Uterine Cervical Cancer

Clinical and Therapeutic Perspectives

Samir A. Farghaly
Editor

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Samir A. Farghaly
The Joan and Sanford I. Weill Medical College/Graduate
School of Medical Sciences, The New York Presbyterian Hospital-Weill Cornell
Medical Center, and Sandra and Edward Meyer Cancer Center, Cornell University
New York, NY, USA

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This book is dedicated to my beloved children Raied and Tamer, and the memory of my mother Amina, and my father Aly who had a great influence on me and my academic and professional medical career. Also, to my sisters Sorya and Nadia, and brother Rafat and their families, and my late siblings, Nabil and Magdy, and their families. In addition to my late nephew, Islam, and my late sister-in-law, Awatif.

Preface

> Uterine cervical cancer is the fourth most common cancer in women, and the seventh overall, with an estimated worldwide 528,000 new cases. A large majority (around 85%) of the global burden occurs in the less developed regions, where it accounts for almost 12% of all female cancers. High-risk regions, with estimated ASRs over 30 per 100,000, include Eastern Africa (42.7), Melanesia (33.3), Southern (31.5) and Middle (30.6) Africa. Rates are lowest in Australia/New Zealand (5.5) and Western Asia (4.4). Cervical cancer remains the most common cancer in women in Eastern and Middle Africa.
>
> There were an estimated 266,000 deaths from cervical cancer worldwide in 2012, accounting for 7.5% of all female cancer deaths. Almost nine out of ten (87%) cervical cancer deaths occur in the less developed regions. Mortality varies 18-fold between the different regions of the world, with rates ranging from less than 2 per 100,000 in Western Asia, Western Europe and Australia/New Zealand to more than 20 per 100,000 in Melanesia (20.6), Middle (22.2) and Eastern (27.6) Africa. [1]

The American Cancer Society's estimates for cervical cancer in the United States of America (USA) for 2018 are about 13,240 new cases of invasive cervical cancer will be diagnosed and about 4170 women will die from cervical cancer [2]. In the USA and Western Hemisphere, cervical precancers are diagnosed far more often than invasive cervical cancer. According to the American Cancer Society, "in the USA, Hispanic women are most likely to get cervical cancer, followed by African-Americans, Asians and Pacific Islanders, and whites. American Indians and Alaskan natives have the lowest risk of cervical cancer in this country" [2]. It has been suggested that declines in cervical intraepithelial neoplasia (CIN2 and CIN3) incidence in the USA are more likely driven by HPV vaccination, introduced in 2006, than by changes in screening or risk behavior.

The purpose of this book is to provide a broad background of several aspects of basic sciences, clinical and therapeutic aspects, and management of uterine cervical cancer. It provides state-of-the-art information on the molecular genetics, biology, and clinical aspects of premalignant lesions of the uterine cervix and uterine cervical cancer. Also, the book chapters provide better understandings of the molecular and cellular events that underlie uterine cervical cancer.

There are 46 contributors to this book who are affiliated with several renowned major academic medical institutions in the USA, the UK, France, Australia, Spain, Greece, Brazil, India, South Africa, and Colombia.

The descriptive and analytical epidemiology of uterine cervical cancer and the role of HPV's infection in the etiology of this disorder are presented in Chap. 1. The strategies for the prevention of uterine cervical cancer which comprises primary, secondary, and tertiary prevention at different stages of the women life are discussed in Chap. 2. The role of several optical technologies in uterine cervical cancer is illustrated in Chap. 3. The program of the screening of uterine cervical cancer in low- and middle-income countries is detailed in Chap. 4. The pathological diagnosis of uterine cervical neoplasia which includes cytopathology, molecular pathology, and surgical pathology is highlighted in Chap. 5. The current information about the prevalence of human papilloma virus (HPV)-associated malignancies in patients with human immunodeficiency virus (HIV) is reported in Chap. 6. The immunological aspects of premalignant conditions of the uterine cervix and the potential efficacy of different immunotherapeutic technologies in treating patients with condition are detailed in Chap. 7. The applicability of sentinel lymph node biopsy in uterine cervical cancer is reported in Chap. 8. The role of fertility-sparing surgery in patients with early-stage uterine cervical cancer due to the trend toward a late childbearing is described in Chap. 9. The current standard and novel surgical treatment of uterine cervical cancer is detailed in Chap. 10. The current management of recurrent and metastatic uterine cervical cancer is discussed in Chap. 11. The role of chemotherapy treatment option for patients with locally advanced and metastatic uterine cervical cancer is highlighted in Chap. 12. The identification of prognostic and predictive biomarkers which allow the knowledge of the subpopulation of patients most likely to respond to radiation therapy is detailed in Chap. 13. The combination of external beam radiotherapy with chemotherapy if fitness allows treating patients with locally advanced and metastatic uterine cervical cancer is discussed in Chap. 14. Finally, negative and positive impact of uterine cervical cancer diagnosis and treatment on the quality of life of these patients are illustrated in Chap. 15.

This book volume is intended for all clinicians and basic medical scientists caring for women with uterine cervical cancer, including attending surgeons and physicians, clinical fellows, and residents in the disciplines of gynecologic oncology, medical oncology, and surgical oncology and also doctoral students and postdoctoral fellows in basic medical sciences.

I would like to thank Margaret Burns, the development editor of this book, and Samantha Lonuzzi, editor at Springer, for their efficiency and valuable help in the process of development, editing, and publishing of this book.

I hope that you find this book very useful and benefit from the extensive experience of the knowledgeable team of contributors who have authored its contents.

New York, NY, USA Samir A. Farghaly

References

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer incidence and mortality worldwide: IARC CancerBase No. 11 [Internet]. Lyon: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr. Accessed 28 Aug 2018.
2. https://www.cancer.org/cancer/cervical-cancer/about/key-statistics.html

