

Chapter

Epidemiology of gynaecological cancers

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Introduction

Gynaecological cancers encompass a diverse group of tumours with different epidemiological and pathological features, clinical presentations and treatment strategies. This chapter aims to provide an overview of basic concepts in cancer epidemiology and to describe the global patterns and trends in incidence and mortality, aetiology and prevention of the five main types of gynaecological cancer.

What is epidemiology?

Epidemiology is the basic science underpinning public health and clinical medicine. It describes the occurrence of health-related states or events (incidence, prevalence), quantifies the risk of disease (relative risk) and its outcome (prognosis, survival, mortality), and postulates causal mechanisms for disease in populations (aetiology, prevention). The main function of epidemiology is to provide evidence to guide public health policy and clinical practice to protect, restore and promote health.

The applications of epidemiology can be summarized as follows:

- To describe the spectrum and extent of disease in the population – e.g. what is the prevalence of human papillomavirus (HPV) infection among young girls?
- To identify factors that increase or decrease the risk of disease – e.g. what factors increase the risk of, or protect against, endometrial cancer?
- To study the natural history and prognosis of disease – e.g. does early diagnosis of cervical carcinoma *in situ* through cytological screening prevent future morbidity and improve survival?
- To monitor and predict disease trends in the population – e.g. what impact will the increasing prevalence of obesity in women have on future disease trends and healthcare needs?
- To provide evidence for developing public health policy and making regulatory decisions – e.g. will a smoking ban in public places promote smoking cessation and reduce the incidence of smoking-related disease?
- To evaluate the efficacy of preventive and therapeutic interventions – e.g. does post-menopausal hormone replacement therapy (HRT) do more harm than good?

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- To evaluate public health programmes – e.g. will the mandatory vaccination of school girls against oncogenic HPV prevent vulvar/vaginal/cervical cancers and save lives?
- To evaluate the effectiveness of health services – e.g. are known contacts of people with sexually transmitted diseases (STDs) followed up and treated?

Classification of gynaecological cancers

- The *International Classification of Diseases* (ICD): this is the global standard diagnostic classification for epidemiological, clinical and health service data. It is used by hospital records departments, cancer registries and government agencies responsible for collection of health statistics (e.g. the Office for National Statistics in the UK) to classify diseases and other health problems recorded on many types of health and vital records. The ICD is essential for compilation of morbidity (e.g. cancer incidence) and mortality statistics (e.g. underlying cause of death) and allows comparison at an international level of health data collected in different countries at different times. In the Tenth Revision of the ICD (ICD-10), the malignant neoplasms of female genital organs are coded from C51 to C58. The category C57 includes neoplasms of the fallopian tube, broad and round ligaments, uterine adnexa and overlapping lesions (e.g. tubo-ovarian) (Table 1.1).
- The *International Classification of Diseases for Oncology* (ICD-O-3): this is used principally by cancer registries for coding the site (topography) and the histology (morphology) of neoplasms, usually obtained from a pathology report.
- The *Tumour Node Metastasis Classification of Malignant Tumours* (TNM-6): this is a cancer staging system used for describing the anatomical extent of cancer (see Appendix 3). It is based on the assessment of three components: T – describes the extent of the primary tumour; N – describes the absence/presence and extent of regional lymph node involvement/metastasis; and M – describes the absence/presence of distant metastasis. The classification is used to: (i) aid the clinician in the planning of treatment; (ii) assist in evaluation of the results of treatment; (iii) give some indication of prognosis; and (iv) facilitate the exchange of information between treatment centres. The TNM system is approved by the International Federation of Gynecology and Obstetrics (FIGO), and its categories have been defined to correspond to the FIGO classification.

Measuring the risk or burden of gynaecological cancers

Incidence

Incidence (or incident cases) is a count of *new cases* of cancer in the population during a specified time period. The incidence rate is the number of *new cases* of cancer in a defined population within a specified time period (usually a calendar year), divided by the total number of people in that population. Cancer incidence rates are typically expressed as per 100 000 population.

