RESEARCH COMMUNICATION

Trends in Incidence and Mortality Rates of Squamous Cell Carcinoma and Adenocarcinoma of Cervix - Worldwide

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Abstract

The objective of the present paper is to summarize and quantify the trends in incidence and mortality rates of cervical squamous cell carcinoma (SCC) and adenocarcinoma (AC) worldwide. All indexed publications, which provided information on time trends in incidence or mortality rates of cervix cancer, published during the past 12 years were included. The details of studies have been identified through searches on the MEDLINE database. 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. The results suggested that 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 (except in Ireland) as well as in some of the Asian countries. Increasing incidence and mortality rates of cervical AC has reported in many 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. In conclusion, cytology screening in combination with HPV screening for high-risk HPV types may maximize the possibilities of having early cervical lesions detected and treated.

Key Words: Cervical cancer - SCC - AC - incidence - mortality

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Introduction

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 reflects changing data sources, cancer registry results indicated a fairly dramatic decline in rates in recent years. 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., 2004).

A significant decline in incidence of cervical squamous cell carcinoma (SCC) 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). The predominant pattern shown by cancer registries in developed countries is of a reduction in the incidence of SCC (Vizcaino et al., 2000). A significant increase in the incidence of cervical adenocarcinoma (AC) in women born in the mid-1930s and in successive cohorts thereafter in some populations in the US (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 (Vizcaino et al., 1998).

Time trend analysis of cervix cancer incidence or mortality rates have been carried out using different regression models such as log-linear model, Poisson regression model, Join Point regression model etc. by estimating the overall annual percent change as well as age, period and birth cohort effects. The objective of the present paper is to summarize and quantify the estimated annual percent change as well as the age, period and birth cohort effect in incidence and mortality rates of cervical SCC and AC worldwide.

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Materials and Methods

The studies included in this quantitative review were all indexed publications, which provided information on time trends in incidence or mortality rates of cervix cancer, published during the past 12 years. The details of studies have been identified through searches on the MEDLINE database, using keywords "cervix cancer", "adenocarcinoma of cervix", "squamous cell carcinoma of cervix", "time trend", "incidence rates" and "mortality rates". Papers were also searched among those quoted as references in the retrieved studies. A description of the main characteristics such as the authors, year of publication, country, the analytic method, the estimated percent change and the corresponding 95% confidence intervals (CI), age, calendar period and birth cohort effect (if available) according to SCC and AC were obtained.

Results

Overall cervical cancer death rates for US-born women decreased uniformly in all regions in the US (Seeff and McKenna, 2003; Day et al., 2007). Trends in incidence and mortality rates were estimated for cervical SCC (1976-2000) and for squamous carcinoma in-situ (CIS) as well as adenocarcinoma in-situ (AIS) and AC (1976-1995) by age (< 50 years, > or = 50 years) and race (whites, blacks) in the US using the Surveillance, Epidemiology, and End Results program (SEER) data. Among all groups, CIS rates approximately doubled whereas rates for SCC declined. Among younger blacks, mortality for SCC decreased from 2.69 to 1.96/10^5 women. Among older blacks, the mortality rates declined from 14.88 to 9.15/10^5 women. AIS rates have increased dramatically among whites and younger blacks, while incidence and mortality rates of AC have not changed greatly (Wang et al., 2004; Asulin et al., 2005).

Trends in incidence rates of invasive cervical carcinoma in the US women less than 30 years old from 1973 to 1999 by histologic type were obtained from the SEER data. The estimated annual percent change (EAPC) was calculated by joinpoint regression to measure trends during the above period and a sub-period (1985-1999). Incidence rates of cervical carcinoma overall and SCC specifically declined during 1973-1999, with EAPC of -0.94% (95% CI: -1.47%, -0.41%) and -1.10% (95% CI: -1.59%, -0.62%), respectively. Rates of AC increased (EAPC: 2.90%; 95% CI: 1.34%, 4.49%), though trends have been stable since 1990 (Chan et al., 2003).