About the Editors

Samir A. Farghaly is a Professor and Physician/Scientist and national and international expert in Obstetrics and Gynecology at Joan and Sanford I. Weill College of Medicine, Sandra and Edward Meyer Cancer Center and, the New York Presbyterian Hospital/Weill Cornell Medical Center- Cornell University, New York, NY – USA. He received his M.D. from London University and his PhD degree in molecular biology from London University. He was affiliated with major London University teaching hospitals, Columbia University College of Physicians and Surgeons/ Columbia University medical center, New York, NY-USA. He received several national and international clinical and research awards. He has been an invited speaker at several national and international conferences on Women's health, Molecular genetic of female cancers, Gynecological cancer and oncologic radical surgical techniques. He is a member of several national and international societies, organizations, foundations of Women health and Cancer. He is the founder Editor-in Chief of Current Trends in Gynecologic Oncology, and The International journal of Gynecological, Obstetrical and Reproductive Medicine Research journals. Also, he serves as Editor-in- Chief of Enliven: Challenges in Cancer Detection and Therapy Journal and Journal of Reproductive Medicine, Gynecology& Obstetrics. He acts as Senior Editor/ Editor and member of editorial boards, editorial advisory boards of (18) international medical journals on Gynecological Cancers, Gene expression &Therapy, Women's Health and Gynecology. He acted as guest editors of (4) special issues of international medical journals on oncology, Gynecology and gene therapy. He is a reviewer for several medical journals on Obstetrics & Gynecology, molecular Genetics and therapy, Oncology, and Surgery. He has published 105 articles in reputed peer review journals. He has written several book chapters, and is an author and editor of (2) books on ovarian cancer published in 2012, and the third one published in Nov. 2013. The fourth book on endometrial cancer was published in January 2015. The fifth book on recent advances in diagnosis and management Gynecologic cancers was published in March 2016, and the sixth book on ovarian cancer immunotherapy will be published in August 2018. The seventh book on uterine cervical cancer will be published in 2019. The eight's book on ovarian cancer will be published in 2019. The ninth's book on endometrial cancer will be published in 2019.

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Contributors

Yaa Achampong Department of Women's Health, University College London Hospital, London, UK

Georgios Androutsopoulos Department of Obstetrics and Gynaecology, University of Patras, Rion, Achaia, Greece

Peter Bannister Department of Primary Care and Public Health, Brighton and Sussex Medical School, Brighton, UK

Claudia Blancafort Department of Gynecology, Hospital Universitari Quiron-Dexeus, Barcelona, Spain

Stergios Boussios Department of Medical Oncology, Ioannina University Hospital, Ioannina, Greece

Joana Froes Bragança Department of Gynecology and Obstetrics, Hospital Dr. José Aristodemo Pinotti, State University of Campinas, Sao Paulo, Brazil

Mariana Canepa Department of Pathology and Laboratory Medicine, Brown University Warren Alpert Medical School, Providence, RI, USA

Shyrly Carrillo Research Group in Cancer Biology, National Cancer Institute, Bogotá, Colombia

Edward Chandy Clinical Oncology Department, Charing Cross Hospital, London, UK

Catherine Louise Cherry Department of Infectious Diseases, Monash University and Alfred Health, Melbourne, VIC, Australia

Burnet Institute, Melbourne, VIC, Australia

Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Amuthachelvi Daniel Department of Medical Physics, Anna University, Chennai, Tamil Nadu, India

Konstantinos Doufekas Department of Gynaecological Oncology, University College London Hospital, London, UK

Gemma Eminowicz Department of Clinical Oncology/Radiotherapy, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK

Samir A. Farghaly The Joan and Sanford I. Weill Medical College/Graduate School of Medical Sciences, The New York Presbyterian Hospital-Weill Cornell Medical Center, and Sandra and Edward Meyer Cancer Center, Cornell University, New York, NY, USA

Oscar Gamboa Unit of Analysis, National Cancer Institute, Bogotá, Colombia

Research Group in Radiobiology Clinical, Molecular and Cellular, National Cancer Institute, Bogotá, Colombia

Maria Luisa Garcia-Moliner Department of Pathology and Laboratory Medicine, Brown University Warren Alpert Medical School, Providence, RI, USA

Aristides Kefas Department of Medicine, Ioannina University Medical School, Ioannina, Greece

M. T. King Faculty of Science, School of Psychology, University of Sydney, Sydney, Australia

Faculty of Medicine, Sydney Medical School, Central Clinical School, University of Sydney, Sydney, Australia

Maria Lombarte Gynecologic Oncology Unit, La Paz University Hospital, Madrid, Spain

Nicolas Magné Department of Radiation Oncology, Institut de cancérologie de la Loire-Lucien Neuwirth, Saint-Priest en Jarez, France

Silvia Marín Gynecologic Oncology Unit, La Paz University Hospital, Madrid, Spain

Alejandra Mateos Gynecologic Oncology Unit, La Paz University Hospital, Madrid, Spain

Diana Mayorga Research Group in Radiobiology Clinical, Molecular and Cellular, National Cancer Institute, Bogotá, Colombia

Anjum Memon Department of Primary Care and Public Health, Brighton and Sussex Medical School, Brighton, UK

R. Mercieca-Bebber Faculty of Science, School of Psychology, University of Sydney, Sydney, Australia

Faculty of Medicine, Sydney Medical School, Central Clinical School, University of Sydney, Sydney, Australia

Linda Mileshkin Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Pablo Moreno-Acosta Research Group in Cancer Biology, National Cancer Institute, Bogotá, Colombia

Research Group in Radiobiology Clinical, Molecular and Cellular, National Cancer Institute, Bogotá, Colombia

Elisa Moreno-Palacios Department of Gynecology, Hospital Universitario La Paz, Madrid, Spain

Raj Naik Department of Gynaecology, Northern Gynaecological Oncology Centre, Queen Elizabeth Hospital, Gateshead, UK

Adeola Olaitan Department of Gynaecological Oncology, University College London Hospital, London, UK

Alexandra Papadaki Department of Medical Oncology, Ioannina University Hospital, Ioannina, Greece

Nimesh R. Patel Department of Pathology and Laboratory Medicine, Brown University Warren Alpert Medical School, Providence, RI, USA

Evangeline Ponnusamy Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Chloe Rancoule Department of Radiation Oncology, Institut de cancérologie de la Loire-Lucien Neuwirth, Saint-Priest en Jarez, France

Romelie Rieu Department of Clinical Oncology/Radiotherapy, Charing Cross Hospital, Imperial College Healthcare NHS Trust, London, UK

Alfredo Romero-Rojas Group of Pathology Oncology, National Cancer Institute, Bogota, Colombia

C. Rutherford Faculty of Science, School of Psychology, University of Sydney, Sydney, Australia

Wilfred Prasanna Savarimuthu Department of Physics, Madras Christian College, Chennai, Tamil Nadu, India

M. Tait Faculty of Science, School of Psychology, University of Sydney, Sydney, Australia

Konstantina Tatsi Gynaecology Unit, General Hospital "G. Hatzikosta", Ioannina, Greece

Diama Bhadra Vale Department of Gynecology and Obstetrics, Hospital Dr. José Aristodemo Pinotti, State University of Campinas, Sao Paulo, Brazil

Alexis Vallard Department of Radiation Oncology, Institut de cancérologie de la Loire-Lucien Neuwirth, Saint-Priest en Jarez, France

Ignacio Zapardiel Gynecologic Oncology Unit, La Paz University Hospital-IdiPAZ, Madrid, Spain

George Zarkavelis Department of Medical Oncology, Ioannina University Hospital, Ioannina, Greece

Luiz Carlos Zeferino Department of Gynecology and Obstetrics, Hospital Dr. José Aristodemo Pinotti, State University of Campinas, Sao Paulo, Brazil

Ioannis Zerdes Department of Medical Oncology, Ioannina University Hospital, Ioannina, Greece

Epidemiology of Cervical Cancer

1

Anjum Memon and Peter Bannister

Concepts in Cancer Epidemiology

What Is Epidemiology?