Incidence rate measures the rapidity (or ‘speed’) at which new cases of cancer are occurring in the population within a specified time period. Increase in incidence of a cancer in the population can be due to: in-migration of susceptible people, a change in diagnostic criteria, improved case ascertainment, introduction of a new screening/diagnostic test, introduction of new, or changes in exposure to, existing aetiological agent(s). Incidence rate is used to: predict

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Table 1.1 ICD-10 codes and morphological classification of malignant neoplasms of female genital organs

ICD-10 code	Organ	Morphological subtypes
C51	Vulva	Squamous cell carcinoma Extramammary Paget's disease Malignant melanoma
C52	Vagina	Squamous cell carcinoma Adenocarcinoma, botryoid Rhabdomyosarcoma
C53	Cervix uteri	Squamous cell carcinoma Neuroendocrine carcinoma Adenocarcinoma
C54	Corpus uteri	Endometrial adenocarcinoma Malignant mixed Müllerian tumours Leiomyosarcoma
C55	Uterus (part unspecified)	
C56	Ovary	Surface epithelial tumours Serous adenocarcinoma Endometrioid adenocarcinoma Mucinous adenocarcinoma Clear cell carcinoma Germ cell tumours Dysgerminoma Yolk sac tumour Choriocarcinoma Mature and immature teratoma Sex cord-stromal tumours Granulosa cell tumour Sertoli–Leydig cell tumour
C57	Other and unspecified female genital organs	
C58	Placenta	Hydatidiform mole Placental site trophoblastic tumour Choriocarcinoma

the average risk of developing cancer; research causes and treatment of cancer; describe trends of cancer over time; and evaluate the effectiveness of prevention programmes.

Age-standardized incidence (or mortality) rate (ASR)

As the risk of cancer increases exponentially with age, the crude incidence rate, which is influenced by the population age structure, cannot be used to evaluate whether the risk/

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burden of cancer differs between populations. It is therefore necessary to use ASRs when comparing rates of populations that have different age structures. The ASR is obtained by applying the (crude) age-specific rates in the observed population to the age-specific population counts (or weights) of a fixed reference (or standard) population. The most commonly used standard population is the *world* (and also *European*) *standard population* of Doll. Age-standardization controls for the confounding effect of age on cancer incidence and allows direct comparison of different populations.

Cumulative incidence (or cumulative risk)

Cumulative incidence is the probability or risk of developing cancer during a specified period (e.g. lifetime). It measures the number or proportion of people (out of 100 or 1000) who would be expected to develop a particular cancer by the age of 64 (or 74) years if they had the rates of cancer currently observed. Like the ASR, cumulative incidence permits comparisons among populations of different age structures. For example, the cumulative risk of a woman in the UK developing ovarian cancer by age 74 is 14 per 1000, which can be interpreted as a 1.4% (1 in 71) probability or (lifetime) risk of developing ovarian cancer by the time she completes 74 years.

Prevalence

Prevalence is the number of *existing cases* of cancer in a defined population at a notional point in time, divided by the total number of people in the population at that time. It is usually expressed as an absolute number of existing cases or as the proportion of a population that has the disease. For example, the prevalence of cervical cancer can be defined as the number of women in a defined population who have been diagnosed as having the cancer, and who are still alive at a given point in time.

Mathematically, prevalence can be defined as follows:

let a = the number of individuals in the population with the disease at a given time

let b = the number of individuals in the population without the disease at a given time

$$\text{then prevalence} = \frac{a}{a + b}$$

Thus prevalence is a measure of the burden of cancer in the population. The prevalence of a cancer in the population can increase due to: in-migration of cases, increase in incidence and/or improved prognosis/survival (e.g. due to better treatment).

Prevalence data are used for planning health services, resource allocation and organization of prevention programmes.

- *Partial prevalence* is the estimation of the number of cases of cancer diagnosed within one, three and five years to indicate the number of patients undergoing initial treatment (cases within one year of diagnosis), clinical follow-up (within three years) or not considered cured (before five years). Patients alive five years after diagnosis are usually considered cured because, for most cancers, the death rates among such patients are similar to those in the general population.
- *Complete prevalence* represents the proportion of patients alive on a certain day who previously had a diagnosis of cancer, regardless of how long ago the diagnosis was, or if the patient is still under treatment or is considered cured.

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Survival

Survival is the proportion (%) of people still alive one, three, five and 10 years after they have been diagnosed as having cancer. This *observed* survival probability is influenced by mortality both from the cancer itself and from other causes. For this reason, relative survival (%) is usually calculated (ratio of the observed survival in a particular group of patients to the survival expected in a group of people in the general population).