Declining trends were observed in a few countries in South America also. In Argentina, declining trends were observed for cervical cancer mostly between the 1960s and the 1980s (Muñoz et al., 1998). Contrary to the declining trend, increasing trend was observed in Rio Grande do Sul, Brazil. Standardized mortality ratios during the period 1979-1998 reported positive linear trend of 0.17, and the mean annual mortality rate was 7.58/10^5 women (Kalakun et al., 2005).

Incidence rate of cervical SCC in the Canadian provinces of Ontario, Saskatchewan and British Columbia decreased from 11.1 in 1970-1972 to 5.3 /10^5 women in 1994-96, while the rate for cervical AC increased from 1.1 to 1.5/10^5 women over the same period. Mortality rate declined from 7.9/10^5 women in 1953-1955 to 1.9 in 1995-1997. The patterns in age-specific mortality rates in 1953-1972 were different from those in 1973-1997; younger women experienced larger reductions in mortality during the earlier period while older women benefited to a greater extent during the latter period. Age-period-cohort modeling showed that cohort effects were responsible for the decreasing trends in incidence of cervical SCC and increasing trends in AC, and both period and birth cohort effects accounted for the observed trends in mortality (Liu et al., 2001). Cervical SCC incidence assessed using Join Point regression methodology in Ontario between 1981 and 2002 showed significantly decreased trends since at least 1981. Conversely, the incidence of cervical 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).

Declines in cervical cancer incidence (-10%) and mortality (-20%) were reported based on data from New South Wales (NSW), Australia for 1972-2001. 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, followed 3 years later by a sustained mortality decline (-20%) (Taylor et al., 2006).

In Sweden, using nationwide data on incidence and mortality of more than 3 decades, the incidence of CIS 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. Poisson-based age-cohort model indicated 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). Further it is reported that in Sweden, the incidence of AC increased substantially at younger age groups towards the end of the period 1958-1996, where as cervical SCC declined since 1960 (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). The rate of AC has been increasing in all the Nordic countries (Sigurdsson et al., 1999). Declining trends in incidence and mortality from cervical cancer in the Netherlands were reported. However, the proportional decrease was lower than Finland (van der Aa et al., 2008).

Overall mortality from cervix cancer has been declining in the UK for the period 1970-2000. The rate of decrease has been greatest in England, Wales and Scotland and has accelerated in these countries since 1980s. Mortality in Northern Ireland is also decreasing, but at a

lesser rate and without significant change over the same period. In contrast, cervical cancer mortality in the Irish Republic has been increasing by an average of 1.5% per year since 1978. The mortality rate, which was half of that in the UK in the late 1970s, exceeded that in any of the region of the UK (Comber and Gavin, 2004). In England between the periods 1971-1997, the risk of cervical AC was 14 times (95% CI: 11-19) greater in women born in the early 1960s than in cohorts born before 1935 (Sasieni and Adams, 2001).

No overall change in the incidence and mortality rates of cervical cancer was reported in Scotland over the period 1975-1989, but exhibited a pronounced decline from 1990 onwards. All-ages mortality rates showed clear evidence of decline during the period 1975-1994, the rate for 1994 being some 30% lower than that for 1975. Annual age-specific incidence rates showed different patterns by age group, with clear evidence of decreasing trends in the age range 50-64 years but different patterns in younger and older age groups. Most age groups showed steep declines in incidence from 1990 onwards. Age specific mortality rates for 1975-1994 exhibit the most pronounced decreasing trends in the age range 50-64 years. The overall (all ages) incidence of invasive cervical 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. This decline has been accompanied by a commensurate fall in mortality in the same age range (Walker et al., 1998).

The incidence rate of cervical AC in East Anglian cancer registry was 0.85 /10^5 women in 1971-1976, rising to 2.54/10^5 women 1989-1994. There has been a marked age shift with the main increase in incidence occurring in younger women aged 30-39. The incidence rate of cervical SCC has decreased from 9.78 to 8.74/10^5 women over the periods 1971-1976 and 1989-1994. Again there has been an age shift, moving from a single incidence peak in the 45-59 age group, in earlier years to incidence peaks in both the 30-39 and 55-69 age groups in later years. Similar trends were noted in England and Wales. Birth cohort analyses showed that both tumours are occurring progressively earlier (about five years earlier in each five year birth cohort). Although the overall incidence of cervical carcinoma is declining, the study has shown an increased incidence of cervical AC, particularly in the younger age groups (Stockton et al., 1997).