Epidemiology is the art and science of understanding the determinants of health and causation and prevention of disease in the population. It underpins public health and clinical medicine and describes the occurrence and distribution of health-related states or events (incidence, prevalence), quantifies the risk of disease (relative risk, attributable risk, odds ratio) and its outcome (prognosis, survival, mortality) and postulates causal mechanisms for disease in populations (aetiology, prevention) [1]. The main function of epidemiology is to provide evidence to guide public health policy and clinical practice to protect, restore and promote health of individuals and populations. Cancer epidemiology is a branch or subspecialty of epidemiology that studies factors influencing the occurrence (i.e. increase or decrease in incidence of a specific cancer) and prevention of neoplastic and preneoplastic diseases and related disorders.

Measuring the Risk or Burden of Cancer

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

A. Memon (✉) · P. Bannister
Department of Primary Care and Public Health, Brighton and Sussex Medical School, Brighton, UK
e-mail: a.memon@bsms.ac.uk; P.Bannister1@uni.bsms.ac.uk

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year), divided by the total number of people in that population. Cancer incidence rates are typically expressed as per 100,000 population [1, 2].

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 or burden of cancer differs between different populations. It is therefore necessary to use ASRs when comparing incidence rates in populations that have different age structures (e.g. the USA and China). 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 *US* and *European*) *standard population* proposed by Sir Richard Doll. Age-standardization controls for the confounding effect of age on cancer incidence and allows direct comparison between 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 between populations of different age structures. For example, the cumulative risk (or lifetime risk) of a woman in the USA developing cervical cancer by age 74 is 0.63% (or 1 in 159) probability [3].

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.

- Partial (or limited duration) prevalence is the estimation of the number of cases of cancer diagnosed within 1, 3 and 5 years to indicate the number of patients undergoing initial treatment (cases within 1 year of diagnosis), clinical follow-up (within 3 years) or not considered cured (within 5 years). Patients alive 5 years after the diagnosis of cancer 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.

Survival

Survival is the proportion (%) of people still alive 1, 3, 5 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).

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 in adults are usually 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

Definition – Screening is the presumptive identification (detection) 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 (i.e. phases of pathological progression/cellular transformation) that includes a clearly defined preclinical phase with biological characteristics, which allows for detection of the disease in an early (presumably) treatable stage that, in turn, will reduce the risk of future morbidity and improve survival. For example, cytological screening detects preinvasive cervical disease → intervene with treatment → cure or reduce risk of invasive cervical cancer. Randomized controlled trials and both case-control and cohort observational study designs are used to evaluate cancer screening programmes.

Screening test performance – The performance of a screening test is based on its sensitivity, specificity and predictive value (Table 1.1).

- 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).
- Predictive value positive (PVP) — this is the proportion of individuals *who test positive* and actually have the disease. PVP is a function of sensitivity, specificity and prevalence of the detectable preclinical phase. A high PVP is essential for a

Table 1.1 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) × 100 (%)
Specificity = D/(B + D) × 100 (%)
Positive predictive value = A/(A + B) × 100 (%)
Negative predictive value = D/(C + D) × 100 (%)
Prevalence of disease = A + C/(A + B + C + D) × 100 (%)

successful population-based screening programme (e.g. cervical cancer), whereas a low PVP implies that resources are being wasted on diagnostic follow-ups of false-positive individuals.

- Predictive value negative (PVN) — this is the proportion of individuals *who test negative* and actually do not have the disease.

Descriptive Epidemiology of Cervical Cancer

Global Burden: Incidence and Mortality

Worldwide, cervical cancer is the fourth most common cancer among women, with an estimated 528,000 new cases (7.9% of cancer in women) and 266,000 deaths (7.5% of cancer deaths in women) in the year 2012 and a 5-year prevalence of 1.5 million cases (9% of women with cancer). In contrast with endometrial cancer, which predominantly occurs in developed countries, the large majority (about 85%) of the cases of cervical cancer occur in developing countries, where it accounts for 12% of all cancers in women [4]. The incidence rates of cervical cancer vary substantially between different populations, from a low of 3.6 per 100,000 women in Switzerland to a high of 75.9 per 100,000 in Malawi (over 20-fold difference). The highest rates are observed among populations in 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 (Figs. 1.1 and 1.2).

In the USA, cervical cancer is the 13th most common cancer among women, with an estimated 12,820 new cases (and 4210 deaths) in the year 2017 accounting for around 2% of all cancers in women, with a cumulative risk of 0.63% (1 in 159) by age 74 (Fig. 1.3) [5–8]. There are an estimated 256,078 women currently living in the USA with cervical cancer [5]. In contrast to endometrial cancer, which predominantly occurs in postmenopausal women, cervical cancer is largely a cancer of middle-aged women [9]. In most European and North American populations, the incidence rates of cervical cancer begin to increase at

