# Oncology in midlife and beyond

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## ABSTRACT

The onset of the menopause is often a time when women's concerns can act as a powerful trigger to encourage healthy modifications in lifestyle which will maintain, or improve, their general health. This document aims to help women to understand their potential risks, to encourage them to find proactive preventive strategies by modifying some of their attitudes, and to use health resources (when available) to be screened. Cancer is an important cause of death but not the primary cause of mortality. Cardio/circulatory diseases represent 35–40% of causes of death in most developed countries and 20–25% of women will die from cancers in Western Europe, Australasia, high-income North America, high-income Asia Pacific, East Asia and Southern Latin America. Breast cancer, lung cancer and colorectal cancer are prevalent in most regions of the world. Cervical cancer remains a hallmark of low access to health care. Preventive strategies (decreasing smoking and alcohol consumption, losing weight, eating a healthy diet and undertaking physical activity) and implementation of screening could help to significantly decrease the incidence of and mortality from cancer. The mortality/incidence ratio is higher in developing countries compared to high-income regions as well as in subgroups of populations in developed countries with lower socioeconomic levels. Implementation of better diagnostic methods and management of cancer according to the local resources will help to decrease the mortality rate in developing countries, and effort has to be made to decrease social inequities and improve access to health care for low-income groups. In conclusion, cancer incidence is increasing as a consequence of longer life expectancy all over the world. National health programs are mandatory to implement screening and to improve individual management. Finally, educating women so that they are aware of ways to improve their general health, to minimize their own risk factors and to identify signs of change in their own health which may be markers of impending cancer will help to reduce the burden of disease and improve the prognosis for tumors detected at an earlier stage.

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## INTRODUCTION

The onset of the menopause, with its attendant changes, is often a time when women take stock of their health and express concerns about the chance of becoming ill. Such concerns can act as a powerful trigger to encourage healthy modifications of lifestyle which will maintain, or improve, general health.

This document aims to help women to understand their potential risks, to encourage them to find proactive preventive strategies by modifying some of their attitudes, and to use health resources (when available) to be screened. It is also extremely important to consult one's doctor as soon as abnormal symptoms occur as this could help to achieve a better prognosis by providing an early diagnosis, especially in the case of cancer. There are many misconceptions about cancer, and accurate information about risk factors, incidence and mortality is important in improving women's knowledge and helping them to achieve healthy aging. We aim to describe the epidemiologic data on the main cancers arising in women according to the different world regions and to address the main risk factors and clinical symptoms in these regions in order to help women to decrease their risk factors and increase prevention.

Progress in the management of most diseases, including cancer, in regions of the world where access to health care is optimal has helped to increase life expectancy. The average female life expectancy at birth is 57.8 years in low-income countries, 69.3 years in lower–middle-income countries, 74.4 years in upper–middle-income countries and 82.4 years in high-income countries[1].

*Cancer is an important cause of death but not the primary cause of mortality.* Cardio/circulatory diseases represent 35–40% of causes of death in most developed countries, 32–48% in Latin America and the Caribbean[2], peaking at 70% in Eastern Europe, 60% in Central Europe and Central Asia, and 45% in North Africa and the Middle East[3]. In Sub-Saharan Africa and Oceania, less than 20% of women will die from cardio/circulatory diseases[3]. The main cause of death in Southern Sub-Saharan Africa is HIV[3]. Cancers accounted for 8 million deaths world-wide in 2010, representing 15.1% of all deaths world-wide for both sexes[4]. Among women, 20–25% die from cancers in Western Europe, Australasia, high-income North America, high-income Asia Pacific, East Asia and Southern Latin America.

It is important to understand that the increase in cancer incidence is related at least partially to increasing life expectancy. Looking at the age-standardized rates for mortality and incidence (Figures 1–6), it is clear that the incidence is higher in developed countries, mostly because of the availability of screening and diagnostic procedures but also because mortality varies less from one region to another. However, there are some differences in the ratio between incidence and mortality between different countries (Figures 1–6). Screening policies and the management of cancers vary from one country to another depending on available resources and health-care policy. Increased mortality is usually associated with low access to the health-

care system and low socioeconomic development. In addition, the availability of registries varies widely and is usually low or absent. Accurate epidemiology needs to correctly collect information on diagnosis and mortality. Recent attempts have been made to increase the availability of information on the real frequency of diseases[3]. The numbers and incidences reported in this document rely on publications in peer-review journals, mostly from the IARC website combining Globocan[5] and World Health Organization (WHO) sources[6] and the recent data available from the Institute for Health Metrics and Evaluation (IHME)[3].

Breast, lung and cervical cancers are the most pre-eminent in women, followed by colorectal cancer. Mortality from breast cancer represents 13.7% of the mortality from cancer in women, followed by lung cancer at 12.8%, colorectal cancer at 8.6% and cervical cancer at 8.2%[5]. Mortality from ovarian cancer (4.2%) and uterine corpus (endometrial) cancer (2.2%) is much less[5].

Breast cancer is as common in developed countries (49%) as in developing countries (51%), occurring predominantly in postmenopausal women (67%); however, it occurs more frequently in postmenopausal women in developed countries (39%) than in developing countries (28%). In 2010, over 1.5 million new cases of breast cancer were reported and there were over 400,000 deaths[7].

Cervical cancer is more frequent in developing regions, where 76% of cervical cancer cases occur. This could be taken as an index of poverty or low access to health care. In 2010, more than half a million new cases of cancer of the cervix were reported together with 200,000 deaths due to the disease. Both breast and cervical cancer together represent about 4.2% of causes of mortality world-wide.

The incidence of lung cancer is 515 999 new cases/year in women and the mortality rate is still very high, reaching 427,586 deaths[5]. World-wide the incidence of lung cancer is beginning to level off and will decrease in western countries because of the decrease in smoking, but it continues to increase in Asia and especially in China where smoking is highly prevalent[8].

## REGIONAL INCIDENCES

Northern, Western and Southern Europe, North America and Australia display similar incidences and mortality rates for cancers. The most prevalent ones are breast, colorectal and lung cancers (Figures 1–3)[3-6]. In Latin America and the Caribbean, the most prevalent incidence and mortality rates for malignancies in women by far are for breast and cervical cancers[5].

These regions have a much higher incidence of breast cancer than the low-income countries and intermediate countries with age-standardized rates ranging from 100/100,000 women/year (the highest rate being 109/100,000 in Belgium) in high-income countries to about 60/100,000 in intermediate countries and 20/100,000 in eastern and central Africa (Figure 1)[5]. Despite a very high incidence of breast cancer, this cancer does not always constitute the main cause of mortality in some of the developed countries because of the high difference between incidence and mortality[5,6]. In most developed countries, the mortality to incidence ratio is 20–25% of breast cancer diagnosed (Figure 1), whereas it is 35% in developing countries[7]. Another way of expressing the risk is by the life cumulative incidence for breast cancer, which is very high in North America, Australasia and Western Europe and reaches more than 10% of cumulative probability (even 12% in USA White women). By contrast, some countries in Sub-Saharan Africa and South Asia show a cumulative risk of less than 3%.

