6%) between 1981 and 1995, and subsequently declined by 4.0% per year (95% CI: -7.4%, -0.5%) (Howlett et al., 2007).

In NSW Central Cancer Registry for 1972-2001, cervix cancer incidence (-10%) and mortality (-20%) is declined. Incidence plateaued during the 1980s, but mortality fell further (-7%) due to an increased proportion of localized cancers (without change to degree-of-spread specific survival). A marked and sustained incidence decline to 2001 (-35%) occurred after the introduction of the NSW Cervical Screening Program in 1992. This was followed 3 years later by a sustained mortality decline (-20%) (Taylor et al., 2006).

In all Western European countries, except Ireland, substantial declines in cervix cancer mortality in younger women were observed, although the falls were larger and earlier for some Nordic countries. The trends were irregular in the UK, with earlier declines between 1960 and 1970, followed by a rise between 1970 and 1985, and a subsequent fall. In Ireland, mortality from cervix cancer at age 20-44 years has been risen since the early 1980s, to reach 3.4/10^5 women in 1995-1996. In Eastern Europe, some fall in mortality was observed in Hungary and Poland, while trends were upwards in Romania since 1980, and in Bulgaria. In all these countries, moreover, the rates remained appreciably higher than in most of Western Europe, and in the late 1990s there was over a 10-fold variation between the highest rates in Romania (10.6/10^5 women aged 20-44 years) and the lowest ones in Finland (0.5/10^5 women) or Sweden (0.9/10^5 women). Within the European Union, the highest rates were registered in Ireland (3.4/10^5 women) and Portugal (3.2/10^5 women) (Levi et al., 2000). Cervix cancer mortality rates from 1980-2000 steadily decreased in 25 countries of the European Union (Levi et al., 2004).

There were period-specific declines in cervical SCC in several European countries, with the largest decreases seen in northern Europe. A pattern emerged across Europe of escalating risk in successive generations born after 1930. In the western European countries, a decrease followed by a stabilization of risk by cohort was accompanied by period-specific declines. In southern Europe, stable period, but increasing cohort trends, was observed (Bray et al., 2005a). Incidence rates of AC of cervix increased throughout Europe, the rate of increase ranged from around 0.5% per annum in Denmark, Sweden,
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and Switzerland to $\geq 3\%$ in Finland, Slovakia, and Slovenia. The increases first affected generations born in the early 1930s through the mid-1940s, with risk invariably higher in women born in the mid-1960s relative to those born 20 years earlier. The magnitude of this risk ratio varied considerably from around 7 in Slovenia to almost unity in France. Declines in period-specific risk were observed in United Kingdom, Denmark, and Sweden, primarily among women ages $>30$ years (Bray et al., 2005b).

Incidence of in situ cancers of cervix in Sweden increased rapidly during 1958-1967. Incidence rates of SCC, fairly stable before 1968, decreased thereafter by 4-6% yearly in women aged 40-64 years, with a much smaller magnitude in younger and older women. An age-cohort model indicated a stable 70-75% reduction in incidence for women born 1940 and later compared with those born around 1923. The incidence of AC doubled during the 35-year study period. The mortality rate increased by 3.6% before 1968 and decreased by 4.0% yearly thereafter (Bergström et al., 1999). The incidence of AC in Sweden increased substantially at young age groups towards the end of follow-up (Hemminki et al., 2001).

All Nordic countries showed declining trends in incidence and mortality rates. Through the period 1986-1995, the reduction in both the mortality and the incidence rates was greatest in Iceland (mortality: 76% and incidence: 67%) and Finland (73% and 75%, respectively), intermediate in Sweden (60% and 55%, respectively) and Denmark (55% and 54%, respectively), and lowest in Norway (43% and 34%, respectively) (Sigurdsson 1999). During 1989-1998, incidence rate of SCC of cervix in the Netherlands decreased significantly from 7.1 to 6.1 per $10^5$ women ($p < 0.001$), with the greatest decrease in women aged 60-74 (-5.5%). While the overall incidence rate of AC remained stable, it increased in women aged 15-29 (15.8%) and in women aged 30-44 (2.5%), though the number of cases was small (Bulk et al., 2005).

Mortality from cervix cancer has been declining in the UK for at least the past 30 years. The rate of decrease has been greatest in England, Wales and Scotland and has accelerated in these countries since the reorganization of screening services in the late 1980s. Mortality in Northern Ireland is also decreasing, but at a lesser rate and without significant change over the same period (Comber and Gavin 2004). In England, using data
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On cancers from 1971 to 1997, the risk of cervical AC was estimated to be 14 times (95% CI: 11-19) greater in women born in the early 1960s than in cohorts born before 1935 (Sasieni and Adams 2001).