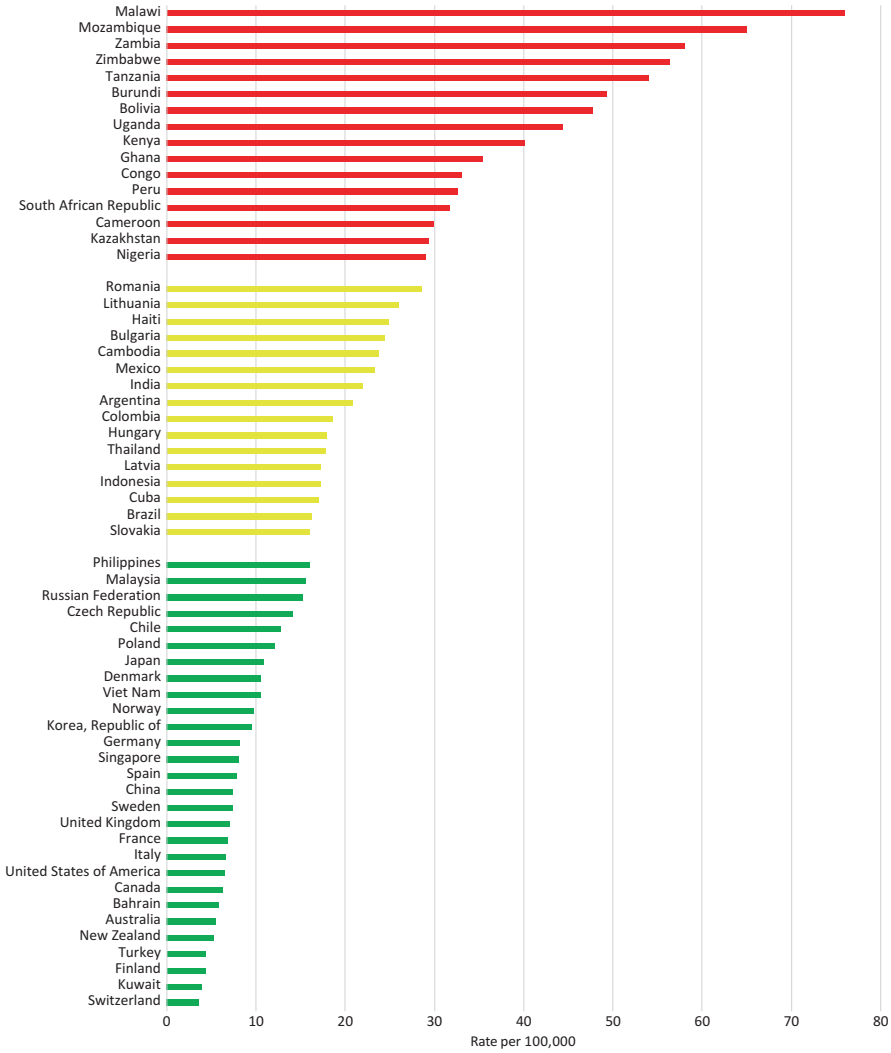

Fig. 1.1 Age-standardized (world standard) average annual incidence rates of cervical cancer in different populations. (From Ferlay [4], with permission)

ages 20–24 years, and thereafter the risk increases rapidly to reach a peak usually around 35–39 years (Fig. 1.4). Cervical cancer is most frequently diagnosed at ages 35–64 years (66% of the cases), and the median age of diagnosis is 49 years (and 58 years at death) [5]. In the USA, the highest incidence rate (9.1/100,000) is observed in Hispanic women followed by 8.7 in black, 7.4 in white and 6.1 in Asian and Pacific Islander women (Fig. 1.4) [5]. The incidence rates of cervical cancer also vary greatly across different states, with the highest incidence in Mississippi (10.4/100,000) and the lowest in Utah (4.59/100,000) [7].

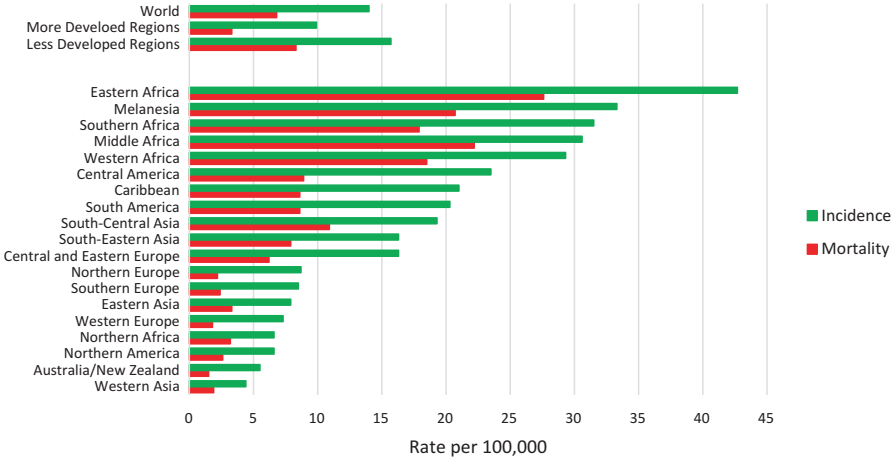

Fig. 1.2 Age-standardized (world standard) incidence and mortality rates as per (10000) of cervical cancer in different populations. (Data from GLOBOCAN [4])

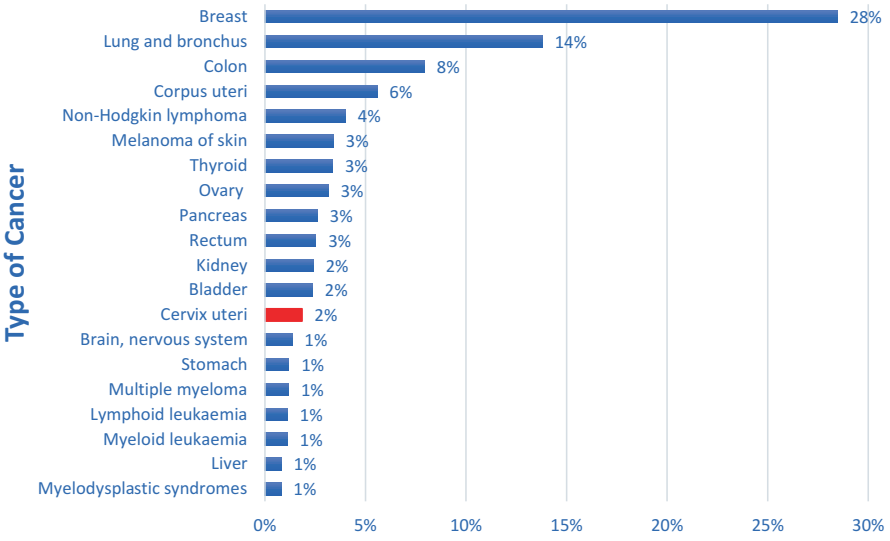

Fig. 1.3 Frequency distribution (%) of the 20 most common cancers in women (all ages and races), USA, 2003–2007. (Data from Forman et al. [3])

Almost nine out of ten (87%) cervical cancer deaths occur in the developing countries. The mortality rates vary substantially between different regions of the world – from less than 2/100,000 in Western Europe to more than 20/100,000 in Africa [4]. In 2014, 890 women in the UK died from cervical cancer (2.8/100,000), accounting for around 1% of all female deaths from cancer. Cervical cancer generally has an excellent prognosis – overall, in the UK, about 63% of women