Quality-adjusted life-years (lost)/disability-adjusted life-years (lost)

Quality-adjusted life-years (QALYs) and disability-adjusted life-years (DALYs) quantify the spectrum of morbidity (between the diagnosis and cure/death) due to cancer in terms of its duration and severity. The calculation of these indices requires three elements: the incidence of cancer, its mean duration (survival probability) and a measure of life ‘quality’ between the diagnosis and cure/death. These indices are used to estimate the impact of cancer on the individual and society, and for establishing priorities for healthcare programmes.

Mortality

Mortality is the number of deaths occurring, and mortality rate is the number of deaths in a defined population within a specified time period (usually a calendar year), divided by the total number of persons in that population. Cancer mortality rates are expressed as per 100 000 persons per year. Mortality is the product of the incidence and the fatality of a given cancer, and measures the average risk to the population of dying from a specific cancer within a specified period. Fatality, the complement of per cent survival, is the probability (%) that a cancer patient will die from the disease.

Cancer screening

Screening is the presumptive identification of an unrecognized disease or defect by the application of tests, examinations or other procedures that can be applied rapidly. Cancer screening is the testing of apparently healthy volunteers from the general population for the purpose of separating them into high and low probabilities of having a given cancer. The rationale behind cancer screening is that the disease has a natural history that includes a clearly defined preclinical phase with biological characteristics, which allows for detection of the disease in an early treatable stage that, in turn, will reduce the risk of future morbidity and improve survival (e.g. cytological screening for carcinoma *in situ* of uterine cervix → intervene with surgery → cure/reduced risk of invasive cervical cancer). Randomized controlled trials and both case-control and cohort observational study designs are used to evaluate cancer screening programmes.

The performance of a screening test is based on its sensitivity, specificity and predictive value (Table 1.2).

- Sensitivity – this is the ability of the test to identify correctly those who *have* the disease (true positives).
- Specificity – this is the ability of the test to identify correctly those who *do not have* the disease (true negatives).

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Table 1.2 Calculation of sensitivity, specificity and predictive value of a screening test

		Disease according to gold standard		
		Present	Absent	Total
Screening test result	Positive	A (True +)	B (False +)	A + B
	Negative	C (False –)	D (True –)	C + D
Total		A + C	B + D	A + B + C + D

Sensitivity = $A/(A + C) \times 100$ (%)
Specificity = $D/(B + D) \times 100$ (%)
Positive predictive value = $A/(A + B) \times 100$ (%)
Negative predictive value = $D/(C + D) \times 100$ (%)
Prevalence of disease = $A + C/(A + B + C + D) \times 100$ (%)

- Positive predictive value (PPV) – this is the proportion of individuals *who test positive* and actually have the disease. PPV is a function of sensitivity, specificity and disease prevalence. A high PPV is essential for a successful screening programme, whereas a low PPV implies that resources are being wasted on diagnostic follow-ups of false-positive individuals.
- Negative predictive value – this is the proportion of individuals *who test negative* and actually do not have the disease.

Ovarian cancer

Incidence and mortality

Worldwide, ovarian cancer is the sixth most common cancer among women, with an estimated 204 000 new cases (4% of cancer in women) and 125 000 deaths (4.3% of cancer deaths in women) in the year 2002 and a five-year prevalence of 538 000 cases. The incidence rates of ovarian cancer vary from a low of about 2 per 100 000 women in Algeria to a high of 15 per 100 000 in Poland. In general, incidence rates are relatively higher in developed countries – the highest rates are observed in European populations – followed by the Philippines and Brazil (11–15/100 000 women), intermediate rates are observed in North America, Australia/New Zealand and some populations in Asia and South America, and the lowest rates (2–7/100 000 women) are observed in Africa, the Caribbean, the Middle East and parts of Asia. Evidence from the USA suggests that ovarian cancer is relatively more common in white than in black women (10.6 vs. 7.2/100 000 women).

In the UK, ovarian cancer is the most common gynaecological cancer. It is the fourth most common cancer among women, with 6615 new cases in the year 2004 accounting for around 5% of all cancers in women, with a cumulative risk of 0.8% (1 in 125) by age 64 (Fig. 1.1). In most European populations, the incidence rates of ovarian cancer generally increase exponentially with age, with a sharp increase after about 40 years. It is predominantly a disease of older, postmenopausal women – almost 85% of cases occur in women aged over 50 (Fig. 1.2). In developed countries, the mortality/incidence ratio is 56% and ovarian cancer accounts for more deaths than all the other gynaecological cancers

