Chapter 4
Smoking-Related Cancer Epidemiology

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Objectives This section intends to describe the epidemiology of cigarette smoking-related cancers. For each disease, the epidemiology and the scientific evidence will be discussed.

Learning Outcomes

At the end of this chapter the reader will be able to:

– Know the main smoking-related cancers and their epidemiology

4.1 Introduction

In 1926, Lane-Clayton conducted the first case–control study assessing the etiology of breast cancer (Lane-Clayton 1926).

As more and more evidence accumulated indicating tobacco as the major cause of lung cancer and a number of other diseases, the tobacco industry claimed that there was no proof that the tobacco was responsible for causing these diseases. The battle continued for years, and Bradford Hill subsequently published a series of criteria to be considered when making a judgment of whether a given "exposure" was truly a cause of a given disease. These are now commonly referred to as "Hill's Criteria" for causal inference (Doll and Hill 1950) (Fig. 4.1).

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G. La Torre, *Smoking Prevention and Cessation*, DOI 10.1007/978-1-4614-7046-5_4,

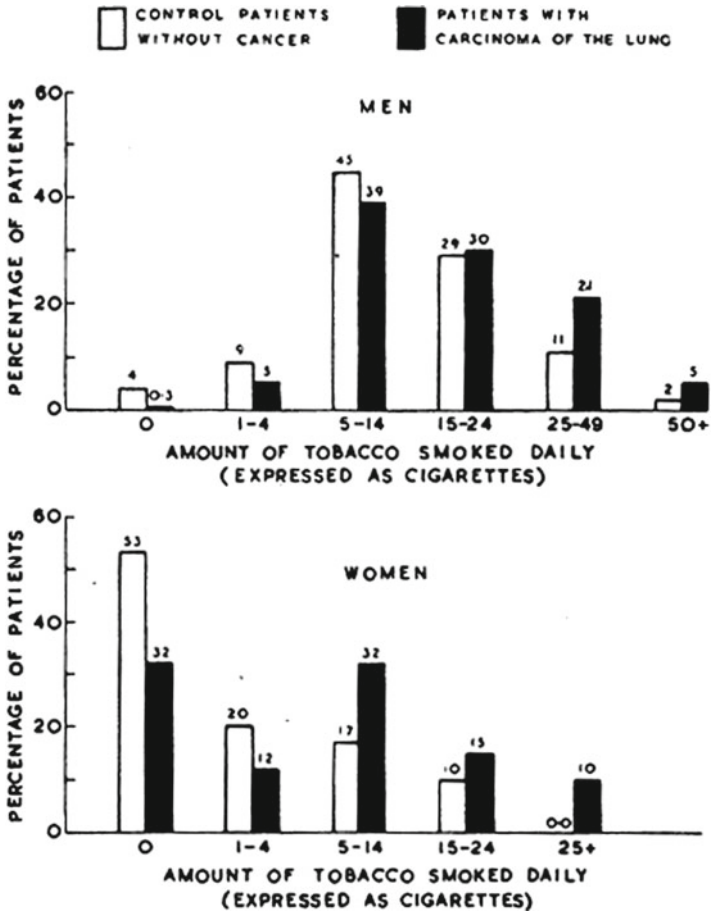

Fig. 4.1 Percentage of patients smoking different amounts of tobacco daily (Doll and Hill 1950)

In 1985, under the auspice of the International Agency for Research on Cancer (IARC) an international Working Group of experts recognized a causal relationship between tobacco smoking and cancer of the lung, oral cavity, pharynx, larynx, pancreas, urinary bladder, renal pelvis, and urethra (Tobacco Smoking 1986).

The association was primarily based on worldwide epidemiological studies. Recently, in a revised Monograph on Tobacco Smoke and Involuntary Smoking (IARC 2004), the IARC added cancers of the nasal cavities and nasal sinuses, the esophagus, stomach, liver, kidney (renal-cell carcinoma), uterine cervix, and bone marrow (myeloid leukemia) to the list of smoking-related cancers.

In a stately study of English in the long term, Doll et al. followed 34,439 male British doctors. Information about their smoking habits was obtained in 1951, and

periodically thereafter, cause-specific mortality was monitored for 50 years. The excess mortality associated with smoking chiefly involved vascular, neoplastic, and respiratory diseases that can be caused by smoking.

Longevity has been improving rapidly for nonsmokers but not for men who continued smoking cigarettes. Cessation at age 50 halved the hazard, while cessation at 30 avoided almost all of it.

On average, cigarette smokers die about 10 years younger than nonsmokers. Stopping at age 60, 50, 40, or 30 gains, respectively, about 3, 6, 9, or 10 years of life expectancy (Doll et al. 2004).

Jacobs et al. (1999) collected data on 16 cohorts from seven different populations of Europe, Asia, and the USA showing that the devastating effect of smoking on health is independent of the state of residence and that the differences observed between countries are to be found in the first place differences in smoking habits.

In the same way, even light smoking, that is a small amount of cigarettes, significantly increases the risk of dying from smoking-related diseases (Bjartveit and Tverdal 2005).

In addition, smokers are responsible for the increased incidence of tobacco-related diseases in nonsmokers exposed to secondhand tobacco smoke. Lifelong nonsmoking spouses of smokers who smoke at home had a significant and consistent 20–30 % increase in lung cancer risk. Similarly, never smokers exposed to secondhand tobacco smoke at the workplace have a 16–19 % increase in risk to develop lung cancer (Sasco et al. 2004).

The highest rate of male smokers is in South Korea (68 %), the highest rate of female smokers is in Denmark (37 %); a third of women smoke in developed countries and 1/8 in developing countries. The majority of smokers are found in developing countries (Peto et al. 2006).

Tobacco-attributable mortality is projected to increase from 3.0 million deaths in 1990 to 8.4 million deaths in 2020 (Murray and Lopez 1997). If current trends will continue, 80 % of premature deaths related to tobacco will be among people living in low- and middle-income countries. Over the course of the twenty-first century, tobacco use could kill a billion people or more unless urgent action is taken (World Health Organization 2011).

The vast scientific literature on smoking and health contains few large studies with direct estimates of long-term mortality by smoking habits. A population-based cohort study performed in Norway enrolled 24,505 women and 25,034 men who were born between 1925 and 1941. Rates of smoking-associated lung cancer were similar in women and men, while lower cardiovascular mortality rates in women explained most of the difference in smoking-associated all-cause mortality between men and women. Despite similar rates for lung cancer death, women who smoked had lower mortality rates in middle age than men with similar smoking histories due to fewer cardiovascular deaths in women (Vollset et al. 2006).

4.2 Cancers: Main Smoking-Related Cancers

Tobacco smoking is the main cause of cancer-related death worldwide and it is responsible for 1.8 million cancer deaths per year; it causes about 25 % of all cancers in men and 4 % in women and approximately 16 % of cancers in developed countries and 10 % in less developed countries (Stewart and Kleihues 2003) (Fig. 4.2).

Cigarette smoke contains about 4,000 chemical agents, including over 60 substances that are known to cause cancer in humans (carcinogens). In addition, many of these substances, such as carbon monoxide, tar, arsenic, and lead, are poisonous and toxic to the human body. Nicotine is a drug that is naturally present in the tobacco plant and is primarily responsible for a person's addiction to tobacco products, including cigarettes. During smoking, nicotine is absorbed quickly into the bloodstream and travels to the brain in a matter of seconds (U.S. Department of Health and Human Services 1988).

As a matter of fact, smoking is currently responsible for a third of all cancer deaths in Western countries. The earlier in life a person starts smoking, the greater will be his risk to develop a cancer in older age. The risk of smokers to develop lung, urinary, oral, esophagus, larynx, and pancreas cancer increased three to fivefold compared to nonsmoker, while nasopharynx, stomach, liver, kidney, uterine cervix cancer, and myeloid leukemia show a 1.5- to 2-fold increased risk (Sasco et al. 2004).

Since 1920s evidence of the association between cigarette smoking and cancer was observed and by the 1950s a causal relationship with lung cancer was established (Levin et al. 1950).

During the last decades the International Agency for Research on Cancer (IARC) have recognized a causal relationship between tobacco smoking and cancer of the lung, oral cavity, pharynx, larynx, pancreas, urinary bladder, renal pelvis, urethra, cancers of the nasal cavities and nasal sinuses, esophagus, stomach, liver, kidney (renal-cell carcinoma), uterine cervix, and bone marrow (myeloid leukemia) (IARC 2004).

In developing regions, 67 % of smoking-attributable cancer deaths were between the ages of 30 and 69 compared to 52 % in industrialized regions (Ezzati et al. 2005).

