Chapter 2: The burden of HPV-related cancers

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Abstract

On the basis of current evidence regarding human papillomavirus (HPV) and cancer, this chapter provides estimates of the global burden of HPV-related cancers, and the proportion that are actually “caused” by infection with HPV types, and therefore potentially preventable. We also present trends in incidence and mortality of these cancers in the past, and consider their likely future evolution.

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1. Burden of HPV-related cancer

1.1. Cancer of the cervix

Cancer of the cervix uteri is the second most common cancer among women worldwide, with an estimated 493,000 new cases and 274,000 deaths in 2002\textsuperscript{[2]}. Some 83\% of the cases occur in developing countries, where cervical cancer accounts for 15\% of female cancers, with a risk before age 65 of 1.5\%, while in developed countries it accounts for only 3.6\% of new cancers, with a cumulative risk (ages 0–64) of 0.8\%\textsuperscript{[2]}. The highest incidence rates are observed in sub-Saharan Africa, Melanesia, Latin America and the Caribbean, South-Central Asia, and South East Asia (Fig. 1).

Fig. 2 shows incidence rates recorded in cancer registries around 1995\textsuperscript{[3]}. There is a range in incidence of at least 20-fold. In general, the lowest rates (less than 15 per 100,000) are found in Europe (except some Eastern European countries), North America and Japan. The incidence is generally higher in the developing countries of Latin America (age-standardized incidence rates (ASR) 33.5 per 100,000) and the Caribbean (ASR 33.5), sub-Saharan Africa (ASR 31.0), and South-Central (ASR 26.5) and Southeast Asia (ASR 18.3). Very low rates are observed in China, and in Western Asia (Fig. 1); the lowest recorded rate is 0.4 per 100,000 in Ardabil, northwest Iran\textsuperscript{[4]}. The majority of cases of cervical cancer are squamous cell carcinomas (SCCs); adenocarcinomas are less common. In general, the proportion of adenocarcinoma cases is higher in areas with a low incidence of cervical cancer, and this histology may account for up to 25\% of cervical cancer cases in many Western countries\textsuperscript{[3]} (Fig. 2). The relatively high proportion of adenocarcinomas is a consequence of cytological screening, which historically, probably had little effect in reducing the risk of adenocarcinoma of the cervix, because these cancers, and their precursors, occur within the cervical canal (from the glandular epithelium), and were not readily sampled by scraping the epithelium of the ectocervix\textsuperscript{[5]}.

Mortality rates are substantially lower than incidence. Worldwide, the ratio of mortality to incidence is 55\%. Survival rates vary between regions with quite good prognosis in low-risk regions (73\% at 5 years in US registries\textsuperscript{[6]} and 63\% in Europe\textsuperscript{[7]}), but even in developing countries, where many cases present at relatively advanced stages, survival rates are fair (for example, 30.5\% in the African population of Harare, Zimbabwe\textsuperscript{[8]}).

Because cervical cancer affects relatively young women, it is an important cause of lost years of life in the developing...
world. Yang et al. [9] found that it was responsible for 2.7 million (age-weighted) years of life lost (YLL) worldwide in 2000 and it is the biggest single cause of YLL from cancer in the developing world. In Latin America, the Caribbean and Eastern Europe, cervical cancer makes a greater contribution to YLL than diseases such as tuberculosis, maternal conditions or AIDS. It also makes the largest contribution to YLL from cancer in the populous regions of sub-Saharan Africa and South-Central Asia.

1.2. Cancers of the external genitalia

1.2.1. Cancer of the penis

On a global basis, cancer of the penis is a rare cancer, accounting for less than 0.5% of cancers in men. In Western countries, the ASR is less than 1 per 100,000. Incidence rates greater than this are observed in cancer registries in India, Southeast Asia (Thailand and Viet Nam), Latin America (Paraguay, Puerto Rico, Peru, Brazil) and in Eastern and Southern Africa (Fig. 3). Incidence in Jewish populations is particularly low (0.04 per 100,000 in the Jewish population of Israel in 1993–1997) [3].