**REGIONAL MORTALITY**

In some countries, lung cancer is the leading cause of cancer mortality, such as in the USA, Canada, Hong Kong, China, UK, Denmark, Norway, Sweden and Korea (Figure 2 and Supplementary Figure 2)[5,6]. Whereas the mortality from breast cancer represents about 15% of the total mortality by cancer in these countries, lung cancer accounts for 24–25% of mortality by cancer in Canada and the USA, 22% in Denmark, Hong Kong and China, 19% in the Netherlands and 18% in Norway (Supplementary Figure 2). Mortality from lung cancer is just above that from breast cancer in Australia and Sweden (16%)[6] (Supplementary Figure 2). In some other developed countries, breast cancer is the first cause of mortality by cancer including Argentina (20.6%), Belgium (20%), Israel (19%), France (18.6%), Germany (17.3%), Switzerland (17%), Italy (16.8%), Portugal (16.5%), Austria (16.2%), Brazil (14%) and Chile (12.3%)[6] (Supplementary Figure 1).

Latin America and the Caribbean are unusual in that breast cancer and cervical cancers both lead to similar death rates in most countries. This suggests that there are large differences in populations, socioeconomic levels and access to care.

Also, in any single country, the differences in genetics, access to health care, and socioeconomic disparities can lead to differences in the mortality rate for a given cancer, such as is illustrated in the USA where African-American women have a 7% lower incidence rate of cancers compared to White women, while their overall cancer-related death rate is 17% higher[9], or in South Africa concerning cervical cancer (see following).

## SPECIFICITIES OF MAIN CANCERS

### Breast cancer

The incidence of breast cancer is changing due to screening and lifestyle modifications. Breast cancer incidence has increased in countries all over the world. Only 5–10% of cases are associated with strong genetic susceptibility. It is a multifactorial disease associated with increasing sociocultural levels and education. Breast cancer incidence has increased by 3.1%/year in the past 30 years[7], especially in Asian countries such as India, Japan, Singapore and Taiwan, where the incidence has been traditionally low, suggesting that adoption of a more Western lifestyle is associated with increased incidence[10]. Similarly in Latin America and the Caribbean, although there are data gaps in many countries, increases in incidence and mortality rates have been observed. Breast cancer prevalence also shows some specific differences according to countries and regions or ethnic groups.

Whereas in the Western world breast cancer is mostly a postmenopausal disease, in Asia its incidence seems to have a bell-shaped curve, with the peak incidence occurring at 45–55 years of age[11,12]. In Singapore, the breast cancer incidence peaks at age 50 years and levels off after that[10,12]. In India, Pakistan, North Africa, and Western Africa (Niger), breast cancer occurs predominantly in young women and is more aggressive[12,13].

There are differences between ethnic groups in both the histological characteristics of breast cancer and the hormone receptor status. The prognosis is usually considered to be worse in estrogen-receptor (ER)-negative breast cancers. In some Asian patients (Taiwanese, Malaysian, etc.), there is a higher prevalence of ER-positive tumors in women less than 50 years old (68% vs. 58%, $p < 0.001$) and progesterone receptor (PR)-positive tumors (63% vs. 50%, $p < 0.001$) when compared to women more than 50 years old[11,14]. In contrast, in other Asian populations, a higher prevalence of HER2 tumors has been observed[15].

Indian[12] and African-American US women as well as native African women have a higher incidence of triple negative (ER-negative, PR-negative, HER2-negative) breast cancers than Caucasian women and less frequently have luminal A types of breast cancer[13]. Luminal A breast cancers are thus predominant in some Asian (including Japanese), White, and postmenopausal African-American populations, their incidence reaching more than 50% and decreasing to 40% in premenopausal African-Americans and to only 27% in indigenous Africans[13,16].

**Cervical cancer**

Cervical cancer is the third most common cancer in women with more than half a million new cases occurring annually world-wide. The world incidence of cervical cancer has increased by 0.6%/year in the past 30 years, but more than 85% of the global burden occurs in developing countries. The cumulative probability of cervical cancer between 1980 and 2010 fell in all the regions of the world[7]; the increase in incidence of 0.6% per year and of deaths by 0.46% per year are due to increasing population sizes and population aging, respectively[7]. Mortality has decreased in most countries with the exception of Zambia, Iraq, Sri Lanka and Thailand[7]. There is a specific efficient method of screening which, when properly implemented, can decrease rates of disease and mortality. More recently, vaccination has been implemented in some regions of the world, but, unfortunately, this preventive method remains extremely expensive and still has not reached the continents at high risk and need such as India, Africa and most countries in Latin America and the Caribbean. If the cost were to be reduced in the future, universal vaccination would be of value.

*Asia: an example of the efficacy of screening*

The incidence of cervical cancer has declined over the last 30 years in Asia. This is largely attributable to widespread cancer screening. Of the three island states, Hong Kong, Singapore and Taiwan, Taiwan was the first to have a comprehensive national screening program for cervical cancer in 1995 followed by Hong Kong in 2002 and Singapore in 2004. Women in these three states are well aware of cervical cancer and preventive means using Pap smear screening, although their awareness and understanding of the role of HPV in cervical carcinogenesis are low[17]. In South-east Asia, cervical cancer remained a leading cancer but its incidence is less than in Sub-Saharan Africa (Figure 4). The standard Pap smear has been available for opportunistic screening in South-east Asia, but organized programs have yet to be implemented[18]. Prophylactic HPV vaccinations have been licensed in most of the Asian countries but their availability is limited by cost.

*The example of South Africa*

Not only is cervical cancer the most common cancer in Black women, and the second most common in Colored women, but a large proportion of cases have incurable stage III or IV cancer when diagnosed; in the majority of cases only palliative therapy is possible, and the burden of avoidable suffering is considerable. Especially among women of low socioeconomic status, cervical cancer remains by far the most important, urgent and

rectifiable public health problem in the cancer field. In the apartheid era, Pap smear screening was carried out, opportunistically and incompletely, in family planning clinics. Consequently, screening was largely performed in the wrong age group (very young women)[19]. Screening is now seldom performed in that setting. HIV infection rates are routinely monitored in antenatal clinics[20] and among Black, Colored, White, and Indian/Asian women. Since HIV potentiates the risk of cervical cancer, an adequate preventive strategy has to include steps to control its spread. Currently, antiretroviral therapy is routinely and extensively provided, and coverage is becoming increasingly complete. In addition, the national health policy recommends that Pap smears be performed when HIV is diagnosed and regularly thereafter.

The lower incidence of cervical cancer among South African women of high socioeconomic status serves to demonstrate the extent to which adequate preventive services could reduce the burden of this disease among women of low socioeconomic status. The principal reasons for the lower incidence among the former women are the ability to pay for regular receipt of Pap smears, adequate medical insurance, early detection, adequate education, and a lower prevalence of HIV infection.