The risk of tobacco smoking depends on cumulative exposure to carcinogens in tobacco smoke; therefore, it varies with the amount smoked, duration of smoking, the type of cigarette smoked, and time since cessation (in ex-smokers).

For both sexes, between 43 and 60 % of cancers of the upper aerodigestive tract (esophagus, larynx, and oral cavity) are attributable to tobacco (Boyle et al. 2003).

In the UK it has been estimated that 36,102 (22.8 % of the total) cancers in men and 23,722 (15.2 % of the total) in women in 2010 are attributable to smoking tobacco (Parkin 2011).

According to several population surveys in Italy, the prevalence of male smokers reached a maximum (almost 80 %) in the 1920–1930 birth cohorts and decreased to 60 % among males born in the 1940–1950s. In that period, the mean number of cigarettes per day increased while the age of starting smoking decreased; in addition, the market trend changed from unfiltered black tobacco to filtered low-tar cigarettes and this trend reflects the decreasing incidence and mortality of both larynx

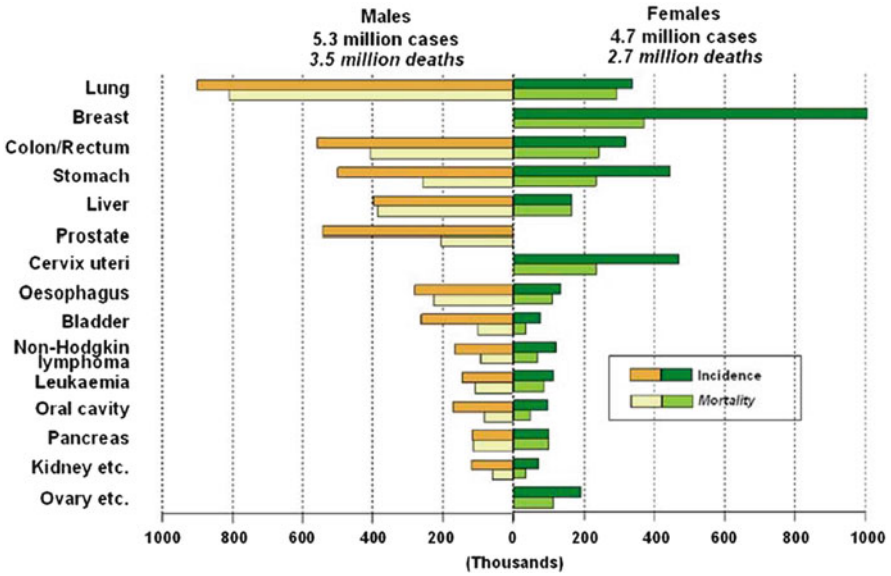

Fig. 4.2 Estimated new cases and deaths worldwide, by sex, in 2000 (Parkin 2004)

and lung cancer in young male cohorts and the persistent increase of both cancers in older males. The prevalence of female smokers increased from 10 % in the 1920s birth cohorts to over 30 % among women born in the late 1940s; this is reflected by an increase in respiratory cancer mortality which, however, is still lower than the mortality for males (Berrino 1992).

A systematic meta-analysis of observational studies from 1961 to 2003 was performed to quantify the risk for 13 cancer sites, recognized to be smoking-related by the International Agency for Research on Cancer (IARC), and to analyze the risk variation for each site. The highest pooled RR for current smokers was for lung cancer (RR = 8.96; 95 % CI: 6.73–12.11) and the risk of lung cancer increases by 7 % for each additional cigarette smoked per day (RR = 1.07; 95 % CI: 1.06–1.08) and it appears to be slightly higher in women (RR = 1.08; 95 % CI: 1.07–1.10) than in men (RR = 1.07; 95 % CI: 1.05–1.08) ($p < 0.001$). Then, laryngeal (RR = 6.98; 95 % CI: 3.14–15.52) and pharyngeal (RR = 6.76; 95 % CI: 2.86–15.98) cancers presented the highest relative risks for current smokers, followed by upper digestive tract, oral cancers, stomach, pancreas, cancer of the nasal cavity, lower urinary tract, kidney, cancer of the cervix uteri, liver, myeloid leukemia. Pooled relative risk for former smokers was highest for stomach cancer (RR = 1.31; 95 % CI: 1.17–1.46) followed by pancreatic cancer, cancer of the nasal cavity, lower urinary tract cancer, kidney cancer, cancer of the cervix uteri, for liver cancer, and myeloid leukemia (Gandini et al. 2008) (Table 4.1).

For most of these associations a dose–response effect of tobacco use on cancer risk is evident, as is a decline in risk on cessation of tobacco use.

Table 4.1 Pooled RRs by cancer site and type of exposure to cigarette smoking (Gandini et al. 2008)

Cancer site ICD 10	Smoking status	RR[a] (95 % CI)	No. of studies	*p*-Value heterogeneity	I^2%
Upper digestive tract C10–15	Current	3.57 (2.63, 4.84)	11	0.010	53
	Former	1.18 (0.73, 1.91)	14	<0.001	84
Oral cavity C10	Current	3.43 (2.37, 4.94)	12	0.001	65
	Former	1.40 (0.99, 2.00)	9	0.098	40
Pharynx C14	Current	6.76 (2.86, 16.0)	7	<0.001	85
	Former	2.28 (0.95, 5.50)	3	0.034	71
Esophagus C15	Current	2.50 (2.00, 3.13)	22	<0.001	81
	Former	2.03 (1.77, 2.33)	21	0.175	20
Stomach C16	Current	1.64 (1.37, 1.95)	32	<0.001	75
	Former	1.31 (1.17, 1.46)	33	<0.001	51
Liver C22	Current	1.56 (1.29, 1.87)	24	<0.001	69
	Former	1.49 (1.06, 2.10)	12	0.009	53
Pancreas C25	Current	1.70 (1.51, 1.91)	18	0.038	37
	Former	1.18 (1.04, 1.33)	22	0.172	24
Nasal-sinuses, C11	Current	1.95 (1.31, 2.91)	10	<0.001	68
Nasopharynx, C30–31	Former	1.39 (1.08, 1.79)	6	0.830	0
Larynx C32	Current	6.98 (3.14, 15.5)	10	<0.001	89
	Former	4.65 (3.35, 6.45)	3	0.550	0
Lung C34	Current	8.96 (6.73, 12.1)	21	<0.001	75
	Former	3.85 (2.77, 5.34)	20	<0.001	51
Cervix C53	Current	1.83 (1.51, 2.21)	23	<0.001	77
	Former	1.26 (1.11, 1.42)	22	0.645	0
Kidney C64	Current	1.52 (1.33, 1.74)	14	0.031	39
	Former	1.25 (1.14, 1.37)	12	0.001	59
Lower urinary tract C65–67	Current	2.77 (2.17, 3.54)	21	<0.001	76
	Former	1.72 (1.46, 2.04)	15	<0.001	63
Myeloid leukemia C92	Current	1.09 (0.70, 1.70)	4	0.183	36
	Former	1.27 (0.28, 5.83)	3	0.030	66

[a]Reference category "Never smokers"; I^2 represents the percentage of total variation across studies that is attributable to heterogeneity rather than to chance

In addition, even secondhand tobacco smoke have its own carcinogenicity, since the risk of developing smoking-related cancers increases with increasing the exposure to passive smoke.

4.3 Lung Cancer

At the beginning of the twentieth century, lung cancer has become the most common, in terms of incidence and mortality, nonskin malignancy worldwide (Parkin et al. 1999) (Fig. 4.3).