Cervix cancer mortality rates in Scotland showed clear evidence of decline during the period 1975-1994, the rate for 1994 being some 30% lower than that for 1975 with clear evidence of decreasing trends in the age range 50-64 years but different patterns in younger and older age groups. Age-specific mortality rates for 1975-1994 exhibited the most pronounced decreasing trends in the age range 50-64 years. The overall incidence of cervix cancer in Scotland changed little during the period 1975-1989, but declined sharply from 1990 onwards. The most pronounced decline in incidence across the period 1975-1994 appears to have taken place in the age range 50-64 years (Walker et al., 1998). Incidence data for both SCC and ACs were obtained from the East Anglian Cancer Registry for the period 1971-94. Similar data were obtained for England and Wales. The rate of cervical AC was 0.85 per 10^5 in 1971-76, rising to 2.54 per 10^5 in 1989-94. There has been a marked age shift, with the main increase in incidence occurring in younger women aged 30-39. Incidence of SCC of the cervix has decreased from 9.78 to 8.74 per 10^5 over 1971-76 and 1989-94 (Stockton et al., 1997).

Cervix cancer mortality decreased in young Spanish women aged 25-49 born before 1939-1948 and increased in women born later. These women aged less than 50 years are suffering an increase in mortality rates (Llorca et al., 2006). Trends in incidence by histological type in two districts of Central Italy (Florence and Prato), covered by the Tuscany Cancer Registry where cytological screening had been available since the 1970s were estimated. Incidence increased for AC (EAPC = +5.7%; 95% CI: +2.8; +8.6); whereas, it decreased for SCC (EAPC = -1.9%; 95% CI-3.8; 0) and for other or not specified types (EAPC=-4.4%; 95% CI-10.0; +1.5). AC increased significantly among younger women (<55 years) but not among older ones, whereas SCC decreased among older women only (Visioli et al., 2004). In the Umbria Region (Central Italy), over the period 1978-1998, the incidence rate of cervix cancer decreased. By contrast, the mortality rates for cervix cancer rose slightly (Minelli et al., 2004). Mortality rate in Belgium decreased continuously over the period 1954 to 1994, from over 14 to 5 per 10^5 woman (slope -0.26/10^5 woman-years, 95% CI: -0.28 to -0.24) (Arbyn and Geys 2002).
In Asian countries also declining trends in incidence and mortality from cervix cancer were noted. The overall cervix cancer mortality rates in Korea decreased from 5.2 in 1993 to 3.9/10^5 women in 2002 (EAPC:-4.05%, 95% CI:-4.88,-3.22). While cervix cancer mortality showed a decreasing trend among women aged 30-69 years, it increased substantially in women aged >=70 years (EAPC: 3.62%, 95%CI: 1.92-5.35) (Shin et. al, 2008). Rates from Shanghai Cancer Registry, China from 1972 to 1994 were declined by at least one-half for cervix cancer (Jin et al., 1999). Mortality rates declined during 1987-1999 with increasing mortality in the younger population reported in China (Yang et al., 2003). Cervix cancer incidence showed notable declines in Qidong, Jiangsu Province, China (EAPC: -4.7%) for the period 1978-2002, but increasing trends in the younger generations (Chen et al., 2006).

In Taiwan, according to age-period-cohort model, age was found to be the strongest factor predicting cervix cancer mortality over the period from 1974 to 1992. Women in 50-54 age group have 89.3-fold risk of cervix cancer compared to those in the 30-34 age group. Declining trend was observed among women born after 1938-1963 (Wang and Lin 1997).

In India, during the years 1990-1997, the incidence rates for cervix cancer varied from 10.9 to 65.4 per 10^5 women among various registries with the highest incidence in the Ambillikai, Tamilnadu registry (Murthy et al., 2005). Incidence of cervical cancer in India (Mumbai, Bangalore, Chennai, Delhi, Bhopal, and Barshi) over the period 1990 to 2003 reported significant declining trends in cervix cancer incidence in Bangalore and Chennai (Yeole 2008; Takiar and Srivastav 2008).