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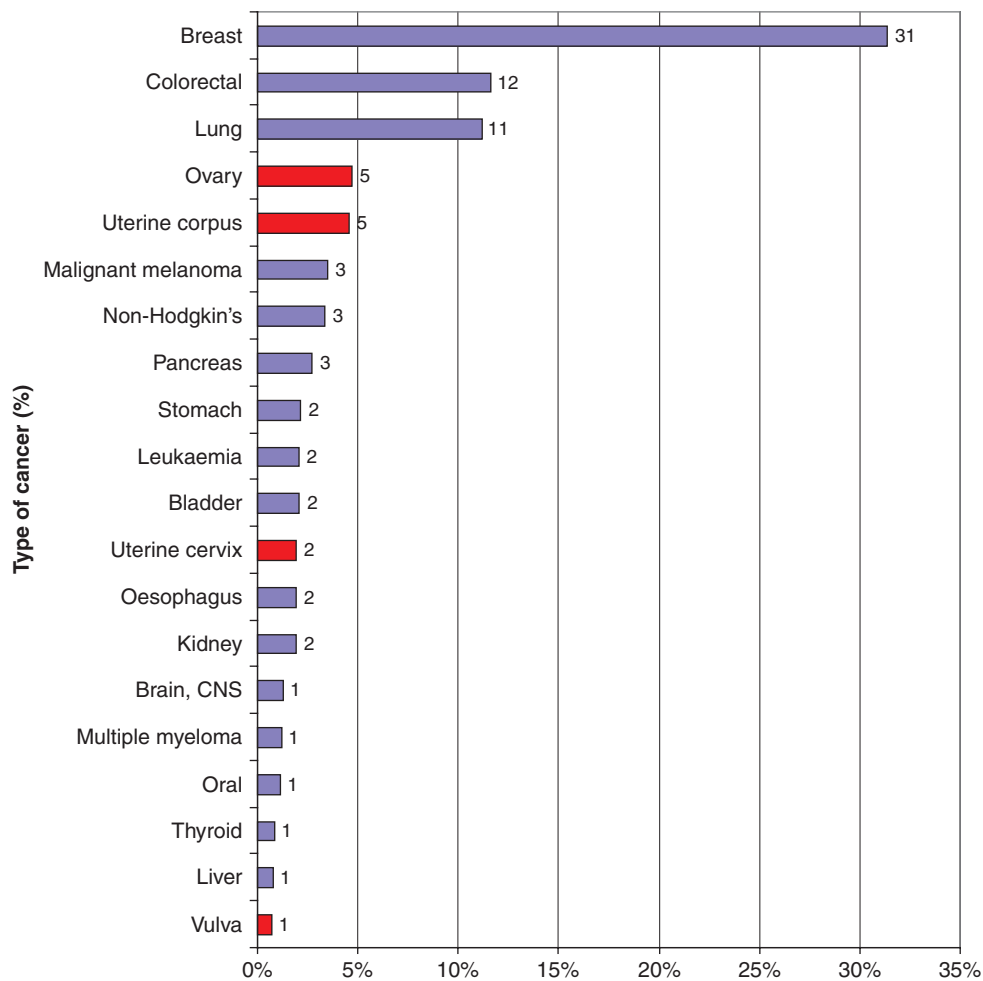


Fig. 1.1 Frequency distribution (%) of the 20 most common cancers in women (UK, 2004).

put together. In 2005, 4447 women in the UK died from ovarian cancer, accounting for around 6% of all female deaths from cancer. Ovarian cancer has a relatively poor prognosis as most cases (about 75%) are diagnosed at an advanced stage – with overall survival rates of about 30–40%. When diagnosed at the localized stage, the five-year relative survival rate is about 75%.

Trends in incidence and mortality

In most developed countries there has been little change in the incidence of ovarian cancer over the past 40 or so years. In the UK, the age-standardized (European standard) incidence rates of ovarian cancer increased by 16% during the period 1975–2004 (from 14.7/100 000 to 17.1/100 000 women). Most of this increase was observed in women aged over 65, in whom the rates increased by 48% during that period. The incidence in younger women has