The importance of circumcision in determining the risk of penile cancer has been evident for many years, and this has been confirmed by case-control studies which suggest that the risk is reduced about threefold [10,11]. Circumcision protects against sexually transmitted infections, like HIV [12], by preventing accumulation of infected vaginal secretions, or more likely by simply reducing the surface area of non-keratinized epithelium. The geographical correlation between the incidence of penile and cervical cancers (Fig. 4c), has suggested a common aetiology, as has concordance of these two cancers in married couples [13]. HPV-DNA is detectable in about 40–50% of all penile cancers, and serological studies have confirmed the role of HPV-16 and -18 [1].

1.2.2. Cancers of the vulva

Fig. 5 shows some incidence rates of cancers of the vulva worldwide. ASRs mostly lie between 0.5 and 1.5 per 100,000. The geographical pattern is not immediately obvious, and is not similar to that of cervical cancer, since high rates are observed in several European populations (Scotland, Denmark, Spain, Italy), and low rates in several populations in sub-Saharan Africa, Southeast Asia, and Latin America. Bosch and Cardis [14], using cancer incidence data from 1978 to 1982, found that the incidence of cervical cancer was strongly correlated with penile cancer, and of other cancers of the female genitalia; however, this is not
Fig. 2. Age-standardised (World) incidence rates of cervical cancer by histological subtype in selected cancer registries circa 1993–1997 [3].

<table>
<thead>
<tr>
<th>Location</th>
<th>Squamous</th>
<th>Adenocarcinoma</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zimbabwe, Harare: African</td>
<td>56.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uganda, Kyadondo County</td>
<td>44.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brazil, Goiania</td>
<td>43.7</td>
<td></td>
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<tr>
<td>Viet Nam, Ho Chi Minh City</td>
<td>32.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thailand, Chiang Mai</td>
<td>28.6</td>
<td></td>
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<tr>
<td>Ecuador, Quito</td>
<td>28.0</td>
<td></td>
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<tr>
<td>India, Bangalore</td>
<td>24.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA, California, LA: Hispanic</td>
<td>23.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slovak</td>
<td>18.7</td>
<td></td>
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<tr>
<td>Singapore; Chinese</td>
<td>17.4</td>
<td></td>
<td></td>
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<tr>
<td>Poland, Lower Silesia</td>
<td>16.8</td>
<td></td>
<td></td>
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<tr>
<td>Estonia</td>
<td>16.0</td>
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<tr>
<td>Denmark</td>
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<tr>
<td>Algeria, Algers</td>
<td>13.6</td>
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<tr>
<td>UK, Scotland</td>
<td>12.4</td>
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<tr>
<td>USA, SEER: Black</td>
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<td></td>
</tr>
<tr>
<td>Australia, New South Wales</td>
<td>10.3</td>
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<td></td>
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<tr>
<td>Canada</td>
<td>9.0</td>
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<tr>
<td>Switzerland, Zurich</td>
<td>8.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA, SEER: White</td>
<td>8.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Netherlands</td>
<td>7.9</td>
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<td>Italy, Varese Province</td>
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<td>Spain, Navarra</td>
<td>4.4</td>
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<td>China, Beijing</td>
<td>2.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Israel, non-Jews</td>
<td>2.5</td>
<td></td>
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</tbody>
</table>

Fig. 3. Age-standardised (World) incidence rates of penile cancer in selected cancer registries circa 1993–1997 [3].
obvious when rates for the period 1993–1997 are compared (Fig. 4a).

Although the majority of tumours are SCCs, distinct subtypes are recognised, particularly the warty and basaloid types, which are associated with HPV infection and the precursor lesions of vulvar intraepithelial neoplasia (VIN), and the verrucous type, which is not [15].

1.2.3. Cancers of the vagina

Cancers of the vagina are less frequent than vulvar cancers: the ASR is 0.3–0.7 per 100,000 in most countries. There is no clear association with incidence of cancers of the vulva or cervix (Figs. 4b and 5). Many SCCs are preceded by vaginal intraepithelial neoplasia (VAIN). Clear-cell carcinoma of the vagina is a well-known complication of exposure to diethylstilboestrol in utero [16]; simultaneous or prior gynaecological malignancy leads to an increased risk, especially if associated with pelvic irradiation [15].

The number of new cases of cancer of the penis and female genitalia worldwide can be estimated from the number of cervical cancer cases, and the ratio of incidence rates at each of these sites to those of cervical cancer, by world area and age group [3]. The estimated numbers in 2002 were 40,000 cases of cancer of the female genitalia and 26,300 cases of cancer of the penis worldwide.