Cervical 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 cervix cancer mortality rates (Llorca et al., 2006) and reported an increased incidence for AC in Florence and Prato, Central Italy (EAPC = 5.7%; 95% CI: 2.8; 8.6); whereas, it decreased for SCC (EAPC = -1.9%; 95% CI:-3.8,-0.9). Cervical 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 cervical cancer decreased. By contrast, the mortality rates for cervical cancer rose slightly (Minelli et al., 2004).

In Belgium the cervical cancer mortality rate decreased continuously over the last 4 decades (1954-1994) from over 14 to 5/10^5 woman (EAPC: -0.26, 95% CI: -0.28 to -0.24). In addition to the linear decrease, substantial nonlinear cohort influences were observed in mortality rates (Arbyn and Geys, 2002).

In all Western European countries, except Ireland, substantial declines in cervical 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 cervical 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 variation was over 6-fold, the highest rates being registered in Ireland (3.4/10^5 women) and Portugal (3.2/10^5 women) (Levi et al., 2000). Using data derived from the World Health Organization database, trends in cervix cancer mortality rates from 1980-2000 demonstrated steady decreases in 25 countries of the European Union (Levi et al., 2004a; 2004b).

Cervical AC incidence rates of women with ages < 75 years increased throughout Europe, the rate of increase ranged from 0.5% per annum in Denmark, Sweden, and Switzerland to ≥ 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 the risk ratio varied considerably from around 7 in Slovenia to almost unity in France. Declines in period–specific risk were observed in the UK, Denmark, and Sweden, primarily among women ages > 30 years (Bray et al., 2005a).

In Asian countries also declining trends in incidence and mortality from cervical 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 the Shanghai Cancer Registry, China from 1972 to 1994 were declined by at least one-half for cervical cancer (Jin et al., 1999). Cervical cancer mortality rates declined during 1987-1999 with increasing mortality in the younger population reported in China (Yang et al., 2003). Cervix cancer (EAPC: -4.7%) showed notable declines in Qidong, Jiangsu Province, China for the period 1978-2002, but increasing trends in the younger generations (Chen et al., 2006).

The mortality data of cervical cancer were analyzed over the period from 1974 to 1992 among Taiwanese

women using a log-linear Poisson model modified from the method of Osmond and Gardner to examine the effects of age, calendar period of death, and birth cohort on cervical cancer mortality. Greatest risk for cervical cancer was observed among women born between 1893 and 1938, a dramatically declining trend thereafter for 1938-1963 birth cohorts and increasing trend in cohorts (after 1963 birth cohort) (Wang and Lin, 1997).

Trends in the incidence rate of cervical cancer for the Indian population was estimated based on the data published in Cancer Incidence in Five Continents for various Indian registries. During the years 1990-1997, the incidence rates for cervical cancer varied from 10.9 to 65.4/10^5 women among various registries with the highest incidence in the Ambillikai, Tamilnadu registry. The decline in the mean annual percentage change in incidence ranged from 0.9 to 2.6% amongst various registries. The mean annual percentage decrease was higher for women in earlier age groups in most of the registries (Murthy et al., 2005).

Discussion

Incidence and mortality rates due to SCC are declining worldwide. Higher percentage decline in SCC was observed in countries where organized screening programmes are available. The results suggested that Pap smear screening has played a significant role in the reduction in SCC in the US (Wang et al., 2004), Canada (Liu et al., 2001), New South Wales (Taylor et al., 2006), Iceland (Sigurdsson et al., 1999), Finland (van der Aa et al., 2008), Sweden (Bergström et al., 1999), Central Italy (Minelli et al., 2004), Scotland (Walker et al., 1998), England (Gibson et al., 1997), Belgium (Arbyn and Geys, 2002) and in almost all Western countries except in Ireland (Levi et al., 2000). Substantial declines in cervical cancer mortality in younger women were also largely due to screening in all Western European countries, except Ireland (Levi et al., 2000). The absence of population-based screening for cervical cancer in the Republic of Ireland was the most explanation for the differences in trend (Comber and Gavin 2004). The substantial reduction of cervical cancer incidence and mortality in NSW over the last 3 decades was associated with health service interventions that relate to the implementation of population-based organized cervical screening program (Taylor et al., 2006).