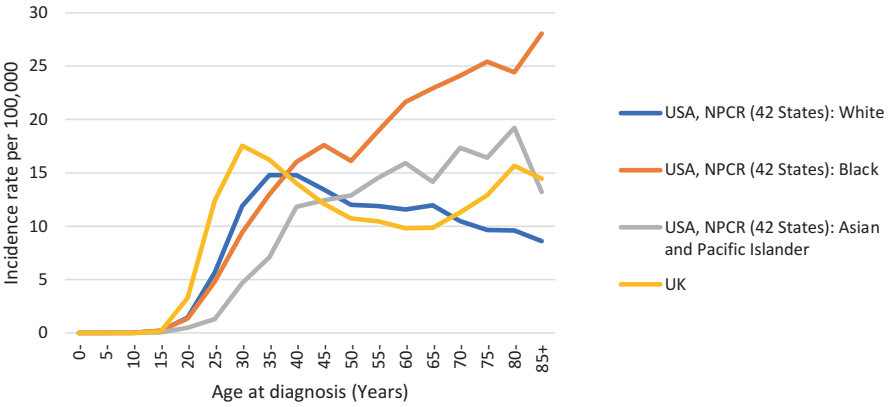

Fig. 1.4 Age-specific incidence rates of cervical cancer in the UK and USA (2003–2007). NPCR, National Programme of Cancer Registries (42 states). (Data from Forman et al. [3])

diagnosed with cervical cancer survive their disease for 10 or more years. When diagnosed at its earliest stage (Stage I), almost all (96%) of the women will survive their disease for 5 or more years, compared to 5-year relative survival of 5% for those diagnosed at Stage IV [10]. In the UK, the 5-year net survival has steadily improved from 51.5% in 1971–1972 to 67.4% in 2010–2011 (an increase of about 31% in the period) [10]. Similarly, in the USA, the overall 5-year relative survival is about 67% and 92% for the localized disease [5]. Due to early diagnosis of precancerous lesions via screening and improvements in treatment, the overall mortality rates of cervical cancer are significantly lower than the incidence. In Western Europe, the cumulative mortality rates are about 4 times lower than the incidence, and in North America cumulative mortality rates are about 2.5 times lower than incidence (Fig. 1.2) [4].

Trends in Incidence and Mortality

Overall, the incidence and mortality from cervical cancer have declined considerably during the past 40 years in Western Europe, North America, Australia/New Zealand, China and Japan (Figs. 1.5 and 1.6). The decline has been attributed to a combination of factors including improved genital hygiene, increased use of condoms, improved treatment modalities, beneficial effects of organized population-based cytological screening programmes for early diagnosis and introduction of the vaccine against HPV infection. In the UK, the age-standardized (European standard) incidence rates of cervical cancer have declined by around 28% since the early 1990s, whereas, in the same period, the mortality rates declined by around 62% [10]. In the USA, the incidence rates of cervical cancer declined by 54% between 1975 and 2014, whereas, in the same period, the mortality rates declined by 59% [5].

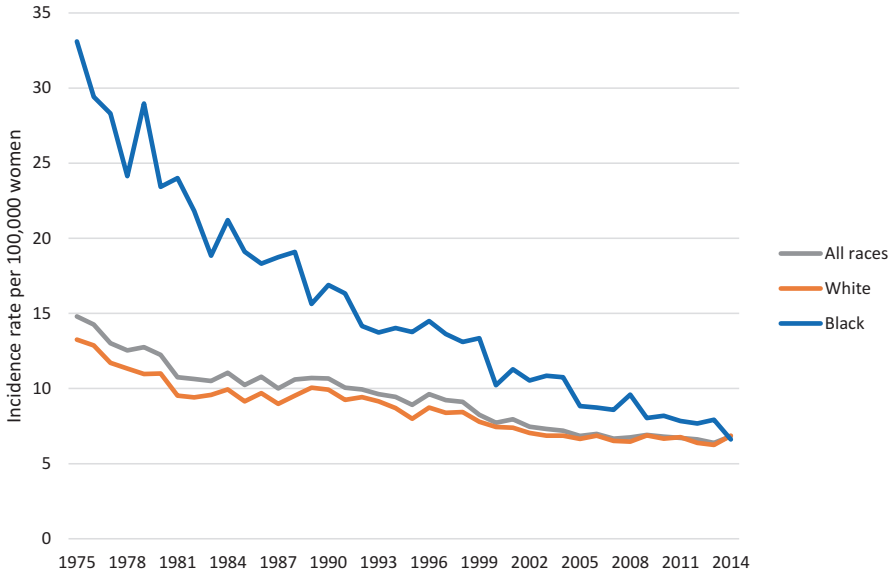

Fig. 1.5 Age-standardized annual incidence rates of cervical cancer in women, USA. (Data from Surveillance, Epidemiology and End Results (SEER) programme [5])

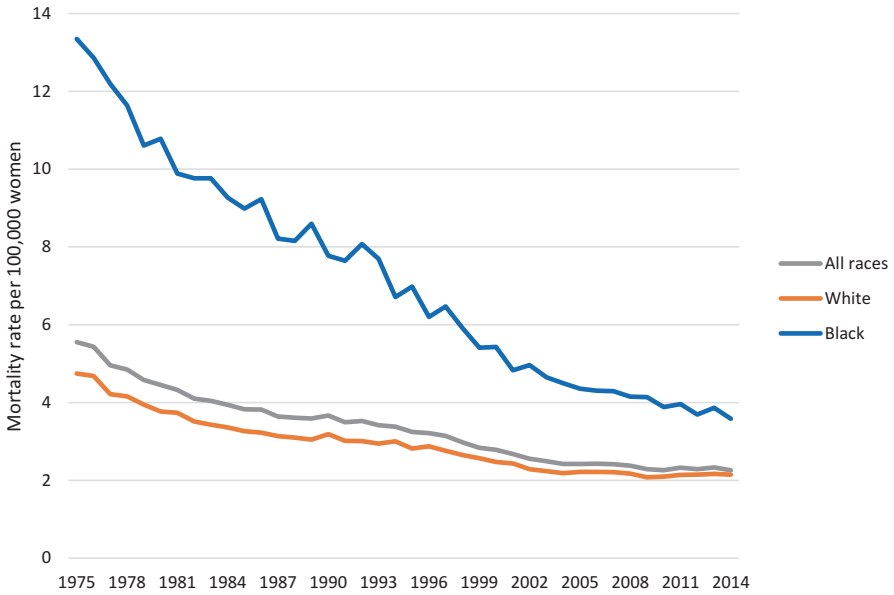

Fig. 1.6 Age-standardized annual mortality rates of cervical cancer in women, USA. (Data from Surveillance, Epidemiology and End Results (SEER) programme [5])

Aetiology of Cervical Cancer

In contrast with endometrial cancer, which is a model of hormonal carcinogenesis, cervical cancer is a model of viral carcinogenesis. The 20-fold variation in age-standardized incidence rates across different populations (Fig. 1.1) point to the role of modifiable factors in the aetiology of cervical cancer – essentially the exposure to, and persistent infection with, the human papillomavirus (HPV) and related cofactors. A persistent infection with an oncogenic HPV type is now recognized as a causal factor for preceding precancerous changes and cervical cancer. However, infection with HPV is extremely common compared with the relatively rare development of cervical cancer. There is compelling evidence that HPV is necessary for cervical carcinogenesis, but infection alone is not sufficient for the cancer to develop. A number of cofactors have been identified as possible modifiers of HPV infection during the developmental stages of cervical cancer, including early sexual debut, increasing number of sexual partners, smoking, long-term oral contraceptive use, high parity, dietary factors, certain human leucocyte antigen (HLA) types and co-infection with other sexually transmitted agents such as *Chlamydia trachomatis*, herpesvirus type 2 and human immunodeficiency virus (HIV) (Fig. 1.7).