1.3. Cancers of the anus

Cancers of the anus are those arising in the anal canal—tumours of the external skin (anal margin) are classified along with skin cancers. The canal is lined in its upper part by colorectal-type of mucosa, and in its lower third by squamous epithelium, with specialized transitional zone epithelium in between. Therefore, cancers are predominantly SCCs, adenocarcinomas, or basaloid and cloacogenic carcinomas. In most populations SCC is twice as common in males as in females [15].

The number of new cases of cancer of the penis and female genitalia worldwide can be estimated from the number of cervical cancer cases, and the ratio of incidence rates at each of these sites to those of cervical cancer, by world area and age group [3]. The estimated numbers in 2002 were 40,000 cases of cancer of the female genitalia and 26,300 cases of cancer of the penis worldwide.

1.4. Cancers of the mouth and oro-pharynx

Cancers of the mucosa of the oral cavity and of the pharynx are frequently considered as a group, as there are many similarities in their epidemiology, treatment and prognosis. Cancers of the nasopharynx and salivary glands differ histologically and aetiologically. The incidence rates of oro-pharyngeal cancers vary widely and are highest in the geographical regions where tobacco use and alcohol consumption are popular. A high incidence of these cancers is observed in the Indian subcontinent, Oceania (Australia, Papua-New Guinea), Switzerland, The Netherlands, France, Latin America (Brazil) and Southern Africa (Fig. 7). In 2002, an estimated 405,000 cases occurred worldwide, two-thirds of them in developing countries, and there were 211,000 deaths [2]. The highest incidences among males are reported in Northern and Eastern France, while the highest incidences in females are in India and Pakistan [3]. The male:female ratio of occurrence varies from 2 to 15:1, depending on the anatomical sub-site, with the extreme ratios characteristic of tongue, mouth and pharyngeal cancers. Cancers of the mouth and of the tongue generally predominate in developing countries, whereas pharyngeal cancers are common in developed countries, including Central and Eastern Europe.

Although HPV is accepted as an aetiological factor for oral and pharyngeal cancers, the major risk factors are tobacco and alcohol, with the effects of these two agents being multiplicative [18]. Tobacco exposure occurs through smoking.
in the high-risk populations of Europe, Australia and Latin America, and has been estimated to be responsible for about 41% of these cancers in men, and 11% in women worldwide [19]. Chewing tobacco is the major exposure in the Indian subcontinent, Papua New Guinea, and to a lesser extent, in Southeast Asia [18]. Chewing has traditionally been in the form of “betel”—a large quid made up of varying proportions of tobacco, lime and condiments wrapped in the leaf of the piper betel. Recently, sales of commercially prepared and marketed powdered tobacco have become increasingly

Fig. 5. Age-standardised (World) incidence rates of vulvar and vaginal cancer in selected cancer registries circa 1993–1997 [3].

Fig. 6. Age-standardised (World) incidence rates of anal cancer by histological subtype and sex in selected cancer registries circa 1993–1997 [3].
popular, and there are indications that these may be even more harmful. Oral snuff (“dipping”) is used in some countries in Europe (Sweden) and in the US amongst the young [18].

Alcohol increases the risk of these cancers, and this risk relates to the quantity of alcohol consumed, rather than the type of beverage [20].

Epidemiological studies worldwide have linked a generally impoverished diet, particularly one lacking in vegetables and fruits, with an excess risk for these cancers. Cancer of the lip is associated with sunlight exposure and outdoor occupations in white populations.

2. Quantification of the role of HPV in human cancer

Oncogenic HPV can be detected by PCR in virtually all cases of cervical cancer, and it is generally accepted that the virus is necessary for the development of cancer, so that all cases of cancer can be “attributed” to infection [1].