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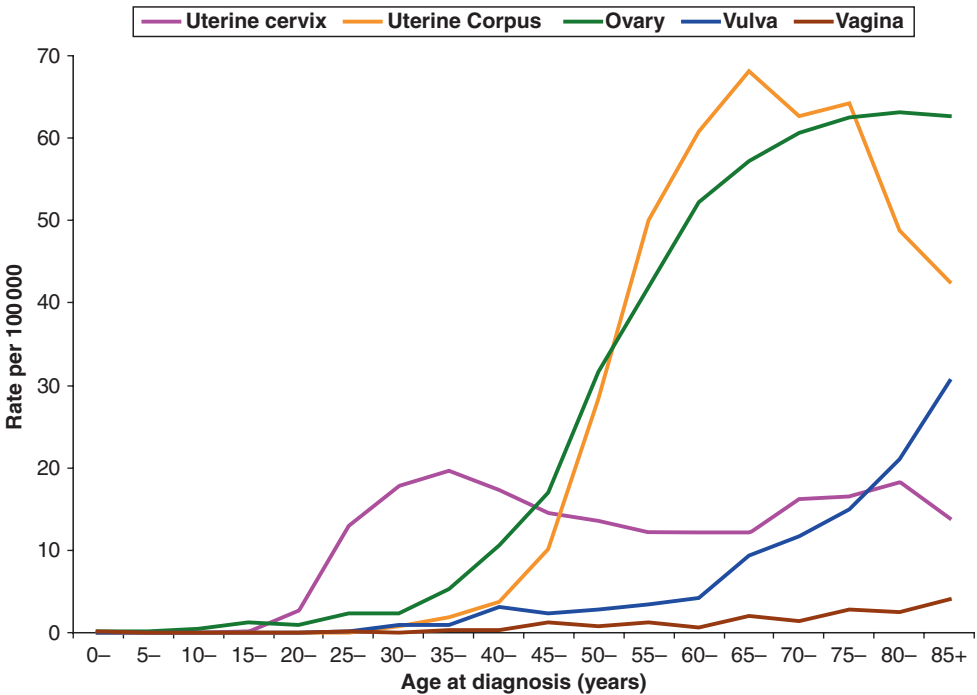


Fig. 1.2 Age-specific incidence rates of gynaecological cancers (West Midlands, UK, 1998–2002). (Source: Curado MP, Edwards B, Shin HR, *et al.*, 2007).

remained fairly stable or may be declining – which in part is owing to the protective effects of oral contraceptives widely used by younger women. In most populations, mortality rates have remained fairly stable or declined slightly over the past 40 years. In the UK, the age-standardized (European standard) mortality rates have remained stable over this period at between 10/100 000 and 12/100 000 women.

Aetiology

Compared with other gynaecological cancers, little is known about the aetiology of ovarian cancer. In most studies, family history of ovarian cancer has been associated with an increased risk, whereas oral contraceptive use, increased parity, breastfeeding, tubal ligation and hysterectomy have been associated with decreased risk.

Prevention

Apart from prophylactic oophorectomy, oral contraception and (possibly) tubal ligation, there are few readily modifiable risk factors for ovarian cancer. There is currently inconsistent evidence for a possible increase in risk with consumption of lactose/galactose-containing foods, intake of saturated or animal fats and use of perineal talcum powder and postmenopausal HRT, and for a decrease in risk with consumption of vegetables. It is unclear whether obesity, body mass index (BMI) and physical activity influence ovarian cancer risk.

Endometrial cancer

Incidence and mortality

Worldwide, endometrial cancer is the seventh most common cancer among women, with an estimated 199 000 new cases (3.9% of cancer in women) and 50 000 deaths (1.7% of cancer deaths in women) in the year 2002 and a five-year prevalence of 776 000 cases. In contrast with cervical cancer, endometrial cancer is relatively more common in developed countries. About 69% of the cases occur in developed countries where it accounts for 5.9% of all cancers in women, with a cumulative risk of 1.3% (1 in 77) by age 64. In developing countries, endometrial cancer accounts for only 2.3% of cancers in women, with a cumulative risk of 0.2% (1 in 500) by age 64. In the UK, endometrial cancer is the fifth most common cancer among women, with 6438 new cases in the year 2004 accounting for around 5% of all cancers in women, with a cumulative risk of 0.8% (1 in 125) by age 64 (Fig. 1.1). In most European populations, the incidence rates of endometrial cancer begin to rise steadily 5–10 years before the menopause and reach a peak usually around 65–70 years (Fig. 1.2). It is a cancer of postmenopausal women – over 90% of cases occur in women aged 50 or older, with very few cases diagnosed under the age of 35. The incidence rates of endometrial cancer vary from a low of 0.9 per 100 000 women in Oman to a high of 18.8 per 100 000 in white women in the USA. The highest rates are observed among women in North America, Europe, Australia/New Zealand and Israel. Incidence rates are generally low in countries in Latin America, Asia (including China and Japan) and Africa. Evidence from the USA suggests that endometrial cancer is considerably more common in white than in black women (18.8 vs. 13.5/100 000 women). Mortality rates are substantially lower than the incidence. Worldwide, the mortality/incidence ratio is 25%. In Europe, the cumulative mortality rates are generally three to four times lower than the incidence; in North America, these rates are about eight times lower. Endometrial cancer has a relatively better prognosis than cervical cancer, with five-year survival rates of 86% in the USA and 78% in European cancer registries.