In summary, cytology screening as well as changes in socio-economic profile has led to declines in cervical SCC incidence and mortality rates worldwide. Higher percentage decline in SCC is observed in countries where organized screening programmes are available. Pap smear screening has played a significant role in the reduction in SCC in the US, Canada, New South Wales, and in almost all European countries as well as in some of the Asian countries. Increasing incidence and mortality rates of cervical AC has reported in countries such as the US, Canada, UK, Iceland, Sweden, England, Spain, Finland, Slovakia, Slovenia, the Netherlands particularly among young women. However the increase was mainly in earlier periods till 1995 and stable or declining trends in cervical AC have been observed in later periods in many of the above
countries such as the US, UK, Canada, Sweden. The increasing risk of AC suggested a major role for an increasing prevalence of persistent oncogenic HPV infection and its cofactors, whereas the downturn in period effects in several countries during the 1990s provided evidence that cytology screening is detecting more preinvasive ACs than in previous decades and suggested that screening might be starting to have a protective impact on AC. The decline in AC incidence might be due to improved specimen collection as well as due to increased awareness of AC pre-cursors among cytopathologists and clinicians, improvements in laboratory training and quality assurance.

**Ovarian Cancer**

Long-term trends of mortality related due to ovarian cancer in Japan between 1958 and 2004 reported declining trend was observed since 1996 (Qiu et al., 2008). Ovarian cancer in Denmark decreased slightly from 14.3 (1978-1982) to 13.3 per 10^5 woman-years (1998-2002). Iceland had the highest incidence in the Nordic countries, whereas Denmark had the highest mortality rate. Danish mortality rate declined from 10.8 (1978-1982) to 9.0 per 10^5 woman-years (1998-1999). Only 19% of ovarian cancer in Denmark from 1978 to 2002 was localized at the time of diagnosis, while 30% had distant metastases. The Danish incidence of ovarian cancer seemed to decrease slightly from 1978 to 2002. Even though the mortality rate declined, Denmark had the highest mortality rate of ovarian cancer in the world (Kjaerbye-Thygesen et al., 2005).

Trends in incidence of 23,239 ovarian cancer cases from 1960 through 1984 in Sweden were best described by a non-linear model with a highly significant negative second-order term, which showed an initial increase followed by stabilization and, in later years, a decline. Both time period of diagnosis and birth cohort were found to have significant effects. These separate models provided consistent evidence for an increasing risk in women born during the last decades of the 19th century, and a slowly decreasing risk in later years and in the youngest birth cohorts (Adami et al., 1990). Incidence of ovarian cancer in Norway rose from 10 per 10^5 person-years in 1954-1958 to a peak of 14 per 10^5 women in 1984-1988. In women older than 50 years, there was an increasing trend in incidence rates during the entire study period. The largest increase was observed among women born between 1870 and 1899. Incidence has increased since 1970,
reaching 4.8 per 10^5 women in 1989-1993 (Bjorge et al., 1997). Trends in age-specific incidence and mortality from ovarian cancer between 1986 and 2003 in the region of the Maastricht Cancer Registry among Dutch women declined after 1992 by 2.6% (p=0.03) and overall mortality after 1991 by 1.7% (p=0.04) (Kellert et al., 2009).

Incidence rate of ovarian cancer in California, US decreased from 15.6 per 10^5 women in 1990 to 12.9 in 2003, a statistically significant decline of 1.3% per year. Rates of epithelial ovarian cancers declined in all age groups examined, with the largest decreases noticed among women 65-74 years old. Substantial differences in trends were detected by race/ethnicity. Epithelial ovarian cancers declined significantly among non-Hispanic black and white women by 2.5% and 1.2% per year, respectively (Morris et al., 2008). Ovarian cancer mortality rates revealed an unexpected significant increase in the calendar-period curve around 1980 in the US. Most of the changes in the calendar-period and birth-cohort curves for ovarian cancer were explained by documented changes in known risk factors and in medical practice (Tarone et al., 2000). Ovarian cancer incidence and mortality rates have declined among U.S. women aged 35-59 years during the period 1970-1995 (Gnagy et al., 2000). Ovarian cancer mortality rates in the US from 1979 to 1995 increased in older women (65 years and older) and decreased in younger women (Oriel et al., 1999).