With respect to SCCs of the vulva and vagina, penile cancer, and anal cancer, the relative risk associated with HPV infection is difficult to quantify, because of the small size of most studies, and the absence of comparable measurements of prevalence of infection in normal subjects. The fraction of these cancers attributed to HPV infection is therefore generally equated with the proportion of cancer cases infected with HPV in various series. In studies using PCR methodology, the prevalence of HPV in vaginal cancer is about 60–65% and 20–50% in vulvar cancers [1] (75–100% in the basa-loid and warty type associated with VIN and only 2–23% of the keratinizing carcinomas [21]). HPV-related vulvar cancer occurs in younger women than the typical keratinizing squamous histology related to chronic inflammatory precursors. For anal cancer, Frisch et al. [22] observed in a series of 386 cases from Denmark and Sweden, 95% and 83% of cancers involving the anal canal in women and men, respectively, were positive for oncogenic HPV. Prevalence in a US case-control study (of about 300 subjects) was approximately 90% of cancers, and HPV-16 was the most frequent HPV type detected (73%), followed by HPV-18 (6.9%) [17]. For penile cancer, Bezerra et al. [23] found HPV DNA in 30% of 71 cases of penile cancer from Brazil, and Rubin et al. [24] found HPV DNA in 42% of 148 cases from the US and Paraguay.

Several studies have investigated the prevalence of HPV in cancers of the mouth and pharynx. In a review of 60 studies, Kreimer et al. [25] calculated the average to be 23.5% for cancers of the oral cavity and 35.6% for oro-pharyngeal cancers. HPV-16 was the predominant type (87% and 68% of HPV-infected oro-pharyngeal cancers and oral cavity, respectively).

The population attributable fraction (PAF) of a disease is defined as the proportion of the new cases of disease observed
in a population that are attributable to exposure to a risk factor. The PAF therefore provides an upper limit to the numbers of cases that could be prevented, for example, if vaccination was 100% effective. The estimated numbers of cases of cancer attributable to infection with all HPV types worldwide have been published [26]. All cases of cervical cancer were assumed to be related to HPV, while for the ano-genital cancers, the estimated attributable fraction was based upon the proportion of tumours in which the virus can be detected; the fractions assumed were 40% of cancers of the external genitalia (vulva, vagina, penis) and 90% of cancers of the anus. This method, however, overestimates attributable fractions, by including some cancer cases in which the presence of the virus was coincidental without, for example, expressing viral oncoproteins. The estimate of HPV-attributable cancers of the oral cavity and pharynx, on the other hand, makes use of data from the International Agency for Research on Cancer (IARC) multi-national study [27] in which prevalence of HPV16 E6 or E7 antibody in controls (1.6%) as well as cases (6.4% mouth cancers, 15.3% oro-pharyngeal cancers) was available. An allowance was also made for the fact that assessment of HPV-DNA presence by PCR assay may lead to an overestimation of cases in which the virus is aetiologically involved, as suggested by the lower proportion of cases with E6/E7 expression (4.6% of oral cancers and 12% of oro-pharyngeal cancers). The resulting attributable fractions (3% for oral cancer, 12% for oro-pharynx) are, therefore rather lower than the percentage of tumours with detectable HPV-DNA (4% and 18%, respectively). The results are shown in Tables 1 and 2.

Although the study of HPV prevalence in oral and pharyngeal cancers by Herrero et al. [27] has the advantage of being the largest available (1670 cases), and allows attributable fractions to be corrected for the presence of HPV in normal control subjects, the prevalence of HPV in tumour tissue in this study (4% of oral cancers, 18% of oro-pharyngeal tumours) was considerably lower that the averages calculated by Kreimer et al. [25], based on 3611 cases from 60 studies (32.5% and 35.6%, respectively), so it is possible that the HPV-attributable cases at these sites in Tables 1 and 2 may be considerably underestimated. Table 1 also provides an estimate of the numbers of cancer cases attributable to HPV 16 and/or 18, based on the percentage of HPV-positive cancers at each site that contained HPV-16 or -18. Of the 561,000 cancers estimated to be caused by HPV, 71.8% were caused by HPV-16 and -18.

3. Time trends of cervical cancer

Time trend studies make use of published rates of mortality and incidence. Comparative studies of mortality, in particular, must take into account the deaths certified as “Uterus, part unspecified”. The proportion of uterine deaths ascribed to this category varies widely, both between countries, and over time, and it can be very high, for example, over 50%
Table 2
HPV infection-attributable cancer in 2002: developed & developing countries (source: [26])