**Lung cancer**

In the last 10 years, adenocarcinoma has become the most common histological subtype of non-small cell lung cancer (NSCLC) in most Western and Asian countries. Histological classification has, however, recently been challenged and new definitions produced that can also explain some modifications in the frequency of each type among the NSCLC[21]. Smoking is the main risk factor. However, it now appears that pollution and particles in the air could also account for some of the increase observed around the world. The proportion of lung cancers attributable to urban air pollution in Europe is estimated to be 11%[8]. It is, however, difficult to exclude the role of second-hand (passive) smoking in the increase of lung cancer. The increased relative risk of passive smoking is evaluated to be between 1.14 and 5.20[8]. The recent epidemiology is characterized by increasing incidence of lung cancer in females and non-smokers. This is apparent in Asia but also in some European countries. Adenocarcinomas are more frequent in never-smokers than squamous adenoma and relatively more frequent in women[22].

One of the characteristic features of lung cancer in Asia is NSCLC in never-smokers, cases of which occur prominently in Asian women, with adenocarcinoma as the predominant histological type[23]. The proportion of never-smoking patients with NSCLC has been steadily increasing over time, from 15.9% in the 1970s to 32.8% in the 2000s[22,23].

Lung cancer in South Africa has a very low incidence. Smoking patterns also have cultural and economic determinants. Cigarettes in South Africa are expensive, and smoking is prohibited in public places. Smoking is rare among Black women but is far more common among Colored and White women; Indian/Asian women tend not to smoke. The proportions of smokers in Black, Colored, White and Indian/Asian in South African women are 4.1%, 39.0%, 26.7% and 13.0%, respectively[20].

**Colorectal cancers**

Colorectal cancers are mostly observed in Western developed countries (Figure 3) and represent 10.1% of all incident cancers in women world-wide[24]. Colon cancer in developed countries represents 63% of all cases of colorectal cancer. The lifetime risk of colorectal cancer is about 5% in Western countries[25]. The highest incidence rates are observed in Australia, New Zealand, Canada, the USA and parts of Europe[24]. The countries with the lowest risk include China, India, and parts of Africa and South America[24]. The differences in these incidences may be due to under-ascertainment, misclassification or underreported data from developing countries.

Colon cancer is strongly dependent upon lifestyle factors, as shown from studies of migrants from Japan to the USA or migrants from southern Europe to Australia[24].

As for breast cancers, approximately 5–10% originate from families with genetic predispositions.

Western countries have developed easy access to colonoscopy and in some regions national screening by repetitive fecal occult blood testing. These procedures can increase the rate of diagnosis and thus the incidence, but early diagnosis helps to decrease mortality (see following). The natural history of colon cancer is progressive from benign adenoma to cancer, and thus screening can prevent effectively the progression to more aggressive lesions, at least in some cases. Mortality has decreased in the USA by 4.3% per year from 2002 to 2005[24].

**Endometrial cancer**

Endometrial cancer remains much less frequent than breast, lung and colorectal cancers but is the most common gynecological cancer in the Western world (Figures 1–6). Its mortality rate is far lower than those for the other cancers (Figure 5) and depends upon the histological types, either type 1 or 2. The number of deaths attributable to endometrial cancer world-wide in 2010 was 58,600[4]. The incidence of uterine cancer, like breast cancer, has increased rapidly during the last two decades in Asian countries. The incidence of uterine cancer in Asian, Latin

American and African women is lower (8–10th rank) than in Western populations, especially the UK, North America and Central and Eastern Europe, where it ranks as the fourth cancer in women (Figure 5). In Asia, the age-specific incidence shows a bell-shaped pattern with the peak age around 45–55 years. This is different from the pattern in Western women, which shows a continuous increase with age and peaks around 70 years. This suggests different risk factors between these regions. Most of the endometrial cancers are hormone-dependent, sensitive to the proliferative effect of estrogens and prevented by administration of progestins. The main risk factors are obesity (through the aromatization of estrogens from androgens in the adipose tissue and through insulin resistance), diabetes types 1 and 2[26,27], and nulliparity. High parity and oral contraceptives are protective. The presence of one and two or more risk factors increases the risk of endometrial cancer by 8- and 18-fold, respectively[28]. Assuming a 2.6% lifetime risk of endometrial cancer, the aforementioned risk factors confer lifetime risks of approximately 18% and 32%, respectively[28]. A small proportion of cases are poorly differentiated and non-hormone-dependent. Usually the prognosis is excellent but an early diagnosis is important. It was reported that, in the USA, African-Americans counted for 7% of new endometrial cancer cases but represented 14% of endometrial cancer deaths. The most consistent contributors to these disparities in mortality were histology (more aggressive) and socioeconomics. Since endometrial cancer is usually revealed by abnormal bleeding, women must consult their doctor in the presence of abnormal bleeding before or after menopause.

**Ovarian cancer**

Ovarian cancer is a severe disease but remains much less frequent than the other cancers (Figure 6). It is a disease of aging women and this can explain its higher incidence in countries with a higher life expectancy. The number of deaths in 2010 was 160,500 (115,900–200,600). The highest incidences are reported in Europe and North America and the lowest incidences in China and Africa, possibly because of shorter life and/or less diagnosis (Figure 6)[5]. The incidence of ovarian cancer around the world has not changed significantly in the last 30 years. The highest incidence is recorded in non-Hispanic White women, followed by Hispanic, African and Asian women[29]. The absolute mortality from ovarian cancer is highly proportional to its incidence; however, developed countries tend to demonstrate improved mortality/incidence ratios due to advances in detection and treatment (Figure 6). Again, African-American women have the highest mortality/incidence ratio (0.71), followed by non-Hispanic White (0.66), Hispanic (0.55), and Asian (0.5) women[29]. Different risk factors and social disparities can explain these differences[29].

Genetic susceptibilities account for about 10% of all ovarian cancers; carriers of BRCA1 and BRCA2 mutations and women affected by Lynch syndrome have, respectively, a 40% and a 12% lifetime risk of developing ovarian cancer compared to a 1.4–2.5% risk in women without a family history[29].

## MODIFIABLE RISK FACTORS

In 2012, the IHME conducted a comparative assessment of the burden of disease attributable to risk factors and risk factor clusters in 21 regions of the world[30] (Table 1).

**Table 1** Deaths attributable to risk factors in 2010 world-wide (from reference 30)

| *Risk factor* | *Number of deaths* | *95% intervals of uncertainty* |
|---|---|---|
| Smoking | 1,443,924 | 920,763–1,743,849 |
| Second-hand smoke | 346,304 | 252,702–439,439 |
| Alcohol | 1,720,059 | 1,541,469–1,886,125 |
| High body mass index | 1,738,466 | 1,454,008–2,036,059 |
| Dietary factors and physical inactivity | 5,815,748 | 5,380,274–6,261,225 |

Many of the risk factors contributing to overall disease burden (including cardiovascular diseases and diabetes) were also significant risk factors for malignant disease. The three leading risk factors for global disease burden in 2010 were high blood pressure, tobacco smoking (including second-hand smoke) and household air pollution, accounting for 7%, 6.3% and 4.3%, respectively, of disability-adjusted life years (DALYs).