Incidence rates of serous, endometrioid, clear cell and germ cell tumours in ovary increased significantly and the rates of sex cord-stromal and other classified epithelial ovarian tumours decreased considerably in Canada, 1969-1993. Cohort effect has a major impact on incidence trends of serous, endometrioid, germ cell, sex cord-stromal and other classified epithelial ovarian cancers. The risk of developing serous tumours increased markedly among birth cohorts of 1895-1930, stabilized thereafter and decreased among young cohorts of 1950-1960; the risk of germ cell tumours increased significantly among young cohorts of 1965-1980; and the risk of sex cord-stromal tumours dropped constantly among cohorts 1910-1950 (Zhang et al., 1999). Trends in incidence and mortality rates in Western Australia showed little change over the three time periods of diagnosis. A significant birth cohort effect showed a peak in the risk in the 1924 (mid-year) cohort followed by a general decrease in both incidence and mortality risk (Laurvick et al., 2003). Ovarian cancer incidence rates in South East England between 1967 and 1996 showed a strong positive correlation between rates and year of diagnosis.
in women aged >= 70 years, and this was particularly marked in women > 85 years of age. There was a negative correlation between rates and year of diagnosis in women aged 45-59 years (Olaitan et al., 2000). Incidence rate in the Umbria Region, Central Italy, over the period 1978-1998 rose but mortality rate from ovarian cancer was decreased (Minelli et al., 2004).

Ovarian cancer mortality in the European Union over the period 1955-1993 proved 2.77-fold (95% CI: 2.60-2.95) higher in northern versus southern Europe over the period 1955-1993. Denmark had the highest rates, namely, 14.3 per 10^5 woman-years for the 1989-1993 5-year period, the last studied, with Portugal (4.5 per 10^5) and Greece (4.5 per 10^5) being the countries with the lowest rates. Spain and Greece, with annual rises of 5.8% (95% CI: 5.3-6.3) and 5.1% (95% CI: 4.2-6.0) respectively. Risk of death associated with the birth cohort effect declined in all northern countries from 1920 to 1930. In the south, Italy and France recorded a decline in risk from 1930. Women in Spain and Greece registered an increase in birth cohort-associated mortality, which became less pronounced after 1930. Mortality in Europe evinces a south-north distribution pattern. The mortality risk for women cohorts born in northern Europe witnessed a gradual decline from 1920 to 1930. In the southern region, Italy and France displayed a cohort effect of decreased risk from 1930; and Greece and Spain showed a cohort effect of increased risk among the different generations of women, though this became less pronounced from 1930 onwards (González-Diego, et al., 2000). Incidence from 1990s to 2000 was generally favorable in the more prosperous countries from Northern and Western Europe (Karim-Kos et al., 2008).

From the period 1954-1958 to 1969-1973, ovarian cancer mortality rates increased from 10.6 to 13.1 per 10^5 woman-years in the Netherlands. Thereafter, a decline was noted to 11.4 per 10^5 woman-years in the period 1989-1993. Mortality rates showed a pattern of rising mortality in the elderly, whereas mortality in the younger age categories was declining. Mortality rates were rising in the elderly and declining in the young (Koper et al., 1996).

During 1962-87, there were significant increases in the overall incidence of ovarian cancer (0.76% per annum) in England and Wales. At young ages incidence of this cancer has declined in recent years, whereas at older ages there have been substantial increases. Mortality data showed similar time trends. In analyses by birth cohort,
incidence of each of the cancers increased steeply for successive cohorts born before the turn of the century, and more slowly for cohorts thereafter, reaching a maximum for those born in the 1920s, and decreased for those born subsequently (dos Santos Silva and Swerdlow 1995; Swerdlow et al., 1998). Mortality from ovarian cancer has been declining in women aged under 55 in England and Wales since the early 1970s but has been rising in women over 55. The international pattern is varied, but several countries showed a decline in mortality in younger women that began in the early 1970s. The incidence in younger women has not fallen to the same degree. In Australia, Canada, Denmark, England, Israel, and Wales, there has been a reduction in ovarian cancer-related mortality in women less than 55 years old since the early 1970s (Mant and Vessey 1994). The most rapid increase of incidence in Warsaw occurred in the 1960s, then the trend stabilized, and another increase began in 1984. The incidence growth was accompanied by similar trends in mortality. Mortality increase was statistically significant in Warsaw rural population and in the total population of Poland (Wronkowski et al., 1993).

A significant increasing trend in incidence of ovarian cancer from 1.23 in 1988 to 3.16 per 10^5 women in 1997 was found in Alexandria (Mahdy et al., 1999). Incidence rose over the study period 1972-89 in Shanghai (China). The increases were most pronounced among women under age 50. When considered by cohort year of birth, risk of ovarian cancer rose among women born since 1925 and 1935 (Jin et al., 1993). The updated trends in Shanghai for 1972-1994 reported that ovarian cancer incidence is doubled (Jin et al., 1999). Ovarian cancer incidence in India (Mumbai, Bangalore, Chennai, Delhi, Bhopal, and Barshi) reported an increasing trend in most of the above areas (Yeole 2008; Murthy, ..., Mathew A, 2009).