| Site          | Attributable to HPV (%) | Developed countries | | % all cancer |
|---------------|-------------------------|---------------------| | | |          |          |
|               | Total cancers | Attributable to HPV |       |          |
| Cervix        | 100          | 83,400              | 83,400 | 1.7       | 409,400 | 409,400 | 7.0       |
| Penis         | 40           | 5200                | 2100   | 0.0       | 21,100  | 8400    | 0.1       |
| Vulva, vagina | 40           | 18,300              | 7300   | 0.1       | 21,700  | 8700    | 0.1       |
| Anus          | 90           | 14,500              | 13,100 | 0.3       | 15,900  | 14,300  | 0.2       |
| Mouth         | 3            | 91,200              | 2700   | 0.1       | 183,100 | 5500    | 0.1       |
| Oro-pharynx   | 12           | 24,400              | 2900   | 0.1       | 27,700  | 3300    | 0.1       |
| All sites     | 5,016,100    | 111,500             | 2.2    |          | 5,827,500 | 449,600 | 7.7       |

in France and Italy for women aged over 30 in 1995. Some form of “reallocation” of these deaths to more specific categories is generally necessary before rates are calculated. Loos et al. [31] have described appropriate methods, and have provided “corrected” mortality figures for 35 European countries. A further problem arises when incidence and mortality rates are calculated using the entire female population as the “population-at-risk”; women who have had a total hysterectomy for reasons other than the presence of cervical neoplasia are not at risk of cervical cancer, and should be excluded from the population-at-risk. However, this is difficult since the prevalence of hysterectomy is generally unknown, although it can be substantial in some age groups and countries, and may vary by time as well as place and age. Correction of the population-at-risk may have a substantial impact on the estimated rates of incidence and mortality, especially in older age groups, although the impact on the observed trends in Ontario and England and Wales was not significant [5].

Cytological screening programmes have been shown to reduce incidence or mortality of cervical cancer in populations where they have been intensive or systematically applied. Often, these reductions have taken place against a background increase in incidence that affects successive generations (birth cohorts). These changes in risk are most likely to result from changing sexual behaviour with increased transmission of oncogenic HPV types. The study of time trends of cervical cancer has therefore been important in assessing both changes in exposure among women born in different generations, as well as the effectiveness of organised screening programmes.

The following section reviews the historic and current patterns of cervical cancer worldwide, and provides scenarios with regards to future rates at the global level. Trends in cervical cancer are also compared with other HPV-related cancers to assess the extent to which HPV-related cancers share the same high-risk (HR) HPV as risk factors.

3.1. Trends before and after introduction of screening

3.1.1. Developed countries

Current patterns of incidence worldwide reflect the net effect of two influences: the underlying risk of disease (presumably related to transmission of HPV) and prevention of its manifestation as invasive cancer by effective screening. The geographic pattern described earlier is relatively recent. Before the introduction of screening programmes in the 1960’s and 1970’s, the incidence in most of Europe, North America, and Australia/New Zealand was much as we see in developing countries today [5] (Fig. 8). Rates of cervical cancer incidence and mortality have declined in the last 40 years in many western countries (Fig. 9). The declines in mortality predated the introduction of screening in some populations (e.g. the US), and was ascribed to factors correlated with improving socioeconomic levels [5], as well as a steady improvement in stage at diagnosis, and more effective treatment and improved survival certainly played a major role [5]. More recently, the beneficial effects of screening programmes have been recognised. Since the efficacy of cervical screening was never tested in randomised controlled trials, much of the evidence of its effectiveness is based on the reduction in incidence and mortality from invasive cervical cancer following the introduction of organised programmes in the 1950s and 1960s. The trends in incidence and mortality in the Nordic countries are the best known examples. Declines in incidence parallel the extent and coverage of the organ-

Fig. 8. Time trends in age-standardised (World) incidence rates of cervical cancer incidence in four Nordic countries [48].
Fig. 9. (a) Time trends in age-standardised (World) incidence rates of cervical cancer incidence based on data from selected cancer registries accepted in successive Volumes of *Cancer Incidence in Five Continents* [48]. (b) Time trends in age-truncated (World, ages 20–34) incidence rates of cervical cancer incidence based on data from selected cancer registries accepted in successive volumes of *Cancer Incidence in Five Continents* [48].
ised programmes, and were most marked in the age groups targeted by these programmes [5]. Similar observations were made in Canada and the US [5].