Dietary risk factors and physical inactivity collectively accounted for 10% of DALYs, with the most prominent risks being diets low in fruit and high in sodium. The leading risk factor in Eastern Europe, Andean Latin America and Sub-Saharan Africa was alcohol use, whilst in most of Asia, Latin America, North Africa, The Middle East and Central Europe it was high blood pressure. Tobacco smoking remained the highest risk factor in high-income North America and Western Europe. Tobacco smoking is, of course, a major risk factor for lung, head and neck and colon cancers and is also implicated in breast cancer[24,31].

### The role of obesity

Obesity and high body mass index have increased globally and together they are the leading disease risk factor in Australasia, high-income North America, Western Europe, North Africa and the Middle East, Southern, Central and Andean Latin America, the Caribbean and

Oceania and also rank high in other regions[30]. An unfavorable trend towards a Westernized diet and obesity has been observed in most developing countries, Asia, the Middle East and, to a certain extent, in North Africa[32]. Obesity seems to affect some groups more than others. In the USA, non-Hispanic Blacks have the highest age-adjusted rates of obesity (49.5%) compared with Mexican Americans (40.4%), all Hispanics (39.1%) and non-Hispanic Whites (34.3%)[33] whilst, in India, there is a high prevalence of metabolic syndrome in the urban Indian population (39.9%), with associated obesity (12.6%)[34], hypertension (30.4%)[35] and polycystic ovarian syndrome (9.13%)[36]. Malnutrition, especially protein deficiency/excess carbohydrates, causes obesity, a major problem throughout Africa, which may also explain some of what is seen among Mexican Americans, Hispanics, and Indians.

Obesity is a risk factor for breast, colon, endometrial and ovarian cancers.

*Breast cancer*

A recent modeling study proposed that obesity accounts for 4.4–9.2% and 3.1–8.4% of the total number of breast cancer deaths in Whites and Blacks, respectively, in the USA[37]. This model considers a positive correlation in postmenopausal women but an inverse correlation in premenopausal women. However, as we have previously discussed[38], the contribution of insulin resistance has probably been under-estimated. More recent studies suggest that obesity associated with insulin resistance is associated with an increase in the risk even before menopause[38]. A recent study in Nigerian women with low prevalence of breast cancer and a growing incidence of obesity showed a strong association between central obesity and breast cancer in pre- and postmenopausal women[39]. Obesity is also a risk factor for having a more aggressive breast cancer and worse survival[40]. This may explain, at least in part, the phenotype of breast cancer in Maghreb, Egypt, India and Pakistan. It is not fully clear whether a lower socioeconomic level can interfere with this worse prognosis: obesity is linked also to lower income and education.

*Colon cancer*

Overweight and obesity[41], low physical activity and type 2 diabetes are linked to insulin resistance and increased risk for colon cancers in all kinds of populations[42,43]. The association between obesity and colon cancer is even stronger in men than in women[42].

*Endometrial cancer*

The incidence of endometrial cancers including sarcomas is increased in obese women. Obesity also negatively affects mortality rate whereas physical activity improves it[44].

**The role of nutrition and alcohol**

*Breast cancer*

Increasing consumption of alcohol is associated with an increase in the risk of hormone-dependent breast cancer[45]. The direct effect of energy intake and especially saturated fat has not been proven in breast cancer but nutrition can act through weight gain and insulin resistance induction and is thus considered as a risk factor. In Japan, the increase in breast cancer can be associated with modification in age at menarche, modifications in reproductive factors but also in nutrition: an increase in energy and protein intake can be directly involved as can an increase in average body length, which has increased[46]. To explain the differences in ER-positive incidence of breast cancer in premenopausal women in South-east Asia, it is speculated that younger women could be consuming a more fatty diet or more xenoestrogens from plastic bags or cans.

*Colorectal cancers*

Intake of alcohol and red and processed meat is considered to be associated with an increased risk in the USA, but in Europe only processed meat remains significantly associated with the risk. The recent increase in Japan could be linked to these modifications[47,48]. The typical Western diet could favor the development of a bacterial flora capable of degrading bile salts to potentially carcinogenic compounds[24]. The positive association with meat consumption is stronger for colon cancer than rectal cancer[24]. A decrease in risks of colon but not rectal cancer is reported with coffee consumption[49]. Coffee can reduce cholesterol, bile acids and neutral sterol secretion in the colon and could display some antimutagenic properties and increased colonic motility[50].

*Lung cancer*

Cured meat, deep-fried cooking and chili have been associated with an increased risk[8].

**Household air pollution, environmental carcinogens and xenoestrogens**

The role of different endocrine disrupters and other potential carcinogens is discussed but not proven in studies of the growing incidence of different cancers and especially of breast

cancer[51]. The potential role of carcinogens during the development of the breast at and after puberty is illustrated by the role of smoking before the first full-term pregnancy[52]. According to local use, there are some specific carcinogens, such as for the use of betel in India[53] or the consumption of hot food contained in plastic bags, that have been suggested as providing xenoestrogens.

The etiology of lung cancer in never-smokers remains unclear. Several risk factors have been proposed such as second-hand smoking; occupational exposures to paints or paint thinners, welding equipment, smoke soot or exhaust; pre-existing lung diseases such as inflammation; dietary intake of grilled or barbecued meat; estrogen; and family history (role of genetics).

**Other modifiable risk factors**

*Cervical cancer*

Risk factors for cervical cancer are especially well identified: the causal agent is papilloma virus. Factors like young age at first sexual intercourse, high parity, poor sexual hygiene and multiple sexual partners increase the incidence. Smoking is a cofactor. The sexual life of the partner who is a reservoir for HPV is also probably involved in the risk but this is not fully evaluated.

*Endometrial and ovarian cancer*

Risk factors for endometrial cancer include obesity, nulliparity, hypertension, diabetes, polycystic ovarian syndrome, endometrial hyperplasia, early menarche, late menopause, unopposed estrogen therapy, family history of cancer, past history of breast cancer and tamoxifen therapy. Risk is strongly decreased by prolonged use of oral contraceptives and the use of progestins[54]. A recent publication suggests that the cessation of hormone replacement therapy (HRT) for menopausal symptoms following the Women's Health Initiative (WHI) publications is associated with an increase of endometrial cancer both in White American and African-Americans[55]. However, the concurrent increase in obesity cannot be excluded as the main factor in this increased rate, especially in African-Americans[55]. It was indeed reported that combined HRT decreased the incidence of endometrial cancer in obese women through the beneficial effect of progestin on the endogenous stimulation of the endometrium by aromatized estrogens.

Risk factors for ovarian cancer include increasing age, nulliparity, use of fertility-enhancing drugs such as clomiphene citrate for more than 1 year, family history of ovarian, breast or colorectal cancer, and past history of breast cancer. Use of oral contraceptive pills is a very

potent way to decrease ovarian cancer risk. Certain gynecological surgeries like tubal ligation, hysterectomy and cure of endometriosis are protective against ovarian cancer[56,57]. Obesity might increase some types but not all, whereas exercise could help to decrease the risk (see below).