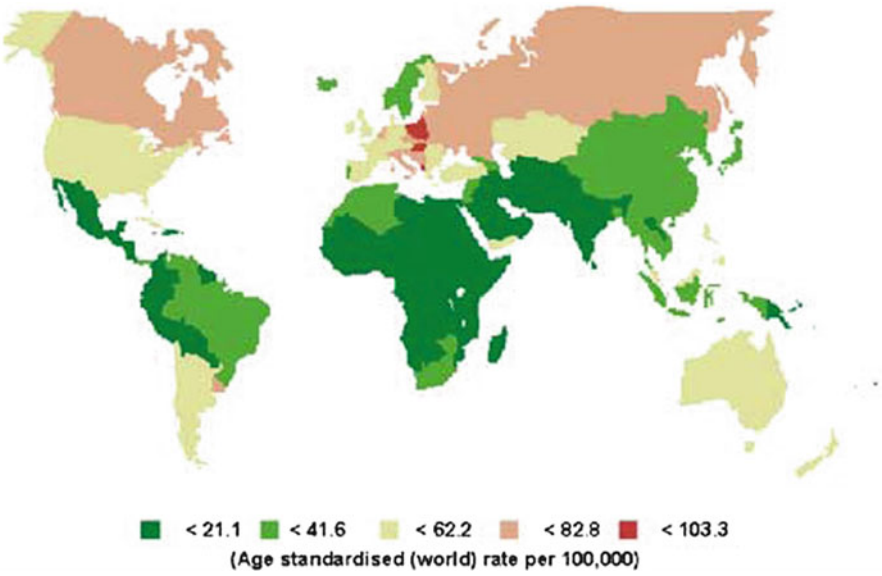

Fig. 4.3 Incidence of lung cancer in males (Parkin 2004)

Lung cancer was the most commonly diagnosed cancer and the leading cause of cancer death in males in 2008 worldwide. It was the fourth most commonly diagnosed cancer among females and the second leading cause of cancer death. Lung cancer accounts for 13 % (1.6 million) of the total cases and 18 % (1.4 million) of the deaths in 2008 (Jemal et al. 2011); 772,000 new cases each year in men (18 % of all nonskin cancers) and 265,000 new cases among women (7 %), 42 % of which occur in developing countries (Kuper et al. 2002).

The highest lung cancer incidence rates for males, are found in East–South Europe, North America, Eastern Asia, Micronesia, and Polynesia. In females, the highest lung cancer incidence rates are found in North America, Northern Europe, and Australia/New Zealand. Despite their lower prevalence of smoking (<4 % adult smokers), Chinese females have higher lung cancer rates (21.3/100,000) than those in certain European countries such as Germany (16.4) and Italy (11.4), with an adult smoking prevalence of about 20 % (Mackay et al. 2006).

Ninety one percentage of all lung cancers in men and 69 % in women are attributable to cigarette smoking (Sasco et al. 2004).

In 1950s, it has been demonstrated that lung cancer is causatively associated with cigarette smoking.

Although cigarette consumption has gradually decreased in the USA, lung cancer death rate amounts 74.9/100,000/year among males and 28.5/100,000/year among females. However, in the younger cohorts, the lung cancer death rate is decreasing in both sexes (Wynder and Muscat 1995).

According to WHO, in 2008 there were 1.37 million deaths from lung cancer worldwide and tobacco use is the most important risk factor causing 71 % of global

lung cancer deaths. Lung cancer kills more people than any other cancer and this trend is expected to continue (World Health Organization 2012).

Almost 90 % of lung cancers in men and 83 % in women are estimated to be caused by smoking. Current smokers are 15 times more likely to die from lung cancer than nonsmokers. Risk of developing lung cancer is affected by level of consumption and duration of smoking.

Doll and Peto, analyzing the data of the British doctors prospective study, concluded that lung cancer risk raises in proportion to the square of the number of cigarettes smoked per day and to the fourth or fifth power of the duration of smoking (Doll et al. 2004, 2005)

Death rates from lung cancer increase dramatically with age (between ages 45 and 74 years), especially in male smokers while rates remained essentially constant in lifelong never smokers. The RR is biphasic, first increasing (in men) and later decreasing (in both sexes). The RR in men increased from 7 (at ages 45–49) to 39 (at ages 55–59) and then decreased to 13.8 (at age 80 and older). In women, the RR decreased from 22.1 (at ages 45–49) to 7.3 (at age 80 and older) (Thun et al. 1997).

Eighty six percentage of the total cases of lung cancer in the UK in 2010 were due to exposure to tobacco smoke, of which 97.4 % are due to current or past active smoking. 87 % of male cases are due to tobacco exposure (of which 97.7 % were due to smoking), and 84 % of cases for women (of which 96.2 % were due to smoking). In total, 60,837 cancer cases (19.4 % of all new cancer cases) are attributable to tobacco: 36,537 (23.0 %) in men and 24,300 (15.6 %) in women (Parkin 2011).

Compared with nonsmokers, those who smoke between 1 and 14 cigarettes a day have eight times the risk of dying from lung cancer and those who smoke 25 or more cigarettes a day have 25 times the risk. However, risk is more dependent on duration of smoking than consumption: smoking one pack of cigarettes a day for 40 years is more hazardous than smoking two packs a day for 20 years (Lubin et al. 2006, 2007).

Smoking cessation has very significant health benefits: a lifelong male smoker has a cumulative risk of 15.9 % for dying from lung cancer by age 75. For men who cease smoking at ages 60, 50, 40, and 30 years, their cumulative risk of dying from lung cancer decreases to 9.9 %, 6.0 %, 3.0 %, and 1.7 %, respectively (Fig. 4.4) (Peto et al. 2000).

The substantial decrease in lung cancer risk occurs 5–15 years after cessation (Thun et al. 1997).

People who stop smoking, avoids most of their risk of lung cancer, and stopping before middle age avoids more than 90 % of the risk attributable to tobacco (Peto et al. 2000).

Age at the start of regular tobacco smoking is also important. There is evidence that starting to smoke at a young age carries additional risks of lung damage: starting before age 15 have a four- to fivefold higher risk of lung cancer than starting at age 25 or later (IARC International Agency for Research on Cancer 1986; Wiencke et al. 1999).

Tobacco smoking induces all major histological types of lung cancer, but the strongest associations are with squamous cell and small cell carcinoma: the RR for adenocarcinoma are four- to fivefold lower than for other histological types (Lubin et al. 1984).

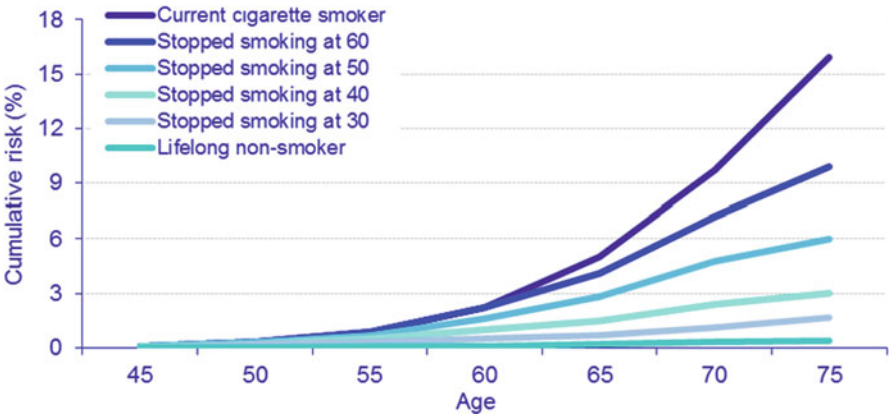

Fig. 4.4 Effects of stopping smoking at various ages on the cumulative risk (%) of death from lung cancer by age 75 for men (Peto et al. 2000)

Over the last two decades in the USA and Europe squamous cell carcinoma has become less common and adenocarcinoma more frequent, and this maybe reflects changes in patterns of tobacco consumption (Levi et al. 1997).

Nonsmokers exposed to environmental tobacco smoke (ETS) have an increased risk of lung cancer. The carcinogenicity of secondhand tobacco smoke is based on the fact that people exposed to secondhand tobacco smoke at home had 20–30 % increased lung cancer risk; similarly, never smokers exposed at the workplace have a 16–19 % increased risk (Sasco et al. 2004).

Meta-analyses have shown that exposure to ETS at home or at work among nonsmokers increases risk by about a quarter, heavy exposure doubles risk (Taylor et al. 2007; Stayner et al. 2007).

Two percentage of lung cancer cases in nonsmoking men and 10.1 % in women would be due to their current partner's smoke as well as 8 % of cases in never-smoking men and 9 % in women would be due to workplace exposure to ETS (Parkin 2011).

Taylor et al. performed a meta-analyses to review the epidemiological evidence for the association between passive smoking and lung cancer. The pooled RR for never-smoking women exposed to ETS from spouses was 1.29 (95 % CI: 1.17–1.43): this statistically significant result indicates an increased risk of approximately 30 % for nonsmoking women exposed to spousal ETS.

Since 1992 the RR has been greater than 1.25. For western industrialized countries the RR for never-smoking women exposed to ETS compared with unexposed never-smoking women, was 1.21 (95 % CI: 1.10–1.33) (Taylor et al. 2001).

Compared with adults, children may be more susceptible to secondhand smoke. Daily exposure for many hours to environmental tobacco smoke exposure during childhood showed an association with lung cancer, mainly among those who had never smoked.