In spite of the overall declines in crude or age-adjusted incidence and mortality in Western countries, increases have been reported among young women, presumably reflecting changing sexual habits and increased transmission of HPV in younger generations. This phenomenon was first described in England and Wales [32], where successive generations of women born since the mid-1930s have been at increasingly high-risk. Similar observations have been made elsewhere in Europe [5]. In some countries of Eastern Europe, where there has been little or no screening, mortality rates have been rising rapidly (e.g. Bulgaria, Romania, and Russia), particularly amongst recently born generations. In more affluent countries, however, there is evidence of recent declines (e.g. the Czech Republic, Hungary and Poland).

3.1.2. Developing countries

Less information is available regarding trends in developing countries. In general, incidence and mortality rates have been relatively stable in many countries, or shown modest declines [5]. The absence of an overall decline – as observed in high resource populations – probably reflects the lack of screening implementation, or where programmes have been introduced, their low population coverage and poor quality cytology. In Fig. 9, declines in incidence are relatively slight in Bombay, India, in contrast to the dramatic declines in cervical cancer in Shanghai. The declines in Chinese populations have been attributed to screening, treatment and improved female genital hygiene, although increasing rates are seen among younger women and this has been linked to changing economic circumstances and sexual behaviour [5]. Despite the steady decline in cervical cancer, incidence in Cali, Colombia (Fig. 9) – rates in the 1990s were one-third of those observed three decades earlier – the population continues to have one of the highest rates in the world [3].

3.2. Trends in cervical cancer incidence by age and histology

Temporal studies have often failed to separate adenocarcinomas from SCCs, even though there may be some heterogeneity in their aetiology, and in their susceptibility to detection by cytology screening. Screening using the Pap test has been shown to effectively detect SCC in early stages, while it has been considered much less effective at detecting adenocarcinoma [5].

In addition to the problems of “Uterus unspecified” cancers, and the changes in prevalence of hysterectomy, alluded to above, the study of trends by histological subtype must take into account changes over time in the proportions of cases of cervical cancer coded as unspecified or of ill-defined histology.

The impact of screening on the incidence of cervical cancer is difficult to separate from the effects of other factors in determining the rate of diagnosis. Screening has been in use for several decades in many parts of the world, so that it is difficult to estimate what the risk of cervical cancer would have been in the absence of screening. There is also lack of information on the extent and quality of screening, particularly when a large proportion of tests are outside organised programmes.

One informal way to evaluate changing risk patterns alongside the impact of screening, is the joint assessment of the effects of age at diagnosis, period of diagnosis, and birth cohort using age-period-cohort (APC) modelling [33]. For cervical cancer, changing rates among successive generations point to modifications in the population prevalence of persistent infection with oncogenic HPV types, while period effects act as surrogate measures of events that quickly change incidence or mortality with the same order of magnitude regardless of the age group under study. They can be viewed as representing the effects of cytological screening as the intervention should deflect trends downwards across targeted age groups over the same period of time.

3.2.1. Trends in SCC of the cervix

Since most cervical cancers are SCC, studies of all types largely reflect trends in rates of this histology. Fig. 10 shows the cervical SCC trends in Sweden and Slovakia as part of a recent APC analysis of trends in 13 European countries [34]. In this analysis, the non-identifiability problem inherent in APC models (the indexes of age, period and cohort are not independent, but are exactly linearly dependent on each other) was addressed assuming a constant pattern of age-specific risk over time. There were large declines in risk by calendar period in Northern Europe, but a pattern of escalating risk in successive generations born after 1930 in many European countries. The decreased incidence of SCC in Sweden is accompanied by a decline in the period slope, implying that it is the consequence of screening. A recent study reported little or no increase in risk in young women in Sweden, due to effective screening, and a levelling off of risk in cohorts born since the mid-1940s [35]. A bleaker picture emerges from several Southern and Eastern European countries (e.g. Slovenia and Slovakia (Fig. 10) where trends by period remained stable, but marked increases in risk among consecutive births cohort have been observed, related to an absence of screening among a population where sexual behaviour has changed.

An earlier birth cohort analysis of cervical SCC trends in 25 countries [36] reported declining rates of SCC in successive generations in the US (except US Hispanic), Australia, non-Maori women of New Zealand, and a number of Northern and Western European countries, in both younger (age<50 years) and older women (age 50–74 years). In contrast, in Finland, the UK, Slovakia, Slovenia and Israel, SCC rates have increased in recent birth cohorts of young women.