Factors Influencing the Risk of Cervical Cancer

Human Papillomavirus (HPV)

The natural history of cervical carcinogenesis as a result of HPV infection is a four-fold process beginning with the virus infecting the metaplastic epithelium of the cervix in the transformation zone [11]. Following initial infection, over 90% of women will go on to clear the virus; however, a small number of women will continue to have viral persistence [11, 12]. This viral persistence can then cause the metaplastic cells to become precancerous cervical intraepithelial neoplasia (CIN) which is graded CIN-I, CIN-II and CIN-III depending upon the extent of the neoplastic change [11]. Invasive cervical cancer develops when these neoplastic cells invade the basement membrane of the cervix [11].

There are many different types of HPV, some of which are low risk and some high risk for developing cervical cancer. HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-45, HPV-52 and HPV-58 are the high-risk HPV types [13–15]. Out of these high-risk types, HPV-16 and HPV-18 are accountable for about 70% of cervical cancers, and 32% of people with an HPV infection are infected with these phenotypes [11].

In order for HPV transmission to occur, genital contact is required with an infected partner [16]. In the USA, HPV is the most common sexually transmitted infection, and there is a strong correlation between HPV infection/persistence and the number of lifetime sexual partners and sexual partners in the past year [16, 17]. The prevalence of HPV is greatest in women aged 20–24 (27.4%), with an increasing prevalence from the age of 14–24 and then a gradual decrease from the age of 25–59 [18]. It is thought that HPV infection/persistence is most common in younger women due to lack of previous exposure and therefore not having developed an

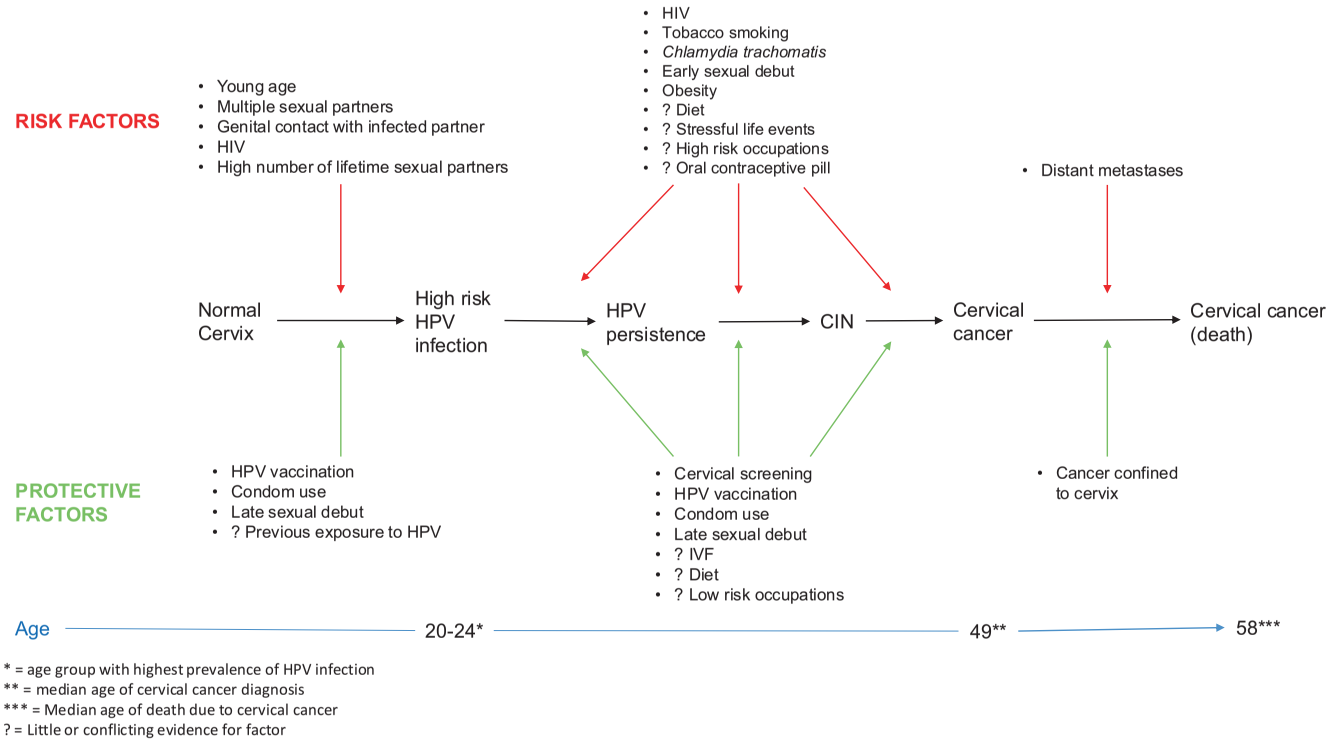

Fig. 1.7 The natural history of cervical cancer

immune response to the virus [16]. Not only does HPV account for almost all cases of cervical cancers; the virus is also associated globally with 113,000 cancers at other anatomical sites, for example, cancers of the vulva, vagina, penis and oropharynx [13, 19].

The prevalence (all ages combined) of HPV differs greatly between populations across the world. The highest prevalence is observed in Africa (22.1%) and lowest in Asia (8.0%) [20, 21]. The overall prevalence of HPV in North America and Europe is 11.3% and 8.1%, respectively [21]. The prevalence of HPV coincides with the incidence rates of cervical cancer in different populations (Fig. 1.1).

Tobacco Smoking

There is convincing epidemiological evidence that tobacco smoking is an independent risk factor for cervical cancer [22, 23]. In the two large collaborative studies on cervical cancer, there was an approximate doubling in risk among current smokers compared to never smokers; and this risk was further increased with younger age at starting smoking and the number of cigarettes smoked per day. In these studies, the effect of smoking appeared to be limited to squamous cell carcinoma of the cervix. In recent studies, an increased risk of cervical cancer has also been reported for women exposed to passive smoking [22, 24, 25]. It has been suggested that cigarette smoking may promote carcinogenicity by affecting local cell-mediated immune response, inducing genetic damage and causing localized immune suppression which may promote HPV persistence [26, 27].