**The place of hormone replacement therapy among risk factors**

In the IHME paper evaluating risk factors and burden of disease, HRT is not mentioned among the risk factors[30]. Following the publication of the WHI randomized, controlled trial in 2002[58], HRT use declined considerably world-wide. This was mainly due to the fear of breast cancer and the absence of clear data for cardiovascular protection arising from that study. However, since then, reappraisals of the cardiovascular risk and other risks have been conducted and it now appears that, for young symptomatic postmenopausal women in the absence of specific risk factors, the benefits of HRT outweigh the risks[59,60].

One of the clear benefits of HRT is that it increases quality of life in symptomatic postmenopausal women. It also significantly reduces the risk of osteoporotic fractures and type 2 diabetes which is itself associated with increasing mortality. Hip fracture is also associated with a high degree of mortality (20%) and disability. Colon cancer risk was also reduced by HRT in the WHI[58]. However, combined HRT increases breast cancer risk after certain duration of use (> 7 years in the WHI). This effect is from the promotion of pre-existing lesions. The risk can probably be decreased by evaluating women with a specific higher risk such as increased breast density in mammograms, strong family history, thoracic radiotherapy or biopsy with atypical hyperplasia. Exercise decreases the risk of breast cancer even in HRT users[61]. HRT does not add any risk to the breast cancer risk associated with obesity and could help to decrease endometrial cancer incidence in these women, as recently shown[54]. The incidences of breast cancer and ovarian cancer were reported to decrease after the massive decline in HRT use[55,62]. However, this decrease was possibly due to several factors including less follow-up of women who stop HRT[63]. Furthermore, several publications have reported a further increase in breast cancer since 2006 (despite low levels of HRT use), suggesting other causes such as lower participation levels in screening programs or possibly a slowing of tumor growth after HRT cessation[63]. Conjugated estrogens alone were shown to decrease the risk of breast cancer at least at 5–6 years of use in the WHI population, where obesity was highly prevalent and in women quite far from menopause[64]. In the rest of the literature, however, estrogens alone mildly increase breast cancer risk to a lesser level and at longer term (> 10–15 years) than combined HRT[63].

Estrogens alone increase endometrial cancer risk and could be also more deleterious for ovarian cancer than combined HRT. It is also likely that the composition of HRT (synthetic progestins versus progesterone) could be associated with different levels of risk, the latter providing a lower risk of breast cancer[65].

Lung cancer was reported to be more invasive in women receiving HRT in the WHI combined trial when diagnosed but not in the women in the estrogen-only trial[66,67]. It is still a controversial issue with opposing results among various studies. Some studies have reported a decrease in risk with early menarche and late menopause and favorable or no effect of HRT[68,69]. Possibly smoking status, histological differentiation, the presence of ERs in the tumor or other unknown factors or bias may explain the discrepancies between studies.

## SCREENING STRATEGIES

### Breast cancer

Breast cancer screening is mostly performed using mammograms. National screening programs are available in most developed countries but still not in all. Programs vary among the countries. The most usual recommendations are to perform mammograms every 2 years from 50 to 74 years of age. In the USA, in some of the states 40 years is the starting age and an annual mammogram is recommended. There are ongoing discussions about the cost–benefit of screening programs in countries where it has been implemented for years because of possible overdiagnosis and overtreatment. However, in these countries, the mortality to incidence ratio has decreased. The concern of overdiagnosis is a concern of rich countries with high availability of mammograms. However, in most countries, women's breasts are not examined and the development of breast examination and mammograms could probably help to decrease the reported mortality in developing countries. Economic modeling suggests that, in the lower–middle-resource countries, clinical breast examination performed yearly from ages 40 to 60 years can be nearly as efficacious as mammographic screening every 2 years for reducing breast cancer mortality but at substantially lower cost[1]. However, this has not been observed in Chile where a National Breast Cancer Screening Program, started in 1998 and based on clinical breast examination only, had a very limited effect despite the relatively high adherence achieved (65% annual compliance rate), since the survival rate did not improve. New guidelines might be proposed in the next few years by stratifying the screening in high-risk populations in developed countries or using alternatives technologies of diagnosis, including ultrasonography in Asian populations due to their higher breast densities. However,

so far, breast self-examination and clinical examination combined with mammogram remain the gold standard for breast cancer screening.

**Cervical cancer**

Screening for cervical cancer has been implemented in most developed countries and is associated with a strong and significant decrease in incidence and mortality.

Since the introduction of cervical cancer screening in Australia, the number of new cases of cervical cancer has declined from 1092 in 1991 to 778 in 2008 and the age-standardized mortality rate has declined from 3.9 to 1.9 per 100,000 women over the same time period. In New Zealand, the incidence of cervical cancer has fallen by 40% and mortality by 60% since the introduction of screening. Both Australia and New Zealand have a free national HPV vaccination program for girls and young women. Australia commenced a vaccination program for young men in February 2013; the USA and French-affiliated Pacific Island nations introduced a HPV vaccination program during 2007–2010 and Kiribati, followed by The Cook Islands and Fiji in 2011–12[70-72].

In Western Europe as well, the incidence of cervical cancer has declined, but unequally from one country to another. In France, for example, cervical cancer incidence and mortality decreased by four-fold and two-fold, respectively, between 1976 and 1996 by individual screening; 70% of the invasive cancers were diagnosed in women who had not been screened in the last 4 years. HPV vaccination has been implemented in France for female adolescents and young adults, but the compliance remains low at less than 30% and the vaccine is quite expensive.

In the USA, guidelines for Pap tests for cervical cancer have evolved over recent years and women aged 30–65 years are now advised only to have this test every 5 years.

For developing countries, the WHO recommends that Pap smears should be performed, commencing at the age of 30 years, every 10 years[73]. In South Africa it is projected that full implementation of this recommendation would reduce the incidence of cervical cancer by some 70%[74], and the cost is affordable (about R60 or US$7 per smear). The official policy is to follow the WHO guidelines. However, in South Africa, they have not as yet been fully implemented, and without strong leadership, improved management and a strengthened health-care system, it is unlikely that they will be. At the population level, there is also a need for education to attend for Pap smear screening, or, failing that, to detect cervical cancer as soon as symptoms appear (e.g. postcoital bleeding, vaginal discharge).

At a future date, HPV inoculation may perhaps become feasible, but for the present the cost ($270 for three doses) makes widespread vaccination impractical. Negotiations to reduce the cost are now in progress with the aim of providing population-wide coverage to teenage girls, before they commence sexual activity.

**Colon cancer**

Fecal occult blood testing (FOBT) is the most widely used screening test for colorectal cancers and the only screening test currently recommended by the European Union. The concept involves blood detection in the stool. It is non-invasive, cheap, easy to use, and may be carried out at home. As colorectal cancers only bleed intermittently, FOBTs have to be repeated either each year or every other year. There are two tests available, the guaiac fecal occult blood test and the fecal immunochemical tests. A Cochrane meta-analysis quantified the relative reduction in mortality as 16%[75]. However, there is a low sensitivity for both colorectal cancers (25–38%) and advanced adenomas (16–31%) with the sensitivity of the first method (61–91%) possibly higher than that of the second method (27–67%)[25].