3.2.2. Trends in adenocarcinoma of the cervix

Studies in the last twenty years in Europe and North America have reported increasing rates of cervical
Fig. 10. Effects of age, birth cohort and calendar period in the time trends of cervical squamous cell carcinoma and adenocarcinoma incidence in Sweden and Slovakia. Estimates were obtained from an age-period-cohort model that fixed the underlying age curve [34,37].

adenocarcinoma. Most have noted increasing rates among younger women (age<40 years) [5]. The European study [37] reported increases in age-adjusted adenocarcinoma rates in the majority of 13 countries as a result of a generational increase in risk that first affected women born in the early-1930s through to the mid-1940s. As noted earlier, differences in geographic and temporal profiles of the two main subtypes of invasive cervical cancer is in keeping with the relative inability of cytological screening to reduce the rates of invasive adenocarcinoma. In Fig. 10, there are period-specific increases in risk in both Sweden and Slovakia, which may partly be the result of increasing accuracy in the specificity of the diagnosis of adenocarcinoma with calendar time. Interestingly, the trends in cohort-specific risk in both countries coincide more with the corresponding cervical SCC trends. Interpretation is, however, complex as cohort-specific increases among recent generations of women may be the result of an increasing prevalence of oncogenic HPV types. If cohort trends are stable however, it may be that increasing risk has been diminished by screening programmes (e.g. for squamous cell but not adenocarcinoma in Northern Europe). However, other reasons related to sexual behaviour and attitudes to screening cannot be discounted.

Recent work suggests that the efficacy of cytological examinations has improved during the 1990s, and may have been responsible for some reductions in adenocarcinoma in this period [38]. A European study [37] reported declines in period-specific risk of adenocarcinoma among younger women in the U.K., Denmark and Sweden during the 1990s, indicating that the Pap test may have had a recent impact in reducing incidence in Europe.

4. Quantifying the contributions of changes in HPV infection and screening on incidence of cancer

Although observed trends are the net result of changes in risk, as determined by infection and persistence of oncogenic HPV, and prevention of invasive disease via screening, quantifying their relative contributions is difficult. There is little information on changes in incidence or prevalence of HPV infection. Increases in HPV-16 have been reported in Finland in women aged in their twenties [39], while in Sweden, rises in HPV-16 during the 1970s and early-1980s in women aged under 35 have been reported [40]. It would be useful to relate the prevalence and distribution of HR-HPVs to birth
cohorts to better understand how sexual behaviour of different populations subjects women to an increasingly higher average risk of cervical cancer in certain countries relative to others.

In a health services context, it is important to know how many cases are being prevented by screening and how many cases may be prevented in the future. Studies in England and Wales [41] have attempted such a quantification, where an improved programme has successfully countered increases. In estimating the cases prevented in the past, one must specify an appropriate model and provide information on the historical screening process. However, precise quantitative information on organised screening practices is difficult to obtain, and there is little information on the extent and distribution of opportunistic screening [5].

5. Trends in other HPV-related cancers

There are few systematic studies of time trends of cancers of the external genitalia. In Norway, marked increases in the incidence of VIN were observed, but not of invasive cancer between 1973 and 1992 [42]; a similar observation was observed in the US [43]. Possibly early diagnosis and treatment of in situ carcinoma reduces increases in invasive vulvar carcinoma incidence. For anal cancers, there have been marked incidence increases for over 50 years [44]. Conversely, there have been recent declines in mortality rates from oral and pharyngeal cancers in many European countries, as well as in Australia and North America (coinciding with lung cancer); however, they are still rising in most of Central and Eastern Europe, and until very recently, in Japan [45].

In the context of examining the impact of HPV, it is interesting to compare cervical cancer trends in the absence of screening, with those of the external genitalia and of the mouth and of the pharynx. The observation of simple associations between these trends would be expected if a substantial proportion of cancers at these sites due to infection with the same HR-HPV types. In Fig. 11, there are no striking resemblances in the trends in HPV-related cancers and cervical cancer in the four countries studied. However, there is some correlation between the temporal patterns of cervical cancer and those for cancers of the penis and of other female genitalia, at least in the Colombian, Chinese and Indian populations. This may be anticipated given that the PAR estimates indicate that about two-fifths of these cancers can probably be attributed to HPV (40%), whereas the proportion is much lower for mouth and pharyngeal cancer.