Co-infection with Human Immunodeficiency Virus (HIV)

HIV increases the risk of developing CIN and invasive cervical cancer in the presence of HPV [28]. The prevalence of HPV is greater in HIV-positive people than HIV-negative people (37.2% vs 13.7%, respectively) [29]. Furthermore, persistent infection with HPV-16 or HPV-18 is relatively more common in HIV- positive people compared to those who are HIV-negative (20% vs 3%) [30]. However, despite treatment of HIV with antiretroviral therapy, the risk of developing cervical cancer remains substantially higher than in the HIV-negative population [31]. It is believed that there is a synergistic interaction between HIV and oncogenic HPV-16 – HIV infection compromises the immune system and predisposes sexually active women to co-infection by HPV-16 and its persistence [32].

Co-infection with Chlamydia Trachomatis

Co-infection of HPV with *Chlamydia trachomatis* has been associated with an increased risk of developing squamous cell carcinoma of the cervix in several studies [33–37]. In a pooled analysis of the International Agency for Research on Cancer (IARC) multicentred case-control studies, there was a twofold increased risk in HPV DNA-positive women who were also C. *trachomatis* seropositive compared to those who were seronegative [34]. It has been hypothesized that concomitant genital

infections may induce chronic irritation/inflammation of the cervix which could promote HPV-related oncogenic processes.

Reproductive Factors

Currently there is a good epidemiological evidence to support an association between multiparity and invasive cervical cancer (also CIN and carcinoma in situ), controlling for HPV status or other potential reproductive and sexual behaviour variables [25]. Most studies in populations where multiparity is common have reported an increased risk of cervical cancer among both HPV-positive and HPV-negative women [38]. Several hypotheses have been suggested to explain possible biological mechanisms that may influence the risk, including hormonal, nutritional and immunological changes during pregnancy and/or trauma to the cervix that occurs during parturition.

Sexual Behaviour

It has long been recognized that sexual behaviour played an important role in the aetiology of cervical cancer. It is now well established that an early age at first intercourse and increased number of lifetime sexual partners are associated with an increased risk of cervical cancer and its precursor lesions [25]. As would be expected, the use of condoms is associated with a decreased risk of HPV infection and persistence. In a recent study that demonstrated a protective effect of condom use, the incidence rates of both genital HPV infection and cervical intraepithelial lesions were reduced in condom users compared to nonusers [39, 40].

Obesity

There is some evidence to suggest that obesity, particularly weight gain since age 18, may be a risk factor for adenocarcinoma of the cervix [41]. It has been difficult to assess this association due to a large number of potential confounding factors (i.e. HPV, sexual behaviour, hormonal factors). Similarly, it has been difficult to assess the association with physical activity – some studies have demonstrated a protective effect with moderate to high physical activity [42].

Diet

It is plausible that certain foods and nutrients could have a protective effect against the development of cervical cancer. There is some evidence to suggest that high dietary consumption of carotenoids, retinol, vitamins C and E, folate and fruits and vegetables may reduce the risk of CIN and cervical cancer [43].

Prevention of Cervical Cancer

Cervical cancer is one of the most preventable forms of cancer on a global scale. Prevention efforts include increased public awareness about sexually transmitted infections, early detection of precursor lesions by regular cytological

screening, HPV testing and the recently developed vaccine against certain high-risk types of HPV. Cervical cancer screening in the form of cytology (Pap test) and HPV test (to detect the DNA or RNA of HPV) substantially reduces the lifetime risk of developing cervical cancer [44]. The US Preventive Services Task Force recommends that women aged 21–29 years should be screened every 3 years with cytology and women aged 30–65 years should be screened every 5 years with cytology + HPV test or every 3 years with cytology [7]. In the population-based cervical screening programme in the UK, all women aged 25–49 are invited for screening every 3 years; and women aged 50–64 years are invited for screening every 5 years [45]. The cytological screening programme has been highly effective in reducing both the incidence and mortality from invasive cervical cancer [46]. It is estimated that cervical screening is currently preventing 70% of cervical cancer deaths in the UK, and if all women attended their cervical screening appointment, appropriately 83% of cervical cancer deaths could be prevented [46]. There have also been developments in the use of first-void urine self-sampling as an alternative to physician-led cervical screening which may be an alternative option for women who do not attend cervical screening appointments or live in developing countries with no formal cervical screening programme [47, 48].

Prophylactic vaccines against HPV currently available include monovalent (HPV-16), bivalent (HPV-16 and HPV-18) and quadrivalent (HPV-6, HPV-11, HPV-16 and HPV-18) virus-like particle vaccines. In clinical trials, these vaccines have shown excellent safety and nearly 100% efficacy in preventing persistent infections and precancerous lesions due to HPV-16 and HPV-18. In the UK, all girls aged 12–13 years are offered HPV quadrivalent vaccine as part of the childhood immunization programme [45]. In the USA, HPV vaccination is recommended for girls and boys aged 11–12 years and young women through age 26 and young men through age 21 [7]. It has been estimated that almost all the cases of cervical cancer can be prevented by changes in lifestyle and risk factor modification.

Conclusion

Worldwide, cervical cancer is the fourth most common cancer among women – it accounts for an estimated half million new cases and quarter million cancer deaths in women each year. It is a cancer of the developing world (85% of all cases) and predominantly occurs in middle-aged women. In most European and North American countries, there has been a considerable decline in the incidence and mortality from cervical cancer during the past 40 years. This decline is attributed to a combination of factors including improved genital hygiene, increased use of condoms, improved treatment modalities, beneficial effects of organized population-based cervical screening programmes for early detection/diagnosis and introduction of the vaccines against HPV.

A persistent infection with an oncogenic HPV type is now recognized as a causal factor in almost all cases of cervical cancer. Although HPV is considered necessary for cervical carcinogenesis, infection with HPV alone is not always sufficient for the malignant transformation. A number of cofactors have been identified as possible modifiers of HPV during the development of cervical cancer, including tobacco smoking, multiparity, oral contraceptive use and *Chlamydia trachomatis* infection. As one of the leading causes of cancer among women worldwide, cervical cancer is an important public health problem, particularly in developing countries – 85% of all cases and 87% cervical cancer deaths occur in developing countries. It is now believed that a combination of efforts including health education about transmission of HPV, early detection of precursor lesions via regular screening and population-based vaccination programmes could substantially reduce the burden of cervical cancer and make it the most preventable forms of cancer on a global scale.