The proportional decline in cervical cancer decline was lower in the Netherlands compared to Finland. It is reported that in Finland the decline in mortality is completely related to the screening programme whereas in the Netherlands it was considered as a natural decline as well as differences in risk factors. The Netherlands has higher population density and higher percentages of immigrants and (female) smokers. The greater excess smear use in Finland have affected decline in incidence (van der Aa et al., 2008). In Sweden, it is reported that a combination of organized and opportunistic screening reduced the incidence of SCC substantially (Bergström et al., 1999). In the UK, the rate of decrease has been greatest in England, Wales and Scotland and the decline has accelerated in these countries since the reorganization of screening services in the late 1980s (Sasieni and Adams 2001). In the East Anglian Cancer registry, the fall in cervical cancer incidence and a shift to more favorable stage at diagnosis was preceded by a rapid rise in the national uptake of screening. The changes in the organization and management of the national screening programme introduced in 1988 and 1989 led to substantial improvements in effectiveness (Gibson et al., 1997).

Declining trends in cervical cancer incidence and mortality rates have been reported in Asian countries such as China (Chen et al., 2006), South Korea (Jin et al., 1999), Taiwan (Wang and Lin, 1997), and India (Murthy et al., 2005) even though the proportional decline was lower compared to Western countries. It is reported that the declining trend in Korea reflected variations in diagnostic or screening practices, although changes in lifestyle and other environmental exposures are likely to play important roles (Jin et al., 1999). In China, the declining trends primarily reflected the dramatic changes in socioeconomic circumstances and lifestyles in the last 2 decades. It is reported that the available screening programs for cervical cancer and better facilities for cancer therapy, might have helped to reduce mortality for this cancer (Yang et al., 2003). It is interesting to note that the incidence rate of cervical cancer in Trivandrum, Kerala, India is lowest in the country (7 in Trivandrum compared to a range of 17 to 28/10^5 women in other states) (Curado et al., 2007; Trivandrum cancer registry report, 2009). Opportunistic screening programmes as well as higher educational levels among women in Kerala might have played the lowest incidence.

Cytology screening as well as changes in socio-economic profile has led to substantial declines in cervical SCC incidence and mortality rates. However, the cytology screening has been considered less effective at reducing the incidence of cervical AC. Even though, SCC represent the vast majority of cervical malignancies (75-90%), increasing incidence and mortality rates due to cervical AC (absolute number remains relatively small) is reported in many countries such as the US (Wang et al., 2004), Canada (Howlett et al., 2007), UK (Sasieni and Adams, 2001), Iceland (Sigurdsson et al., 1999), Sweden (Bergström et al., 1999; Hemminki et al., 2001), England (Gibson et al., 1997; Stockton et al., 1997) and Spain (Visioli et al., 2004). Statistically significant increases in cervical AC rates of at least 3% per annum was reported in many European countries such as Finland, United Kingdom, Slovakia, Slovenia, the Netherlands particularly among young women (Hemminki et al., 2002; Bray et al., 2005a; Bulk et al., 2005). However the increase was noted mainly in earlier decades till 1995 with stable or declining trends in cervical AC have been observed in later periods in some of the above countries such as the US (Chan et al., 2003; Wang et al., 2004), Canada (Howlett et al., 2007), Sweden (Bergström et al., 1999). Declines in period-specific risk in AC were observed in the UK, Denmark and Sweden (Bray et al., 2005a). In Ontario, Canada between 1981 and 2002 cervical AC rose between 1981 and 1995, and subsequently declined. It is reported that the subsequent decline in AC incidence might be due, in