Fig. 11. Time trends in age-truncated (World, ages 30–64) incidence rates of five HPV-related cancers in four cancer registries accepted in successive Volumes of Cancer Incidence in Five Continents [48].
Table 3
Predicted number of cervical cancer cases in 2010 and 2020 by world area and age. Projections assume rates estimated for 2002 hold into the future. Adapted from [2]

<table>
<thead>
<tr>
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<th></th>
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<tbody>
<tr>
<td>World</td>
<td>493,000</td>
<td>100</td>
<td>584,500 (19%)</td>
<td>702,500 (42%)</td>
<td>100</td>
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<tr>
<td>Women aged &lt;65</td>
<td>396,500</td>
<td>80</td>
<td>470,000 (19%)</td>
<td>549,000 (38%)</td>
<td>78</td>
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<tr>
<td>Women aged ≥65</td>
<td>96,500</td>
<td>20</td>
<td>114,500 (18%)</td>
<td>153,500 (59%)</td>
<td>22</td>
</tr>
<tr>
<td>Less developed areas</td>
<td>409,000</td>
<td>83</td>
<td>505,500 (23%)</td>
<td>639,500 (56%)</td>
<td>83</td>
</tr>
<tr>
<td>Women aged &lt;65</td>
<td>336,000</td>
<td>82</td>
<td>413,500 (23%)</td>
<td>507,500 (51%)</td>
<td>79</td>
</tr>
<tr>
<td>Women aged ≥65</td>
<td>73,000</td>
<td>18</td>
<td>92,000 (25%)</td>
<td>132,000 (80%)</td>
<td>21</td>
</tr>
<tr>
<td>More developed areas</td>
<td>83,000</td>
<td>17</td>
<td>89,000 (06%)</td>
<td>92.500 (11%)</td>
<td>17</td>
</tr>
<tr>
<td>Women aged &lt;65</td>
<td>60,000</td>
<td>72</td>
<td>63,500 (05%)</td>
<td>62,500 (03%)</td>
<td>67</td>
</tr>
<tr>
<td>Women aged ≥65</td>
<td>23,000</td>
<td>28</td>
<td>25,222 (09%)</td>
<td>30,000 (31%)</td>
<td>33</td>
</tr>
</tbody>
</table>

6. Projections of HPV-related cancers

Planning cancer services requires knowledge of the current and likely future patterns of occurrence. Predictions can be used to make decisions on future provision of services (or post hoc, to investigate why their expected impact was not achieved). Both screening and HPV infection will influence future rates, and accurate predictions will depend upon information on both changing levels of persistent infection with HR-HPVs and the relative impact of interventions in the population. The assessment of the impact (epidemiologically and economically) of HPV vaccine, requires fairly complex mathematical modelling with a scenario-based approach [46].

Simpler approaches usually involve a projection based on past trends that represent the composite effect of changing risk and preventive interventions. Here the APC model is commonly applied, wherein the period and birth cohort effects are proxies for events that cannot be measured directly [47]. The cancer burden measured by the number of new cases, is calculated by multiplying the predicted cancer rates with population forecasts.

In countries where the HPV vaccine is likely to be introduced, predicted numbers based on such extrapolations are likely to become increasingly inaccurate; however, they do serve to quantify the effectiveness of a proposed vaccine by comparison of the numbers predicted in its absence with those actually observed subsequently.

6.1. Global projections of cervix cancer 2010 and 2020

We assume here that current incidence rates will apply in the future, and calculate expected numbers using appropriate population forecasts. Anything more complex would be hard to justify, given past trends are quite different between and within world regions, and the temporal landscape will surely be radically altered by the aforementioned interventions. Irrespective of changing risk, population growth and ageing are extremely important in determining likely future burden, and demographic changes will continue to have major consequences over the next half-century, particularly in the developing world.

Table 3 shows the predicted number of new cases of cervical cancer based on the estimated incidence rates in 2002 applied to short-term population projections in 2010 and 2020. In the absence of changing risk or intervention, it is projected that by 2020, 0.7 million cases will occur, about a 40% increase from 2002. Four-fifths of the cervical cancer cases worldwide in 2002 were in less-developed regions, and, as a result of the much more rapid ageing and population growth in these areas, this proportion could increase to over 90% by 2020. The biggest relative increase will occur among the elderly—an 80% increase from 410,000 cases to 640,000 by 2020.

Disclosed potential conflicts of interest

Authors have disclosed no potential conflicts of interests.

References