Flexible sigmoidoscopy allows diagnosis of colon lesions as well as tissue biopsies and polyp removal, but only in the distal part of the colon. Screening with sigmoidoscopy reduced mortality from colorectal cancers by 22–31% and incidence by 18–23% in randomized trials where the compliance was high[25].

Colonoscopy is the best diagnostic tool but has not been evaluated in randomized trials until now. Some data from cohorts reported a reduced incidence by 67–77% and mortality by 31–65%[25].

Virtual colonoscopy is a new technique that has not yet found its place and indication but which can be promising because it is less invasive. However, it is associated with radiation (for the computerized tomography version) and remains expensive.

Each technique has some advantages or limits according to availability in the respective country or regions. Health policies have to be adapted to relative and absolute risks and potential costs.

**Endometrial and ovarian cancers**

There is no recommended screening for endometrial and ovarian cancers. Recently, strategies of prophylactic ovariectomies (risk reduction surgery) have been proposed for women with a strong family history and carriers of BRCA1/2 mutations. Patients with a strong family history of endometrial, ovarian and colorectal cancers might have inherited Lynch syndrome

(hereditary non-polyposis colorectal cancer syndrome) that increases their lifetime risk of developing endometrial and ovarian cancers. It is thus important to develop methods of clinical prevention and education which could contribute to the diagnosis of these cancers at a better stage.

Practitioners have to be aware of the predisposing factors for excess estrogen stimulation of the endometrium such as long history of anovulation, obesity/diabetes, high blood pressure, menstrual irregularity, or long-term use of unopposed estrogen or tamoxifen. Endometrial cancer should be ruled out in perimenopausal and postmenopausal patients with abnormal vaginal bleeding. Histologic evaluation of the endometrium should be carried out in all patients in whom endometrial cancer is suspected.

Recent attempts have been made to propose some algorithms including clinical symptoms to improve the diagnosis of cancers[76].

Changes in bowel habit, new digestive disorders, abdominal pain or distension, urinary disorders and hematuria are all potential signs of ovarian cancer and, in their presence, appropriate investigations, such as pelvic ultrasound, should be performed. Patient education should be designed so that women realize that the onset of such signs should be a prompt to see their doctor.

## PREVENTIVE STRATEGIES

The World Cancer Research Fund (WCRF) and the American Institute of Cancer Research (AICR) have issued recommendations on diet, physical activity, and weight control for cancer prevention[77]. These include (Table 2):

**Table 2** Preventive strategies

| |
|---|
| • Stop smoking |
| • Control weight |
| • Exercise (vigorous exercise for at least 2–3 h/week) |
| • < 15 g/day alcohol intake |
| • Diet rich in vegetables, fibers and fruits (five fruit and vegetables/day but only two fruits, maximum three), low intake of animal fat, and a low proportion of carbohydrates |

(1) Stopping smoking which can decrease the risk of dying from cancer by more than 20%.

(2) Controlling alcohol intake. Low-risk women are advised to limit daily alcohol intake to no more than 15 g/day whilst a more restrictive policy is recommended for women at high risk of breast, colon or endometrial cancer[78].
(3) Vigorous exercise for at least 2–3 h/week has been shown to decrease most cancers and to help decrease body mass index and insulin resistance. The mechanisms that account for the inhibitory effects of physical activity on the carcinogenic process are reduced effects of insulin and insulin-like growth factors, reduced free radical generation, modulation of the immune process and a direct effect on the tumor[79]. In addition, physical activity increases gut motility[24] and can help to decrease breast cancer incidence[80].
(4) A healthy diet combining intake of fruits, fibers and vegetables, low intake of animal fat, and a low proportion of carbohydrates with a high glycemic index load can help to decrease the burden of many diseases. Diet strongly influences the risk of colorectal, breast and endometrial cancers; changes in food habits might reduce up to 70% of the colon cancer burden[24].

Application of the WCRF and AICR recommendations was evaluated in the EPIC study[81]. Using the recommended limits for consumption of red and processed meats (red meat ≤ 500 g/week and processed meat ≤ 3 g/day), alcohol (≤ 10 g/day), fruits and vegetables (≥ 400 g/day) and dietary fiber (≥ 25 g/day), for physical activity (2 h/week of vigorous physical activity, or 30 min/day of cycling/sports) and normal body mass index (BMI, 18.5–24.9 $kg/m^2$), a scoring system was devised with a range of 0–6 for men and 0–7 for women, where higher scores indicated greater concordance with the recommendations. Overall, a one-point increment in the score was associated with a 5% (95% confidence interval (CI) 3–7%) lower risk of developing any cancer. The risk reduction in participants with higher categories of the score compared with those within the first category was 16% for breast cancer, 27% for colorectal cancer, 14% for lung cancer, and 23% for endometrial cancer ($p$-trend = 0.05). Higher scores were not significantly associated with lower risk of ovarian cancer. Overall, 12.6% (95% CI 3.6–21.4%) of all cancers could have been prevented in the whole study population[81]. Interestingly, there was a positive association between a high level of education and a high score. The association between a higher score and a potential reduction in cancer mortality was significant in the UK, Italy and Denmark for women. It is noteworthy that the volunteers participating in the EPIC study were more likely to be healthier than the general population and thus the benefits of lifestyle could be underestimated in this European study[81]. The WCRF/AICR have estimated that appropriate attention to diet, nutrition, physical activity

plus normalization of BMI may lead to a reduction of all cancer by 26% (6–42%) in the UK, 24% (7–40%) in the USA, 19% (3–31%) in Brazil and 20% (5–37%) in China[77].

## WHEN SHOULD WOMEN CONSULT FOR SYMPTOMS?

A systematic follow-up at least once a year by a trained practitioner is recommended for each woman in midlife and beyond. This will allow evaluation of the individual risks for each potential disease associated with aging. In addition, education will be regularly delivered to apply the preventive strategies reported above.
In the meantime, any abnormal symptoms necessitate consultation:

- Abnormal vaginal bleeding, abdominal or pelvic pain, distension, abnormal vaginal discharge, hematuria, or rectorrhagia can reveal an endometrial, ovarian or colon cancer.
- Breast nipple discharge or palpation of a lump, induration of a localized zone of the breast, a skin abnormality on the area of the breasts (skin or nipple retraction, 'peau d'orange') can indicate breast cancer.
- Unusual cough, dyspnea, hemoptysis or thoracic pain can reveal a lung cancer.
- Occurrence of venous thrombosis in women without a family history can reveal a cancer and needs some complementary investigations.

In conclusion, cancer incidence is increasing as a consequence of longer life expectancy in developed and developing countries. National health programs are mandatory to implement screening and to improve individual management. The active correction of modifiable risk factors by motivating women can certainly help to decrease the prevalence and aggressiveness of cancer. Finally, educating women so that they are aware of ways to improve their general health, to minimize their own risk factors and to identify signs of change in their own health which may be markers of impending cancer will help to reduce the burden of disease and may even help to decrease the latency of diagnosis and thus improve the prognosis for tumors detected at an earlier stage, particularly in less developed nations of the world.

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acting as a member of an Advisory Board for Pfizer; by Professor Shapiro for acting as a member of Advisory Boards for Bayer Schering and Merck; by Professor Villaseca for lectures and for acting as a member of an Advisory Board for Glaxo Smith & Kline. Dr Shah and Professor Huang report no conflict of interest.