In summary, ovarian cancer incidence and mortality rates particularly in younger women have been declining over the last few decades. Oral contraceptive use together with reduced parity explains this downward trend, since these factors appear to have a protective effect against ovarian cancer. Even though the incidence rates are lower in India and China, increasing incidence in ovarian cancer is reported, but no data on
mortality. Improvement in diagnosis and in data coding could have determined the increase in ovarian cancer incidence in these regions.

**Corpus uteri cancer**

Many Northern and Western countries reported increasing trends in corpus uteri cancer among post-menopausal women in. Denmark, France and Switzerland were exceptions, with decreasing trends in post-menopausal women. In pre-menopausal and peri-menopausal women, declines were observed in Northern and Western Europe, most evidently in Denmark, Sweden, and the United Kingdom, affecting consecutive generations born after 1925 (Bray et al., 2005a;b). Incidence and mortality from corpus uteri cancer in Maastricht among Dutch women increased in the period 1993-2003 by 3.4% (p=0.03) and 4.0% (p=0.04), respectively (Kellert et al., 2009). In the Umbria Region, Central Italy, over the period 1978-1998, incidence rate of corpus uteri cancer rose. By contrast, the mortality rates due to corpus uteri cancer decreased (Minelli et al., 2004).

Incidence of corpus uteri cancer remained unchanged over the period 1962 to 1997 in South East England. In women aged 35-54 years there was a decrease in incidence and this was significant in the 40-45 year age group. Statistically significant increase in incidence in women aged over 65 years with a greater rate of increase in older women, particularly those aged over 85 (Somoye et al., 2005). The mortality has been falling in England and Wales since 1950 in all age groups. In England and Wales between 1950 and 1991, corpus uteri cancer-related deaths fell 67% for 35-54 year olds, 44.7% for 55-64 year olds, 33.6% for 65-74 year olds and 13.1% for 75-84 year olds (Mant and Vessey 1994).

Among the post-menopausal among women in Sweden during 1960-8, an early increase was followed by stable rates in women over 60 and decreasing rates at ages 50-59 years. In contrast, mortality rates decreased consistently over the study period. The risk increased by 20% in women born around 1900 compared to 1880 and by an additional 40% from the 1910 cohort to the maximum risk attained in those born around 1930. In younger birth cohorts, the risk markedly and continuously declined (Persson et al., 1990).
Highest incidence of corpus uteri cancer is reported in parts of the US where it has shown an annual fall of nearly 3% between 1973 and 1987 (Kneale and Giles 1993). Age-period-cohort analyses are applied to US mortality rates from 1950 through 1995. The calendar-period curve for corpus uteri cancer in the US reveals increased risk between 1960 and 1980 (Tarone et al., 2000). Among 48,510 women with corpus uteri cancer from 1988-2001 from the SEER US database, there was an increase in the proportion of patients dying from advanced corpus uteri cancers (52.1% to 56.0% to 68.8%; p <0.001), grade 3 disease (47.5% to 53.3% to 60.6%; p <0.001), serous tumors (14.3% to 18.4% to 16.6%; p <0.001), and sarcomas (19.1% to 20.4% to 27.2%; p<0.001) over time (Ueda et al., 2008).

Increase in incidence rates of corpus uteri cancers in Shanghai (China) during 1972-89 were observed and restricted generally to those aged 55 to 69 years. Rate of corpus uteri cancers rose 20-50% over the study period (Jin et al., 1993). Updated trends in Shanghai for 1972-1994 indicated that the rates doubled for corpus uteri cancer (Jin et al., 1999). Trends in India also (Mumbai, Bangalore, Chennai, Delhi, Bhopal and Barshi) showed and increasing trend (Yeole 2008; Murthy, ... Mathew A, 2011).

In summary, incidence rate of corpus uteri is increasing in a few countries particularly among post-menopausal women, mortality rate is declining in most of western countries. It is not exactly clear why the numbers of corpus uterine cancer deaths are expected to continue to decline, but it may be a matter of improvement in death-certificate coding or their diagnoses as cervical cancer deaths. Changes in age-related incidence trends might be explained by alterations in life style and behavior.

**Publications**


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