Case–control studies have confirmed the link with exposure to ETS in childhood, showing that risk increases 47–125 %. The European Prospective Investigation into

Cancer and Nutrition (EPIC) has shown that heavy exposure to ETS (daily for many hours) in childhood increases risk of lung cancer by almost four times (OR, 3.63; 95 % CI: 1.19–11.11); the association between childhood secondhand smoke exposure and lung cancer risk has been also confirmed in several studies such as the Mayo Clinic study (OR, 1.47; 95 % CI: 1.00–2.15), and the meta-analysis conducted in the Surgeon General's report (OR, 0.93; 95 % CI: 0.81–1.07) in US studies (Vineis et al. 2005; Olivo-Marston et al. 2009).

As already discussed, it appears clear that the most important and cost-effective management for lung cancer is smoking cessation.

4.4 Cancer of the Larynx

The carcinogenic effect of smoking on laryngeal cancer is well established; though light-inhalation smoking is lower risk than deeper inhalation, carcinogenic effect is confirmed even also for merely puffing on smoking products (Ramroth et al. 2011). 140,000 new cases of laryngeal cancer occurred worldwide in 1990, 120,000 of which were among men (Parkin et al. 1999). Male incidence is particularly high in Southern and Central Europe (the highest mortality rates in the world for laryngeal cancer in men are in Hungary, Poland, Slovakia, and Romania), South America, and amongst Blacks in the USA, while it is low in South-east Asia and Central Africa (Parkin et al. 1997).

From 1978 to 1982, the respective age-adjusted morbidity rate for men in Spain was 17.2/100,000, in Italy 16.2/100,000, in France 12.6/100,000, and in Poland 11.4/100,000. In 1996 in Poland the morbidity rate had reached 13.9/100,000 for men (Bień et al. 2008).

Several studies have shown a dose–response relationship for intensity and duration of smoking, since the odds ratios for current smokers range widely from about 3–20; the risk decreases in past smokers compared to current smokers, although the number of years of quitting needed to have a significant reduction in risk compared with current smokers range from 6–9 to 20 or more (Bosetti et al. 2006; Hashibe et al. 2007; Talamini et al. 2002; Austin et al.1996; Kuper et al. 2002).

A recent study showed that people who stopped smoking before the age of 35 or 20 or more years ago did not have a significantly higher risk of developing upper aerodigestive tract cancer than never smokers (Bosetti et al. 2006).

Moreover, smoking unfiltered high-tar cigarettes leads to a stronger risk (Baron et al. 1996).

A case–control study on larynx and hypopharynx cancer carried out in different European countries (Italy, Spain, Switzerland, France) shows the effect of tobacco is similar for all sites of larynx and the risk associated with ever smoking is of the order of 10. For all sites the risk decreases after quitting (RR = 0.3 after 10 years); exclusive use of filter cigarettes is protective (RR = 0.5 relative to smokers of plain cigarettes only) as is exclusive use of blond tobacco (RR = 0.5 relative to smokers of black tobacco only). Inhalation increases the risk of endolaryngeal cancer but not

that of hypopharynx or epilarynx. The RR for exposure to both alcohol and tobacco are consistent with a multiplicative model (Tuyns et al. 1988).

Also cigar and pipe smoking has been associated with a tenfold increased risk of cancer of the larynx and hypopharynx combined (Lee et al. 2009).

Some studies show that risks associated with smoking are twice as high or more for tumors of the supraglottis than glottis (De Stefani et al. 2004; Menvielle et al. 2004; Dosemeci et al. 1997).

According to a large population-based case–control study in Southern Europe, over 90 % of the incidence of laryngeal cancer could be prevented by avoiding smoking and alcohol consumption; most of the risk is attributable to tobacco smoking, including passive smoking (Berrino and Crosignani 1992).

A population-based case–control study in Germany, found a clear dose–response relationship not only for deep inhalers but also for those puffing on a cigarette; anyway, changing inhalation habits could be considered as a first step to reducing the risk of developing laryngeal cancer (Ramroth et al. 2011).

4.5 Cancer of the Esophagus

There are two main histological types of esophageal cancer: squamous cell carcinoma (SCC) and adenocarcinoma (AC). In the upper two-thirds the most common histology is SCC: in the lower third AC; tobacco consumption increases the risk of both SCC and AC, although the effect is stronger for SCC (Vizcaino et al. 2002) (Fig. 4.5).

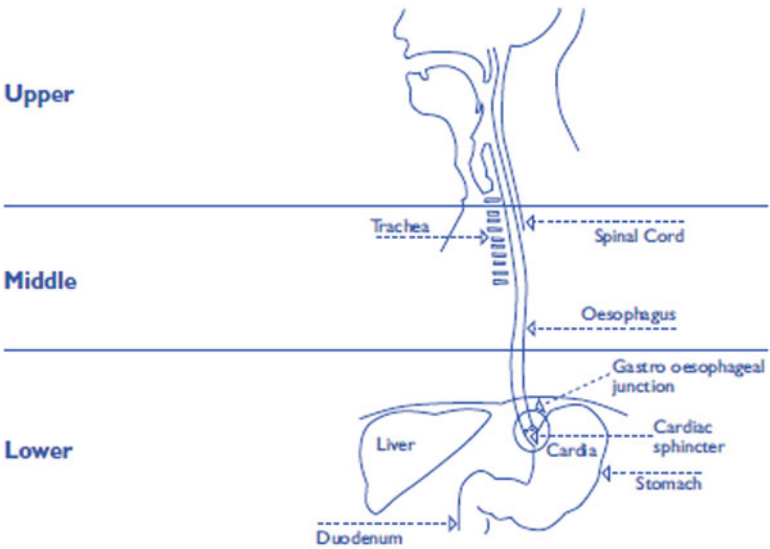

Fig. 4.5 Diagram of esophagus

Worldwide, an estimated 462,000 new cases of esophageal cancer occurred in 2002. About 80–85 % of cases are diagnosed in developing countries where it is the fourth most common cancer in men (Parkin et al. 2005a, b).

The area with the highest reported incidence for esophageal cancer ranges from eastern Turkey through north-eastern Iran, northern Afghanistan, and southern Russia to northern China and also south-east Africa, south America, and parts of Europe have high rates (Parkin 2004; Castellsague et al. 2000).

In Iran, rates are more than 200 per 100,000 and the male/female ratio is 0.8:1.0 (Hormozdiari et al. 1975a, b).

In China, rates per 100,000 are 184 for men and 123 for women compared with 8.4 for English men and 3.5 for English women (Parkin et al. 2002).

In the United Kingdom (UK), esophageal cancer is the fifth most common cause of cancer death in men and women combined with more than 7,000 deaths annually. Incidence rates in the UK are significantly higher than the EU average; during the last 25 years incidence rates for esophageal cancer have increased in Britain. UK men have the third highest rates after French and Hungarian men while UK women have the highest incidence, more than ten times higher than Greek women (IARC 2004). The British male incidence rates rose from 8.8 per 100,000 in 1975 to 14.1 in 2001 while female rates rose from 4.8 to 5.8. In particular, a recent analysis recorded the highest incidence for esophageal cancer in Scotland, North West England, and north Wales. Especially in Scotland the male rates also show a substantial increase from 11.3 per 100,000 population in 1975 to 17.2 in 2001 and women from 6.3 in 1979 to 8.7 in 1996 but have decreased to 6.8 in 2001 (ISD Online 2004; Quinn et al. 2005).

The association between tobacco smoking and cancer of the esophagus was already clear in 1985 (IARC 1986).

Smoking cigarettes, cigars, or pipes or by chewing tobacco increases the risk of esophageal cancer. The RR of esophageal cancer among cigar smokers is similar to that for cigarette smokers. The higher rates for higher numbers of cigars per day or with deeper inhalation confirms a dose–response effect (Burns et al. 1998).

A recent pooled analysis of European studies showing a fourfold risk increased for esophageal cancer among current smokers (Lee et al. 2009).

Smoking increases the risk of both squamous cell carcinoma (SCC) and adenocarcinoma (AC), although the effect is stronger for SCC: a cohort study shows that current smokers have a ninefold risk increase for esophageal SCC and a fourfold risk increase for esophageal AC (Sharp et al. 2001).

In addition, alcohol increases the effect of tobacco consumption (even if they can also act independently). They are the main risk factors for SCC of the esophagus in western countries: heavy smoking and drinking increased the risk by 20-fold for SCC (Zambon et al. 2000).

The quantity of cigarettes smoked and the duration of smoking are directly related to risk and the risk declines on smoking cessation (wipes 10 or more years after giving up) (Zambon et al. 2000) although the study performed by Freedman et al. (2007) shows that the risk of both tumor types remain three times higher than never smokers among ex-smokers who gave up 10 or more years previously.