Trends in incidence and mortality

The trends in incidence of endometrial cancer have varied among populations and by age groups over the past 40 or so years. In the UK, the overall incidence (i.e. all ages combined) remained stable between 1975 and 1992, and then increased by 24% between 1993 and 2004. Most of this increase has occurred in older women – since the mid 1980s, there has been a steady increase in incidence among women aged over 60. Generally, similar trends in incidence are observed in most other European countries. The mortality rates, however, have steadily declined in most developed countries over this time period. In the UK, the age-standardized (European standard) mortality rates decreased by 27% between 1971 and 2005 (from 4.8/100 000 to 3.5/100 000).

Aetiology

In contrast with cervical cancer, which is a model of viral carcinogenesis, endometrial cancer is a model of hormonal carcinogenesis. The 10-fold variation in age-standardized incidence rates across populations point to the role of modifiable factors in the aetiology of endometrial cancer. Among these, oestrogens and progestins are considered to have an important role in malignant transformation. The most compelling evidence has come from studies of HRT

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following the menopause – unopposed oestrogen use for 10 or more years increases the risk about 10-fold. This excess risk can be counteracted substantially by combined use of oestrogens and progestins.

Prevention

Obesity (which increases peripheral production of oestrogens) and diabetes mellitus are associated with an increased risk of developing endometrial cancer, whereas past oral contraceptive use, childbearing and physical activity (potentially mediated by hormones) are associated with risk reduction. It is therefore possible to substantially reduce the incidence of endometrial cancer through modification of lifestyle, maintenance of normal weight and optimal use of oral contraceptives and postmenopausal HRT.

Cervical cancer

Incidence and mortality

Worldwide, cervical cancer is the second most common cancer among women, with an estimated 493 000 new cases (or 9.7% of cancer in women) and 274 000 deaths (or 9.3% of cancer deaths in women) in the year 2002 and a five-year prevalence of 1.4 million cases. About 83% of the cases occur in developing countries, where cervical cancer accounts for 15% of all cancers in women, with a cumulative risk of 1.5% (1 in 67) by age 64. In developed countries, cervical cancer accounts for only 3.6% of cancers in women, with a cumulative risk of 0.8% (1 in 125) by age 64. In the UK, 2726 new cases of cervical cancer were diagnosed in the year 2004, accounting for around 2% of all cancers in women, with a cumulative risk of 0.6% (1 in 167) by age 64 (Fig. 1.1). In most European populations, the incidence of cervical cancer begins to increase at 20–24 years and the risk increases rapidly to reach a peak usually around 35–39 years (Fig. 1.2). The incidence rates of cervical cancer vary substantially between different regions, from a low of 2.8 per 100 000 women in China to a high of 47.3 per 100 000 in Zimbabwe. The highest rates are observed among the populations of sub-Saharan Africa, Melanesia, Latin America and the Caribbean, and south-central and south-east Asia. Incidence rates are generally low in developed countries in Europe, North America, Australia/New Zealand, the Middle East, China and Japan. Mortality rates are substantially lower than the incidence. Worldwide, the mortality/incidence ratio is 55%. Five-year relative survival rates vary between regions and according to the extent of the disease (15–80%), with good prognosis in countries with a low incidence (63% in the European cancer registries).

Trends in incidence and mortality

Overall, incidence and mortality have declined considerably during the past 40 years in Western Europe, North America, Australia/New Zealand, China and Japan. The decline has been attributed to a combination of factors, including improved genital hygiene, improved treatment modalities and the beneficial effects of organized population-based cytological screening programmes. In the UK, the age-standardized (European standard) incidence rates of cervical cancer declined by around 46% during the period 1975–2004 (from 14.9/100 000 to 8.0/100 000), whereas, in the same period, the mortality rates declined by around 63% (from 7.5/100 000 to 2.8/100 000).