References

1. Memon A. Epidemiological understanding: an overview of basic concepts and study designs. In: Pencheon D, et al., editors. Oxford handbook of public health practice. 2nd ed. Oxford: Oxford University Press; 2006. p. 100–11.
2. Memon A. Epidemiology of gynaecological cancers. In: Shafi M, et al., editors. Gynaecological oncology. Cambridge: Cambridge University Press; 2010. p. 1–13.
3. Forman D, Bray F, Vrewster D, et al. Cancer incidence in five continents, Vol X (electronic version) Lyon, IARC. 2013. Available from: http://ci5.iarc.fr/CI5-X
4. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr
5. The Surveillance, Epidemiology, and End Results (SEER) Program. Available from: http://seer.cancer.gov
6. National Cancer Institute. Cervical cancer. 2014. Available from: http://www.cancer.gov/cancertopics/types/cervical
7. Centers for Disease Control and Prevention (CDC), National Programme of Cancer Registries (NPCR). Available from: http://apps.nccd.cdc.gov/uscs and http://www.cdc.gov/cancer/npcr
8. Ryerson A, Eheman C, Altekruse S, et al. Annual report to the nation on the status of cancer, 1975–2012, featuring the increasing incidence of liver cancer. Cancer. 2016;122(9):1312–37.
9. Ylitalo N, Stuver S, Adami H. Cervical cancer. In: Hans-Olov A, et al., editors. Textbook of cancer epidemiology. 2nd ed. New York: Oxford University Press; 2008. p. 446–67.
10. Cancer Research UK. Available from: http://info.cancerresearchuk.org
11. Schiffman M, Castle P, Jeronimo J, et al. Human papillomavirus and cervical cancer. Lancet. 2007;370(9590):890–907.
12. Castle P, Rodriguez A, Burk R, et al. Short term persistence of human papillomavirus and risk of cervical precancer and cancer: population based cohort study. BMJ. 2009;339:b2569.
13. Crosbie E, Einstein M, Franceschi S, et al. Human papillomavirus and cervical cancer. Lancet. 2013;382(9895):889–99.
14. Guan P, Howell-Jones R, Li N, et al. Human papillomavirus types in 115,789 HPV-positive women: a meta-analysis from cervical infection to cancer. Int J Cancer. 2012;131(10):2349–59.
15. Li N, Franceschi S, Howell-Jones R, et al. Human papillomavirus type distribution in 30,848 invasive cervical cancers worldwide: variation by geographical region, histological type and year of publication. Int J Cancer. 2011;128(4):927–35.

16. Cox J. The development of cervical cancer and its precursors: what is the role of human papillomavirus infection? Curr Opin Obstet Gynecol. 2006;18(suppl.1):S5–S13.
17. Sellors J, Karwalajtys T, Kaczorowski J, et al. Incidence, clearance and predictors of human papillomavirus infection in women. CMAJ. 2003;168(4):421–5.
18. Dunne E, Unger E, Stenberg M, et al. Prevalence of HPV infection among females in the United States. JAMA. 2007;297(8):813–9.
19. Plummer M, de Martel C, Vignat J, et al. Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Health. 2016;4(9):609–16.
20. Franceschi S, Herrero R, Clifford G, et al. Variations in the age-specific curves of human papillomavirus prevalence in women worldwide. Int J Cancer. 2006;119(11):2677–84.
21. De Sanjose S, Diaz M, Castellsague X, et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. Lancet Infect Dis. 2007;7(7):453–9.
22. International Collaboration of Epidemiological Studies of Cervical Cancer. Carcinoma of the cervix and tobacco smoking: collaborative reanalysis of individual data on 13,541 women with carcinoma of the cervix and 23,017 women without carcinoma of the cervix from 23 epidemiological studies. Int J Cancer. 2006; 118 6 :1481–95.
23. Kapeu A, Luostarinen T, Jellum E, et al. Is smoking an independent risk factor for invasive cervical cancer? A nested case-control study within Nordic biobanks. Am J Epidemiol. 2008;169(4):480–8.
24. Plummer M, Herrero R, Franceschi S, et al. Smoking and cervical cancer: pooled analysis of the IARC multi-centric case-control study. Cancer Causes Control. 2003;14(9):805–14.
25. Schiffman M, Brinton L. The epidemiology of cervical carcinogenesis. Cancer. 1995;76(suppl.10):1888–901.
26. Palefsky J, Holly E. Molecular virology and epidemiology of human papillomavirus and cervical cancer. Cancer Epidemiol Biomark Prev. 1995;4(4):415–28.
27. Burger M, Hollema H, Gouw A, et al. Cigarette smoking and human papillomavirus in patients with reported cervical cytological abnormality. BMJ. 1993;306(6880):749–52.
28. International Agency for Research on Cancer. Human papillomavirus. IARC monographs. 2012; 100b:255–313.
29. De Vuyst H, Gichangi P, Estambale B, et al. Human papillomavirus types in women with invasive cervical carcinoma by HIV status in Kenya. Int J Cancer. 2008;122(1):244–6.
30. Sun X, Kuhn L, Ellerbrock T, et al. Human papillomavirus infection in women infected with the human immunodeficiency virus. N Engl J Med. 1997;337(19):1343–9.
31. Rohner E, Sengayi M, Goeieman B, et al. Cervical cancer risk and impact of pap-based screening in HIV-positive women on antiretroviral therapy in Johannesburg, South Africa. Int J Cancer. 2017;141(3):488–96.
32. Strickler H, Palefsky J, Shah K, et al. Human papillomavirus type 16 and immune status in human immunodeficiency virus-seropositive women. J Natl Cancer Inst. 2003;95(14):1062–71.
33. Dahlstrom L, Andersson K, Luostarinen T, et al. Prospective seroepidemiologic study of human papillomavirus and other risk factors in cervical cancer. Cancer Epidemiol Biomark Prev. 2011;20(12):2541–50.
34. Smith J, Bosetti C, Munoz N, et al. Chlamydia trachomatis and invasive cervical cancer: a pooled analysis of the IARC multicentric case-control study. Int J Cancer. 2004;111(3):431–9.
35. Smith J, Munoz N, Herrero R, et al. Evidence for chlamydia trachomatis as a human papillomavirus cofactor in the etiology of invasive cervical cancer in Brazil and the Philippines. J Infect Dis. 2002;185m(3):324–31.
36. Wallin K, Wiklund F, Luostarinen T, et al. A population-based prospective study of chlamydia trachomatis infection and cervical carcinoma. Int J Cancer. 2002;101(4):371–4.
37. Koskela P, Anttila T, Bjorge T, et al. Chlamydia trachomatis infection as a risk factor for invasive cervical cancer. Int J Cancer. 2000;85(1):35–9.
38. Munoz N, Franceschi S, Bosetti C, et al. Role of parity and human papillomavirus in cervical cancer: the IARC multicentric case-control study. Lancet. 2002;359(9312):1093–101.