From a case–control study in India emerged that the strongest risk factor for esophageal cancers was tobacco smoking, with OR of 2.83 (95 % CI: 2.18–3.66) in current smokers (Znaor et al. 2003).

4.6 Lower Urinary Tract

A systematic review quantified the impact of different smoking characteristics (status, amount, duration, cessation, and age at first exposure) on urinary tract cancer. Smoking status and increased amount and duration of smoking were associated with a strong increased risk of urinary tract cancer. Smoking cessation and age at first exposure were negatively associated with the risk of urinary tract cancer. The age- and gender-adjusted pooled ORs for current and former smokers compared with nonsmokers were 3.33 (95 % CI: 2.63–4.21) and 1.98 (CI: 1.72–2.29), respectively. Results suggest that current smokers have about threefold higher risk of urinary tract cancer than nonsmokers. In Europe, approximately half of urinary tract cancer cases among males and one-third of cases among females might be attributable to cigarette smoking (Zeegers et al. 2000).

4.6.1 Bladder Cancer

Bladder cancer is categorized as "*non-muscle invasive bladder cancer*" or "*muscle invasive bladder cancer*." Histological classification is based on the architecture and degree of differentiation. *Papillary urothelial neoplasms* of low malignant potential have a very low risk for malignant transformation; low and high grade papillary urothelial carcinoma (UC) and carcinoma in situ (CIS) are malignancies. Staging is based on the 2002 TNM Classification of Malignant Tumors. Ta, T1, and CIS are categorized as non-muscle invasive bladder cancer or "superficial" bladder cancer and is stratified into low, intermediate, and high risk groups. Primary bladder cancers include *transitional cell carcinoma* (TCC), *adenocarcinoma*, *neuroendocrine*, or *mesenchymal* tumors (Arianayagam et al. 2011).

Cancer of the bladder is the ninth most common cause of cancer worldwide (357,000 cases in 2002) and the 13th most numerous cause of death from cancer (145,000 deaths). Rates in males are 3–4 times those in females. Incidence rates are high in many southern and eastern European countries, Africa, Middle East and North America. Egypt has the highest mortality, more than three times greater than in Europe and eight times greater in the USA (Parkin et al. 2008).

During the last two decades, bladder cancer mortality has shown downward trends in several western European countries but is still increasing in some eastern European countries (Pelucchi et al. 2006).

Generally, trends are related to prevalence of known risk factors, especially exposure to tobacco.

Smoking cigarettes is the principal preventable risk factor for bladder cancer in both men and women. Current smokers have 2–6 times the risk of never smokers of developing bladder cancer, with the highest risks for people smoking for the longest or smoking a large amount of cigarettes per day. Two-thirds of bladder cancer cases in men and a third in women are caused by cigarette smoking in Europe. Smoking cessation reduces risk, but risk in ex-smokers remains higher than never smokers for more than 20 years (Brennan et al. 2000, 2001).

The risk of bladder cancer in former smokers decreases at a rate of up to 40 % in the first 4 years after cessation; in addition, continued tobacco use after the diagnosis of cancer has been associated with an increased risk of treatment-related complications, tumor recurrence, second primary malignancies, and morbidity and mortality (Guzzo et al. 2012).

The precise mechanism by which cigarette smoking induces bladder cancer is unclear. Studies show that risk varies by type of tobacco, with a higher risk for black "air-cured" than blond "flue-cured" tobacco (Samanic et al. 2006)

Smokers of black tobacco have higher levels of aromatic amines in their urine than smokers of blond tobacco (Malaveille et al. 1989). These aromatic amines are urothelial carcinogens and the ability to detoxify them is compromised in people who are "slow acetylators" and it is suggested that these people are at higher risk than "fast acetylators" (Marcus et al. 2000)

It has also been suggested that high fruit consumption may reduce the effect of smoking on developing bladder cancer (Kellen et al. 2006).

Even the exposure to environmental tobacco smoke (ETS) during childhood increased the risk of bladder cancer by almost 40 % (Bjerregaard et al. 2006). Supporting this theory, the evidence of a significant increase in risk of bladder cancer in those whose mothers had lung cancer, but no increased risk for paternal lung cancer: the authors interpreted this as evidence that exposure to tobacco carcinogens in utero or while breastfeeding may lead to bladder cancer in later life (Hemminki et al. 2006).

Several European studies estimated that the proportion of cancers of the urinary bladder attributable to tobacco smoking are in average 30 % in ever-smoking women and 66 % in ever-smoking men (Brennan et al. 2000, 2001).

Gandini et al. (2008) estimated that the pooled risk for current smokers among men was greater for cancer of the bladder (RR 5 2.80; 95 % CI: 2.01–3.92) than for cancer of the kidney (RR 5 1.59; 95 % CI: 1.32–1.91). For bladder cancer, this pooled estimate is slightly lower than that of a pooled-analysis (Puente et al. 2006) of 14 case–control studies performed by Puente et al. (RR for current smokers 5 3.89, 95 % CI: 3.53–4.29 for men and RR = 3.55, 95 % CI: 3.06–4.10 for women) but similar to that of a previous meta-analysis of 23 case–control and cohort studies (RR = 2.57; 95 % CI: 2.20–3.00, for men and women combined) (Zeegers et al. 2000).

4.6.2 Kidney Cancer

The two most common types of kidney cancer are renal cell carcinoma (RCC) and urothelial cell carcinoma (UCC) of the renal pelvis. Less common types of kidney cancer include squamous cell carcinoma, juxtaglomerular cell tumor (reninoma), angiomyolipoma, renal oncocytoma, Bellini duct carcinoma, clear-cell sarcoma of the kidney, mesoblastic nephroma, Wilms' tumor (which occurs in children under the age of 5), and mixed epithelial stromal tumor (Ferlay et al. 2007).

In 2002, 208,000 new cases (1.9 % of the world total) and 102,000 deaths of kidney cancer occurred. Kidney cancer is a disease of high-income countries, since the highest rates are in North America, Australia/New Zealand, and western, eastern, and northern Europe, but are low in Africa, Asia (except Japanese males), and the Pacific (Parkin et al. 2005a, b).

In 1988–1992, kidney cancer incidence rates were highest in France (16.1/100,000 man–years and 7.3/100,000 woman–years) and lowest in India (2.0 and 0.9, respectively). Between 1973–1977 and 1988–1992, incidence rates rose among men and women in all regions and ethnic groups; the largest percentage increase for men was in Japan (171 %) and for women in Italy (107 %) (Mathew et al. 2002).

Kidney cancers account for 2–3 % of all adult malignancies in the UK. Men are predominantly affected by renal cancer with an average age at diagnosis of 64 years (Lewis et al. 2012).

Renal and pelvic cancer is the third most commonly diagnosed urinary cancer in USA, accounting for about 3 % of all cancer cases. It is estimated that 30,800 new cases of renal and pelvic cancer may be diagnosed in Americans in 2001 and almost 40 % deaths (Greeenlee et al. 2001).

In the USA, from 1975 to 1995, there were 31,105 invasive cancers of the kidney and 4,985 cancers of the renal pelvis diagnosed; the age-adjusted incidence rates for white men, white women, black men, and black women were, respectively, 9.6, 4.4, 11.1, and 4.9 per 100,000 person–years. The corresponding rates for renal pelvis cancer were 1.5, 0.7, 0.8, and 0.5 per 100,000 person–years. Renal cell cancer incidence rates increased progressively during this lapse of time, by 2.3 % annually among white men, 3.1 % among white women, 3.9 % among black men, and 4.3 % among black women (Chow et al. 1999). 64,770 new cases and 13,570 deaths from kidney (renal cell and renal pelvis) cancer in the USA have been estimated in 2012 (http://www.cancer.gov/cancertopics/types/kidney. Last accessed April 23, 2012).

Epidemiological evidence shows that cigarette smoking is the major risk factor for renal cell carcinoma and cancer of the renal pelvis (IARC 2002).

On average, current smokers have a 50 % increase in risk of kidney cancer (Gandini et al. 2008). The IARC cancer mortality database indicates approximately 20,000 kidney cancer deaths attributable to smoking (US Department of Health and Human Services 2004) and it has been estimated that 24–32 % of renal cell cancer cases in men and 9–16 % in women can be related to smoking (Setiawan et al. 2007; McLaughlin et al. 1995)

Case–control studies have found that smoking doubles the risk and risk increases with the duration of smoking and number of cigarettes smoked per day (Doll 1996).