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## References

1. Anderson BO, Cazap E, El Saghir NS, *et al*. Optimisation of breast cancer management in low-resource and middle-resource countries: executive summary of the Breast Health Global Initiative consensus, 2010. *Lancet Oncol* 2011;12:387–98

2. Regional mortality information system. Regional Health Observatory, Pan American Health Observatory (PAHO), 2011. http://ais.paho.org/phip/viz/mort_chapters_en.asp

3. http://www.healthmetricsandevaluation.org/gbd/visualizations/gbd-2010-patterns-broad-cause-group

4. Lozano R, Naghavi M, Forman K, *et al*. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2095–128

5. http://globocan.iarc.fr/ Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v2.0, *Cancer Incidence and Mortality Worldwide*: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010

6. World Health Organization, mortality database.
http://www.who.int/healthinfo/statistics/mortality_rawdata/en/index.html

7. Forouzanfar MH, Forman KJ, Delossantos AM, *et al*. Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis. *Lancet* 2011;378:1461–84

8. Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. *Mayo Clin Proc* 2008;83:584–94

9. Long B, Liu FW, Bristow RE. Disparities in uterine cancer epidemiology, treatment, and survival among African Americans in the United States. *Gynecol Oncol* 2013 May 23; Epub ahead of print

10. Chia KS, Reilly M, Tan CS, *et al.* Profound changes in breast cancer incidence may reflect changes into a Westernized lifestyle: a comparative population-based study in Singapore and Sweden. *Int J Cancer* 2005;113:302–6

11. Lin CH, Chen YC, Chiang CJ, *et al*. The emerging epidemic of estrogen-related cancers in young women in a developing Asian country. *Int J Cancer* 2012;130:2629–37

12. Khokhar A. Breast cancer in India: where do we stand and where do we go? *Asian Pac J Cancer Prev* 2012;13:4861–6

13. Huo D, Ikpatt F, Khramtsov A, *et al*. Population differences in breast cancer: survey in indigenous African women reveals over-representation of triple-negative breast cancer. *J Clin Oncol* 2009;27:4515–21

14. Yip CH, Taib NA, Mohamed I. Epidemiology of breast cancer in Malaysia. *Asian Pac J Cancer Prev* 2006;7:369–4

15. Su Y, Zheng Y, Zheng W, *et al.* Distinct distribution and prognostic significance of molecular subtypes of breast cancer in Chinese women: a population-based cohort study. *BMC Cancer* 2011;11:292

16. Ly M, Antoine M, Andre F, *et al*. [Breast cancer in Sub-Saharan African women: review]. *Bull Cancer* 2011;98:797–806

17. Tay SK, Ngan HY, Chu TY, Cheung AN, Tay EH. Epidemiology of human papillomavirus infection and cervical cancer and future perspectives in Hong Kong, Singapore and Taiwan. *Vaccine* 2008;26(Suppl 12):M60–70

18. Domingo EJ, Noviani R, Noor MR, *et al*. Epidemiology and prevention of cervical cancer in Indonesia, Malaysia, the Philippines, Thailand and Vietnam. *Vaccine* 2008;265:M71–9

19. Bailie R. The epidemiological basis for cervical cancer screening. *S Afr Med J* 1995;85:8–10

20. Department of Health, Medical Research Council, OrcMacro. *South African Demographic and Health Survey 2003*. Pretoria: Department of Health, 2007

21. Travis WD, Brambilla E, Noquchi M, *et al*. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of lung adenocarcinoma. *J Thorac Oncol* 2011;6:244–85

22. Lee PN, Forey BA. Indirectly estimated absolute lung cancer mortality rates by smoking status and histological type based on a systematic review. *BMC Cancer* 2013;13:189

23. Yano T, HJaro A, Shikada Y, *et al*. Non-small cell lung cancer in never smokers as a representative 'non-smoking-associated lung cancer': epidemiology and clinical features. *Int J Clin Oncol* 2011;16:287–93

24. Haggar FA, Boushey RP. Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. *Clin Colon Rectal Surg* 2009;22:191–7

25. Garborg K, Holme O, Loberg M, *et al.* Current status of screening for colorectal cancer. *Ann Oncol* 2013;24:1963–72

26. Geier AS, Wellmann J, Wellmann I, *et al*. Cancer detection rates following enrolment in a disease management programme for type 2 diabetes. *Diabetologia* 2013 May 31; Epub ahead of print

27. Zendehdel K, Nyran O, Ostenson CG, *et al*. Cancer incidence in patients with type 1 diabetes mellitus: a population-based cohort study in Sweden. *J Natl Cancer Inst* 2003;95:1797–800

28. Torres ML, Weaver AL, Kumar S, *et al*. Risk factors for developing endometrial cancer after benign endometrial sampling. *Obstet Gynecol* 2012;120:998–1004

29. Chornokur G, Amankwah EK, Schildkraut JM, Phelan CM. Global ovarian cancer health disparities. *Gynecol Oncol* 2013;129:258–64

30. Lim SS, Vos T, Flaxman AD, *et al*. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2224–60

31. Gao CM, Ding JH, Li SP, *et al*. Active and passive smoking, and alcohol drinking and breast cancer risk in chinese women. *Asian Pac J Cancer Prev* 2013;14:993–6

32. Golzarand M, Mirmiran P, Jessri M, *et al.* Dietary trends in the Middle East and North Africa: an ecological study (1961 to 2007). *Public Health Nutr* 2012;15:1835–44

33. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. *JAMA* 2012;307:491–7

34. Garg C, Khan SA, Ansari SH, Garg M. Prevalence of obesity in Indian women. *Obes Rev* 2010;11:105–8

35. Gupta R, Deedwania PC, Achari V, *et al*. Normotension, prehypertension, and hypertension in urban middle-class subjects in India: prevalence, awareness, treatment, and control. *Am J Hypertens* 2013;26:83–94

36. Nidhi R, Padmalatha V, Nagarathna R, Amritanshu R. Prevalence of polycystic ovarian syndrome in Indian adolescents. *J Pediatr Adolesc Gynecol* 2011;24:223–7

37. Chang Y, Schechter CB, van Ravesteyn NT, *et al.* Collaborative modeling of the impact of obesity on race-specific breast cancer incidence and mortality. *Breast Cancer Res Treat* 2012;136:823–35

38. Pichard C, Plu-Bureau G, Neves-E-Castro M, Gompel A. Insulin resistance, obesity and breast cancer risk. *Maturitas* 2008;60:19–30

39. Ogundiran TO, Huo D, Adenipekun A, *et al*. Body fat distribution and breast cancer risk: findings from the Nigerian breast cancer study. *Cancer Causes Control* 2012;23:565–74

40. Protani M, Coory M, Martin JH. Effect of obesity on survival of women with breast cancer: systematic review and meta-analysis. *Breast Cancer Res Treat* 2010;123:627–35

41. Larsson S, Wolk A. Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies. *Am J Clin Nutr* 2007;86:556–65

42. Pischon T, Lahmann PH, Boeing H, et al. Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *J Natl Cancer Inst* 2006;98:920–31