part, to improved specimen collection as well as due to increased awareness of AC pre-cursors among cytopathologists and clinicians, and/or improvements in laboratory training and quality assurance (Howlett et al., 2007). An increasing ability to detect endocervical lesions in cervical screening involves the improved diagnostic yield via use of the extended tip spatula or the cervix (endocervical) brush, or a combination of both as well as an understanding and recognition of AC in situ (Mitchell et al., 2004). Some authors have suggested that screening might have been responsible in some reductions in AC during the 1990s (Vizcaino et al., 1998; Mitchell et al., 2003).

It is reported that in the US, etiologic factors explain the rising cervical AC incidence in young white women; rising cervical AC incidence with age in black women reflected either lack of effective screening or a differential disease etiology (Wang et al., 2004). The increasing cervical AC rates in England reflected an increasing ability to diagnose the disease over time (Sasieni and Adams, 2000). The substantial increase in cervical AC from England cancer registries was largely a birth-cohort effect presumably associated with greater exposure to HPV after the sexual revolution in the 1960s (Sasieni and Adams, 2001). European women born in successive generations experienced increasing risk of both cervical SCC and AC within the same time window—during the 1930s and 1940s -points to a homogeneity in the risk factors chiefly responsible for the increases, presumably linked to sexual activity and risk of HPV infection. The widespread increases in cervical AC in Europe among younger cohorts suggested that an increasing number of women are becoming HPV carriers of high-risk HPV types in many European countries. These cohorts might be defined by generational changes in sexual behavior that increase the risk of HPV infection, among them younger age at first intercourse, increased number of sexual partners, and increasing risk that each sexual partner is HPV positive (Bray et al., 2005).

Increases in the incidence and seroprevalence of HPV-16 have been reported in Finland in women in their 20s (Laukkanen et al., 2003), whereas in Sweden the main increases in HPV-16 during the period 1969-1989 occurred during the 1970s and early-1980s in women ages <35 years (af Geijersstam et al., 1998). It has been suggested that the lifetime number of sexual partners is the strongest marker for oncogenic HPV infection, whereas a history of condyloma is associated more with acquiring benign HPV types (Silins et al., 2000). Cofactors may modify the probability of HPV exposure and infection, and the residual effects of high parity, oral contraceptive use, and tobacco smoking on risk of cervical cancer have been reported in a number of epidemiologic studies (Plummer et al., 2003; Smith et al., 2003). Some studies indicated that SCC and AC share many risk factors, including the number of sexual partners, an early age of first intercourse, an early age of first birth, and the use of oral contraceptives (Berrington et al., 2004).

Analysis of cervical SCC and AC trends in the same countries supported the idea of considerable homogeneity in the cohort-specific trends of each subtype in Europe. The cohort-specific increases in Italy, Spain, United Kingdom, Norway, Estonia, Slovakia, Finland, and Slovenia in AC were in accordance with the temporal patterns conveyed for SCC, with risk of both subtypes accelerating among consecutive generations born in the 1930s and 1940s. The rapid increases in the drift estimates of AC noted in Finland and Slovenia in latest years match well those observed for SCC (Bray et al., 2005b).

The decelerations in period-specific risk indicated an intervention that affects all age groups at the same time, and thus explained the declining AC incidence rates during the 1990s in Sweden, United Kingdom, and Denmark in women ages >35. Cytology screening might thus be starting to have a protective impact on AC, as has been postulated by Mitchell et al (2003), and by Sasieni and Adams (2001) on the basis of the observed incidence trends in England.

In conclusion, cytology screening has led to substantial declines in cervical SCC incidence and mortality rates worldwide. The increasing risk of AC in successive generations suggests a major role for an increasing prevalence of persistent oncogenic HPV infection and its cofactors, whereas the downturn in period effects in several countries provides at least some evidence that cytology screening is detecting more preinvasive ACs. Thus cytologic screening - probably in combination with HPV screening for high-risk HPV types - may maximize the possibilities of having early cervical lesions detected and treated.

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