People who smoke more than 20 cigarettes per day increase their risk by 60–100 % compared to nonsmokers. Former smokers have a 25 % higher risk of kidney cancer, while the risk for cancer of the renal pelvis is more than threefold time higher in current smokers (Hunt et al. 2005; McLaughlin et al. 1992).

Some studies reported that long-term quitters (>15 years) have a 15–25 % reduced risk compared with current smokers (Kuper et al. 2002), but others have not found a clear dose–response effect (Doll et al. 1994).

4.7 Pancreatic Cancer

Even if pancreatic cancer has been increasing in incidence over the past 40 years, it still has a relative low incidence (it ranks 13th), but despite that, its mortality rates are high, responsible for 227,000 deaths per year, and is the eighth most common cause of cancer death (Lowenfels and Maisonneuve 2006; IARC 2004).

Pancreatic cancer is one of the most aggressive tumors: the 5-year survival rate is <5 % and a mortality rate is almost 100 % (MacLeod et al. 2006).

The most common type of pancreatic cancer (95 % of the total) is the adenocarcinoma (tumors exhibiting glandular architecture on light microscopy) arising within the exocrine component of the pancreas, while neuroendocrine tumors arise from islet cells (Ghaneh et al. 2008).

The sex ratio is close to one. 61 % of cases and deaths occur in developed countries, where incidence and mortality rates are 7–9 per 100,000 in men and 4.5–6 per 100,000 in women, with lower rates in developing countries (but this probably reflects lower diagnostic capacity rather than etiology). Among developing countries, the highest rates are observed in Central and South America (Parkin et al. 2005a, b).

Incidence rates vary in different countries implying that environmental factors are important. Of these factors, smoking is the most well-documented etiologic agent (Lowenfels and Maisonneuve 2006).

Smoking has been recognized as a cause of pancreatic cancer with an approximate two- to fourfold increased risk (Chiu et al. 2001).

An increased risk of pancreatic cancer was found for current cigarette smokers compared with never smokers (HR = 1.71, 95 % CI: 1.36–2.15), and risk increased with greater intensity and pack–years (Vrieling et al. 2009).

In the UK, smoking is estimated to cause up to 20 % of pancreatic cancers (Iodice et al. 2008). A British study reported that ex-smokers were 1.4 times more likely to die of pancreatic cancer compared with never smoked. Current smokers of less than 25 cigarettes a day had 1.8 times the risk of death and smokers of 25 or more cigarettes a day were at 3.1 times the risk of never smokers (Doll et al. 1994).

A recent meta-analysis showed that smoking could be responsible for about 75 % increase in the risk of pancreatic cancer and that the risk increases with the

number of cigarettes smoked and the duration. The risk of pancreatic cancer was estimated to be 1.74 (95 % confidence interval [CI]: 1.61–1.87) for current smokers and 1.2 (95 % CI: 1.11–1.29) for former ones; the study also showed an increase in pancreatic cancer risk for pipe and/or cigar smokers (Iodice et al. 2008).

Studies have reported a positive trend with number of years of smoking among men but not women; in addition, smokers are diagnosed on average 10 years younger than nonsmokers (Coughlin et al. 2000; Lowenfels and Maisonneuve 2004; Gold and Goldin 1998).

Recent results from the European Prospective Investigation into Cancer and Nutrition (EPIC) showed that former cigarette smokers who quit for <5 years were at increased risk of pancreatic cancer (HR = 1.78, 95 % CI: 1.23–2.56), but risk was comparable to never smokers after quitting for 5 years or more (Vrieling et al. 2009) but some other studies have reported that it takes 10–20 years after cessation for risk to return to the level of a never smoker (Coughlin et al. 2000; Bonelli et al. 2003; Lowenfels and Maisonneuve 2004; Lynch et al. 2009; Heinen et al. 2010).

La Torre et al. performed a meta-analysis of observational studies on association between cigarette smoking and pancreatic cancer. Six cohort studies and 24 case–control studies were selected, with median quality scores of 8 and 10, respectively. Pooled case–control studies' OR and cohort studies' risk ratio were, respectively, 1.45 (95 % CI: 1.33–1.57) and 1.78 (95 % CI: 1.64–1.92). After stratifying for quality scoring, high-quality-scored case–control studies yielded an OR of 1.38 (95 % CI: 1.27–1.49), whereas the others gave an OR of 1.52 (95 % CI: 1.34–1.73). The results of meta-analysis for cohort studies showed a risk ratio of 1.74 (95 % CI: 1.61–1.90) and of 2.10 (95 % CI: 1.64–2.67), respectively, for high- and low-quality score studies. The results obtained shows a significant excess risk of pancreatic cancer associated with cigarette smoking habit of nearly 80 % for cohort studies and nearly 50 % for case–control studies. RR varies from a minimum of 1.60 (95 % CI: 0.95–2.60) to a maximum of 3.81 (95 % CI: 2.08–7.00) for cohort studies and OR ranging from a minimum of 0.98 (95 % CI: 0.77–1.24) to a maximum of 3.25 (95 % CI: 1.94–5.44) for case–control studies; none of the studies selected showed a significant protective effect of smoking. The estimation of the association greatly relies on the studies' quality, showing an increased risk of 74 % and 110 % for cohort studies and of 38 % and 52 % for case–control studies: low-quality studies seem to overestimate the risk (La Torre et al. 2009b).

Risk for pancreatic cancer is increased almost threefold also among cigar smokers who inhaled their smoke, particularly those who smoke higher number of cigars per day but not for cigar smokers overall (Shapiro et al. 2000).

Furthermore pancreatic cancer risk is increased among never smokers daily exposed to ETS (for many hours) during childhood (HR = 2.61, 95 % CI: 0.96–7.10) and exposed to ETS at home and/or work (HR = 1.54, 95 % CI: 1.00–2.39): both active cigarette smoking, as well as exposure to ETS, is associated with increased risk of pancreatic cancer (Vrieling et al. 2009).

4.8 Stomach Cancer

Stomach cancer is the fourth most frequent cancer worldwide: 989,600 new cases (8.7 % of the total) and it is the second most frequent cause of death from cancer with 738,000 deaths (10.4 % of cancer deaths). Over 70 % of new cases and deaths occur in developing countries. Generally, stomach cancer rates are about twice as high in males as in females (Jemal et al. 2011).

Almost 90 % of stomach cancers are adenocarcinomas, originating from glandular epithelium of the gastric mucosa. Histologically, there are two major types of gastric adenocarcinoma: intestinal type or diffuse type (Lauren classification). Intestinal type adenocarcinoma tumor cells describe irregular tubular structures, pluristratification with multiple lumens and reduced stroma. Diffuse type adenocarcinoma tumor cells (mucinous, colloid, linitis plastica, leather-bottle stomach) are discohesive and secrete mucus producing large pools of mucus/colloid and is poorly differentiated. About 5 % of gastric malignancies are lymphomas (MALTomas, or MALT lymphoma); carcinoid and stromal tumors may also occur (Paterson et al. 2006).

Most of cases occur in developing countries. Incidence rates are highest in Japan Korea, China, Eastern Europe, Central and South America. Incidence rates are low in Southern Asia, North-East Africa, North America, Australia, and New Zealand (Parkin 2004) (Fig. 4.6).

Among European countries, the 5-year survival rate varies from 10 to 20 %. In the last two decades, its incidence has gradually decreased in both developing and developed countries, but the risk appears clearly related to strong environmental component (La Torre et al. 2009a, b).

Beyond *Helicobacter pylori* infection, an important cause of stomach cancer is tobacco smoking: smokers have a 50–60 % increased risk of stomach cancer, as compared to nonsmokers; this could explain that the recent decline in smoking prevalence in men from developed countries may account for part of the fall in gastric cancer rates (Bertuccio et al. 2009; Boyle et al. 2003).

Although tobacco smoking has not been considered the major risk factor for gastric cancer, a large number of epidemiological studies reported information on this association. In total, over 80,000 cases of gastric cancer (11 % of all estimated cases) may be attributed to tobacco smoking each year worldwide (Trédaniel et al. 1997).

It has been estimated that 11 % of men and 4 % of women in developing countries and 17 % men and 11 % women in developed countries who have stomach cancer are related to smoking habit (Boyle et al. 2003).

Trédaniel et al. (1997) carried out a meta-analysis to estimate the association between gastric cancer risk and tobacco smoking. Results suggest a risk among smokers of 1.5–1.6 as compared to nonsmokers. The RR was higher in men (1.59) than in women (1.11). Several studies examined the dose–response too.

A more recent quantitative meta-analysis found a statistically significant result for the association between ever-smoking status and gastric cancer risk (OR = 1.48; 95 % CI: 1.28–1.71; $p < 0.00001$). The meta-analysis also showed a 69 % increase in the risk of gastric cancer for current smokers compared to never smokers (OR = 1.69; 95 % CI: 1.35–2.11; $p < 0.00001$). Considering only high quality

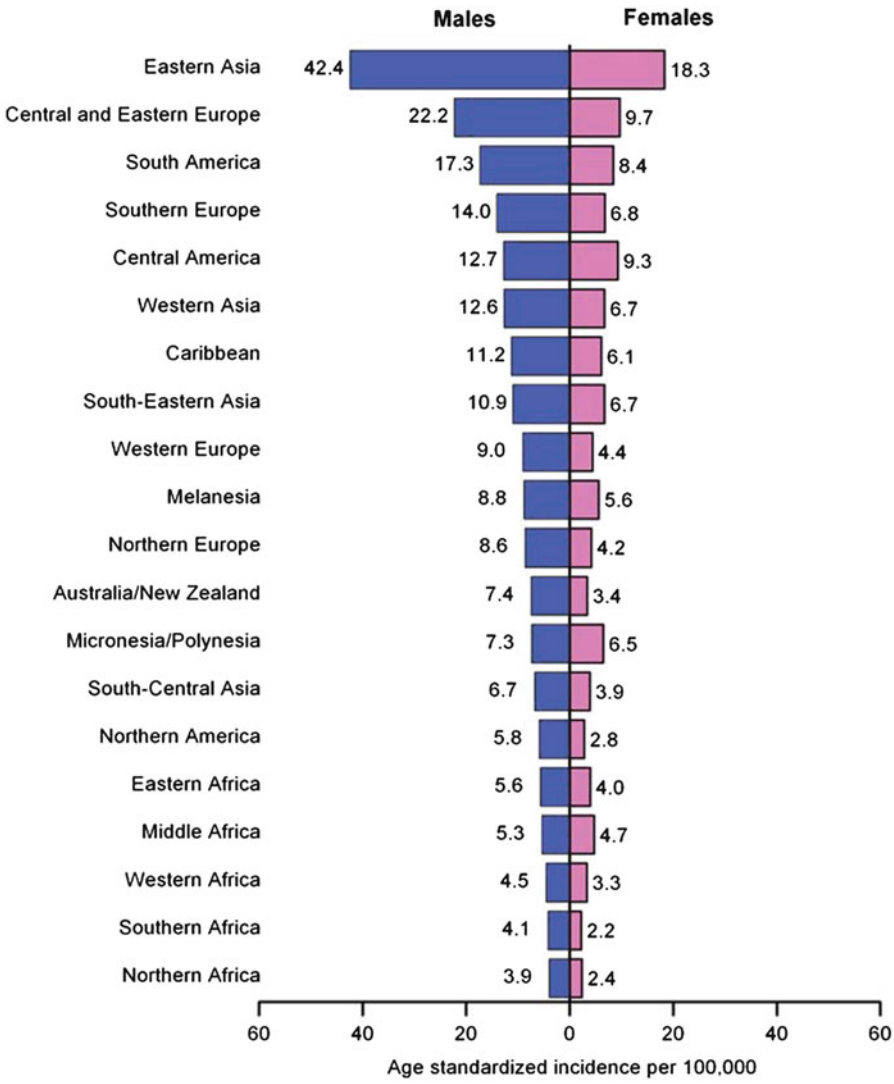

Fig. 4.6 Age-standardized stomach cancer incidence rates by sex and world area (Ferlay et al. 2010)

studies, the OR increased by 43 % for gastric cancer risk in ever smokers (OR = 1.43; 95 % CI: 1.24–1.66; $p < 0.00001$) and by 57 % in current smokers (OR = 1.57; 95 % CI: 1.24–2.01). Taking into account separately Caucasians and Asian studies, we found for ever smokers an OR of 1.46 (95 % CI: 1.25–1.70; $p < 0.00001$) and an OR of 1.47 (95 % CI: 1.13–1.91; $p < 0.00001$), respectively.

Furthermore, considering the two different types of gastric cancer separately, was found for noncardia gastric cancer an OR of 1.32 (95 % CI: 1.11–1.57; $p = 0.30$) for ever smokers and an OR of 2.04 (95 % CI: 1.66–2.50; $p = 0.10$) for current

smokers. For cardia gastric cancer, was found an OR of 1.47 (95 % CI: 1.15–1.87; $p=0.73$) for ever smokers and an OR of 2.05 (95 % CI: 1.50–2.81; $p=0.84$) for current smokers (La Torre et al. 2009a).

Data obtained from a Russian case–control study showed that smoking increases the risk of developing gastric cancer in men, but not in women. In men a dose–response relationship between mean number of cigarettes smoked per day ($p=0.03$), pack–years of cigarettes smoked ($p=0.01$), duration of smoking ($p=0.08$), and the risk of cancer of gastric cardia was observed. The risk of gastric cancer associated with smoking varied according to *H. pylori* infection status since it was significantly increased among *H. pylori*-infected men (OR = 2.3, CI = 1.1–4.7) (Zaridze et al. 2000).

This result suggests that smoking may increase the carcinogenic effect of *H. pylori*.

A pooled analysis of two population-based prospective cohort studies in rural northern Japan (Koizumi et al. 2004) was performed to examine the association between cigarette smoking and the risk of gastric cancer. The pooled multivariate RRs (95 % CI) for current smokers and past smokers were 1.84 (1.39–2.43) and 1.77 (1.29–2.43), respectively. A linear increase in risk associated with the higher number of cigarettes smoked per day was observed: the pooled multivariate RRs (95 % CIs) for current smokers who smoked 1–19, 20–24, and >25 cigarettes per day were 1.41 (1.00–1.98), 1.98 (1.45–2.71), and 2.15 (1.53–3.02), respectively. A linear increase in risk associated with pack–years of smoking was also found: the pooled multivariate RRs (95 % CIs) for <25, 25–39, and >40 pack–years of smoking in comparison to never smokers were 1.55 (1.07–2.25), 2.20 (1.56–3.11), and 2.26 (1.61–3.18), respectively. For past smokers, a significant increase in risk remained for up to 14 years after cessation: the pooled multivariate RRs (95 % CIs) for past smokers who had quit <5, 5–14, and >15 years previously compared to subjects who had never smoked were 1.72 (1.12–2.64), 2.08 (1.41–3.07), and 1.31 (0.77–2.21), respectively.

A systematic review provided solid evidence to classify smoking as the most important behavioral risk factor for gastric cancer, addressing the magnitude of the association for different levels of exposure, and cancer locations. Comparing current smokers with never smokers: the pooled RR estimates were 1.62 in males (95 % CI: 1.50–1.75) and 1.20 in females (95 % CI: 1.01–1.43); the RR increased from 1.3 for the lowest consumptions to 1.7 for the smoking of approximately 30 cigarettes per day in the trend estimation analysis; in addition, smoking was significantly associated with both cardia (RR = 1.87; 95 % CI: 1.31–2.67) and non-cardia (RR = 1.60; 95 % CI: 1.41–1.80) cancers (Ladeiras-Lopes et al. 2008).

4.9 Breast Cancer

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in females worldwide, accounting for 23 % (1.38 million) of the total cancer cases and 14 % (458,400) of the total cancer deaths in 2008. About 50 % of

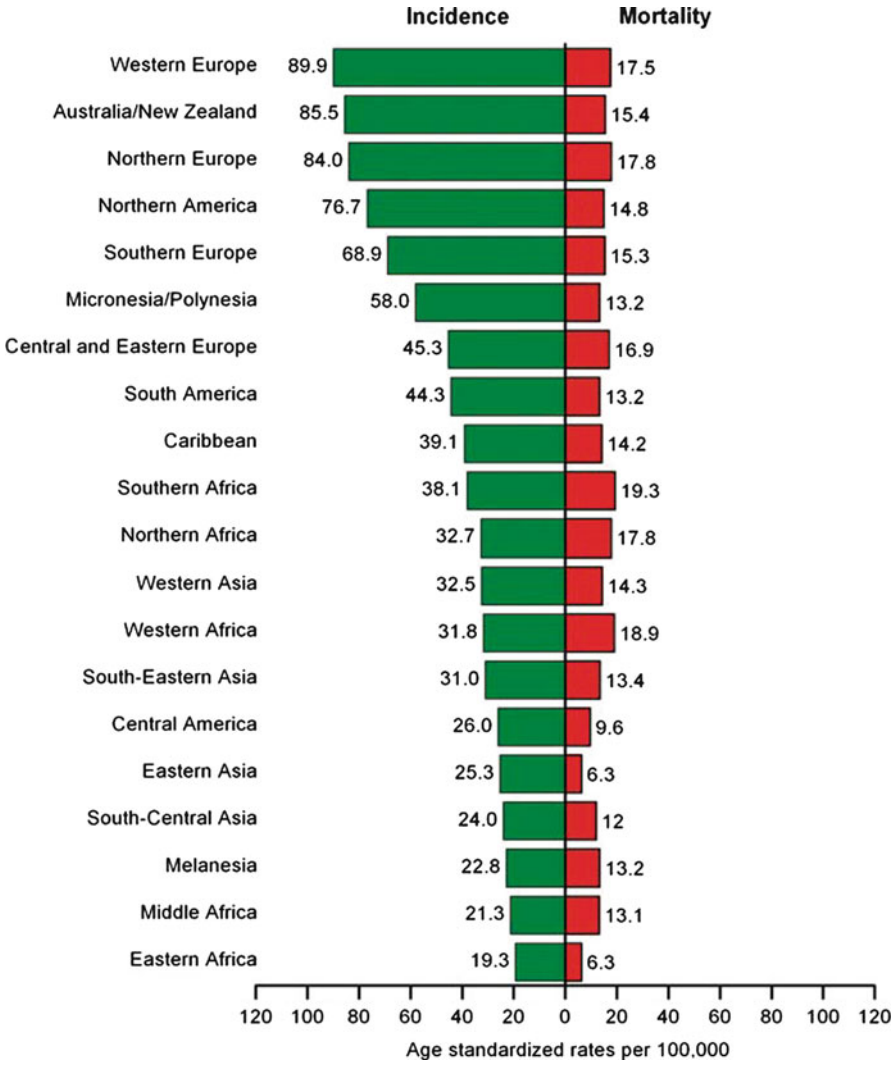

Fig. 4.7 Age-standardized breast cancer incidence and mortality rates by world area (Ferlay et al. 2010)

the cases and 60 % of the deaths occur in economically developing countries. Incidence rates are high in Western and Northern Europe, Australia/New Zealand, and North America; intermediate in South America, the Caribbean, and Northern Africa; and low in sub-Saharan Africa and Asia females (Jemal et al. 2011) (Fig. 4.7).

The familial tendency to develop the hereditary breast cancer is due to the BRCA mutations that confer a lifetime risk of breast cancer of between 60 and 85 %. Some mutations associated with cancer, such as p53, BRCA1, and BRCA2, occur in

mechanisms to correct errors in DNA. These mutations are either inherited or acquired after birth. Presumably, they allow further mutations, which allow uncontrolled division, lack of attachment, and metastasis to distant organs (Dunning et al. 1999).

Most breast cancers are classified as ductal or lobular carcinoma and derived from the epithelium lining the ducts or lobules. Carcinoma in situ is growth of low grade cancerous or precancerous cells without invasion of the surrounding tissue. In contrast, invasive carcinoma does not confine itself to the initial tissue compartment (Hartmann et al. 1999).

During the past 25 years, breast cancer death rates have been decreasing in North America and several European countries as a result of early detection and improved treatment (Jemal et al. 2010), while in many African and Asian countries incidence and mortality rates have been rising (Parkin et al. 2005a, b).

Despite Japan is a low-risk country, it is now the fourth leading cause of cancer death among Japanese women: the incidence and mortality of breast cancer have increased over the past three decades with incidence rates of 17.0 per 100,000 in 1975 compared with 44.4 in 2005 (Matsuda et al. 2011; Shin et al. 2010).

On the opposite, mortality rates in the UK and US have been declining since the early 1990s, maybe attributable to improvements in screening and treatment (Jatoi and Miller 2003).

Geographical distribution and trends in cancer incidence and mortality highlight the influence of environmental factors and lifestyle in cancer etiology (Iwasaki and Tsugane 2011).

A prospective cohort study (Luo et al. 2011) examined the association between smoking and risk of invasive breast cancer among postmenopausal women. The risk was elevated by 9 % among former smokers HR = 1.09 (95 % CI 1.02–1.17) and by 16 % among current smokers HR = 1.16 (1.00–1.34). Significantly higher risk was found in active smokers with high intensity and duration of smoking, who started smoking in the teenage years. The highest breast cancer risk was found among women who had smoked for ≥50 years HR 1.35 (1.03–1.77) compared with all nonsmokers, HR 1.45 (1.06–1.98) compared with nonsmokers with no exposure to passive smoking. Furthermore, an increased risk persisted for up to 20 years after smoking cessation. There was also a suggestion of an association between passive smoking and increased risk of breast cancer: among nonsmokers women, those with ≥10 years' exposure in childhood, ≥20 years' exposure as an adult at home, and ≥10 years' exposure as an adult at work to passive smoking had a 32 % excess risk of breast cancer compared with those who had never been exposed to passive smoking HR 1.32 (1.04–1.67).

The Japan Public Health Center-based Prospective (JPHC) study found that both active and passive smoking are associated with an increased risk of breast cancer among premenopausal women. Adjusted HR (95 % CI) for ever smokers were 3.9 (1.5–9.9) and 1.1 (0.5–2.5) in pre and postmenopausal women, respectively. In never-active smokers, the adjusted HR (95 % CI) for passive smoking was 2.6 (1.3–5.2) in premenopausal women and 0.6 (0.4–1.0) in postmenopausal women (Hanaoka et al. 2005).

With regard to passive smoking, in 2007 a meta-analysis showed that it was associated with a 60–70 % increased risk for breast cancer among younger, primarily premenopausal women who had never smoked. The analysis of case–control studies which included all major sources of lifetime passive smoke exposure (combined childhood residential, adult residential and occupational), showed the pooled RR of 1.91 (95 % CI: 1.53, 2.39). The estimated summary RR was 1.06 (95 % CI: 0.96, 1.17) for those studies with more limited exposure assessment: the cohort and case–control studies yielded summary estimates of 1.02 and 1.14, respectively. The pooled RR got from the analysis of the studies reporting risk for breast cancer in premenopausal women was 1.68 (95 % CI: 1.31, 2.15) (Miller et al. 2007).

On the contrary, the meta-analysis conducted by Pirie et al. found no association between secondhand smoke and breast cancer in studies that collected information on exposure prior to the development of breast cancer (Pirie et al. 2008).

A large prospective cohort study suggest that active smoking especially smoking before first birth may be associated with a modest increase in the risk of BC. It has been estimated a HR of breast cancer (BC) of 1.06 % (95 % CI 1.01 %–1.11 %) for ever smokers compared to never smokers. BC incidence was linked with higher quantity of current ($p=0.02$) and past smoking ($p=0.003$), younger age of initiation ($p=0.01$), longer duration ($p=0.01$) and more pack–years (PKY) of smoking ($p=0.005$). Premenopausal smoking was associated with a slightly higher incidence of BC (HR = 1.11, 95 % CI 1.07–1.15 for increase of every 20 PKY) especially smoking before first birth (HR = 1.18, 95 % CI 1.10–1.27 for increase of every 20-PKY) (Xue et al. 2011).

Data obtained from the Canadian National Breast Screening Study (NBSS) showed that breast cancer risk was associated with the duration (40 years) RR = 1.50 (95 % CI: 1.19, 1.89), intensity (40 cigarettes per day) RR = 1.20 (95 % CI: 1.00, 1.44), cumulative exposure (40 pack–years) RR = 1.17 (95 % CI: 1.02, 1.34), and latency of cigarette smoking (40 years since beginning of smoking) RR = 1.28 (95 % CI: 1.06, 1.55), as well as smoking initiation before a first full-term pregnancy (among parous women, more than 5 years of smoking) RR = 1.13 (95 % CI: 1.01–1.25). These results strongly suggest that cigarette smoking plays an important role in breast cancer etiology, particularly when started early in life and for long durations (Cui et al. 2006; Collishaw et al. 2009).

In 2004, the International Agency for Research on Cancer (IARC) supported the "lack of carcinogenicity of tobacco smoking in humans for cancers of the female breast" (International Agency for Research on Cancer 2004a, b). However, several studies since 2002 have observed an increased risk associated with a long duration and/or high number of pack–years of smoking (Xue et al. 2011; Hanaoka et al. 2005; Luo et al. 2011).

A meta-analysis found a significant interaction between smoking, *N-acetyltransferase* 2 (NAT2) genotype, and risk of breast cancer: higher pack–years were associated with an increased risk among women with the NAT2 slow genotype but not among rapid acetylators (Ambrosone et al. 2008)

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