43. Morrison DS, Parr CL, Lam TH, *et al.* Behavioural and metabolic risk factors for mortality from colon and rectum cancer: analysis of data from the Asia-pacific cohort studies collaboration. *Asian Pac J Cancer Prev* 2013;14:1083–7

44. Arem H, Park Y, Pelser C, *et al*. Prediagnosis body mass index, physical activity, and mortality in endometrial cancer patients. *J Natl Cancer Inst* 2013;105:342–9

45. Suzuki R, Ye W, Rylander-Rudqvist T, *et al*. Alcohol and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status: a prospective cohort study. *J Natl Cancer Inst* 2005;97:1601–8

46. Minami Y, Tsubono Y, Nishino Y, *et al.* The increase of female breast cancer incidence in Japan: emergence of birth cohort effect. *Int J Cancer* 2004;108:901–6

47. Minami Y, Nishino Y, Tsubono Y, *et al.* Increase of colon and rectal cancer incidence rates in Japan: trends in incidence rates in Miyagi Prefecture, 1959-1997. *J Epidemiol* 2006;16:240–8

48. Mizoue T, Tanaka K, Tsuji I, *et al*. Alcohol drinking and colorectal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol* 2006;36:582–97

49. Tavani A, La Vecchia C. Coffee, decaffeinated coffee, tea and cancer of the colon and rectum: a review of epidemiological studies, 1990-2003. *Cancer Causes Control* 2004;15:743–57

50. Li G, Ma D, Zhang Y, *et al.* Coffee consumption and risk of colorectal cancer: a meta-analysis of observational studies. *Public Health Nutr* 2013;16:346–57

51. Calle EE, Frumkin H, Henley SJ, *et al.* Organochlorines and breast cancer risk. *CA Cancer J Clin* 2002;52:301–9

52. Bjerkaas E, Parajuli R, Weiderpass E, *et al*. Smoking duration before first childbirth: An emerging risk factor for breast cancer? Results from 302,865 Norwegian women. *Cancer Causes Control* 2013;24:1347–56

53. Kaushal M, Mishra AK, Sharma J, *et al*. Genomic alterations in breast cancer patients in betel quid and non betel quid chewers. *PLoS One* 2012;7:e43789

54. Brinton LA, Felix AS. Menopausal hormone therapy and risk of endometrial cancer. *J Steroid Biochem Mol Biol* 2013 May 13; Epub ahead of print

55. Wartko P, Sherman ME, Yang HP, *et al*. Recent changes in endometrial cancer trends among menopausal-age US women. *Cancer Epidemiol* 2013;37:374–7

56. Rice MS, Murphy MA, Tworoger SS. Tubal ligation, hysterectomy and ovarian cancer: A meta-analysis. *J Ovarian Res* 2012;5:13

57. Melin AS, Lundholm C, Malki N, *et al.* Hormonal and surgical treatments for endometriosis and risk of epithelial ovarian cancer. *Acta Obstet Gynecol Scand* 2013;92:546–54

58. Rossouw JE, Anderson GL, Prentice RL, *et al*. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321–33

59. Lobo RA. Where are we 10 years after the Women's Health Initiative? *J Clin Endocrinol Metab* 2013;98:1771–80

60. Fenton A, Panay N. The Women's Health Initiative – a decade of progress. *Climacteric* 2012;15:205–94

61. Tehard B, Friedenreich CM, Oppert JM, Clavel-Chapelon F. Effect of physical activity on women at increased risk of breast cancer: results from the E3N cohort study. *Cancer Epidemiol Biomarkers Prev* 2006;15:57–64

62. Yang HP, Anderson WF, Rosenberg PS, *et al*. Ovarian cancer incidence trends in relation to changing patterns of menopausal hormone therapy use in the United States. *J Clin Oncol* 2013;31:2146–51

63. Gompel A, Santen RJ. Hormone therapy and breast cancer risk 10 years after the WHI. *Climacteric* 2012;15:241–9

64. Anderson GL, Chlebowski RT, Araqaki AK, *et al*. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. *Lancet Oncol* 2012;13:476–86

65. Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. *Breast Cancer Res Treat* 2008;107:103–11

66. Chlebowski RT, Anderson GL, Manson JE, *et al*. Lung cancer among postmenopausal women treated with estrogen alone in the Women's Health Initiative randomized trial. *J Natl Cancer Inst* 2010;102:1413–21

67. Chlebowski RT, Schwartz AG, Wakelee H, *et al*. Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled trial. *Lancet* 2009;374:1243–51

68. Brinton LA, Gierach GL, Andaya A, *et al*. Reproductive and hormonal factors and lung cancer risk in the NIH-AARP Diet and Health Study cohort. *Cancer Epidemiol Biomarkers Prev* 2011;20:900–11

69. Gallagher LG, Rosenblatt KA, Ray RM, *et al.* Reproductive factors and risk of lung cancer in female textile workers in Shanghai, China. *Cancer Causes Control* 2013;24:1305–14

70. http://www.cancerscreening.gov.au

71. http://www.nsu.govt.nz

72. WHO 2008–2013 Action Plan for the Global Strategy for the Prevention and Control of Noncommunicable Diseases. Geneva: World Health Organization, 2008

73. World Health Organization. Cervical cancer screening in developing countries: report of a WHO consultation. Geneva: World Health Organization, 2002

74. Hoffman M, Cooper D, Carara H, *et al*. Limited Pap screening associated with reduced risk of cervical cancer in South Africa. *Int J Epidemiol* 2003;32:573–7

75. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. *Cochrane Database Syst Rev* 2007(1):CD001216

76. Hippisley-Cox J, Coupland C. Symptoms and risk factors to identify women with suspected cancer in primary care: derivation and validation of an algorithm. *Br J Gen Pract* 2013;63:11–21

77. World Cancer Research Fund/American Institute for Cancer Research. Policy and action for cancer prevention. In *Food, Nutrition and Physical Activity: a Global Perspective*. Washington DC: AICR, 2009

78. Poli A, Marangoni F, Avogaro A, *et al*. *Moderate alcohol use and health: A consensus document. Nutr Metab Cardiovasc Dis* 2013 ;23:487–504

79. Fair AM, Montgomery K. Energy balance, physical activity, and cancer risk. *Methods Mol Biol* 2009;472:57–88

80. Steindorf K, Ritte R, Eomois PP, *et al*. Physical activity and risk of breast cancer overall and by hormone receptor status: the European prospective investigation into cancer and nutrition. *Int J Cancer* 2013;132:1667–78

81. Romaguera D, Vergnaud AC, Peeters PH, *et al*. Is concordance with World Cancer Research Fund/American Institute for Cancer Research guidelines for cancer prevention related to subsequent risk of cancer? Results from the EPIC study. *Am J Clin Nutr* 2012;96:150–63

**Figure 1** Breast cancer incidence and mortality rates as age-standardized rate adjusted to the world standard population (ASR (W)) per 100,000 women in seven main regions of the world (from Globocan 2008[5]). M/I, mortality to incidence ratio in percent

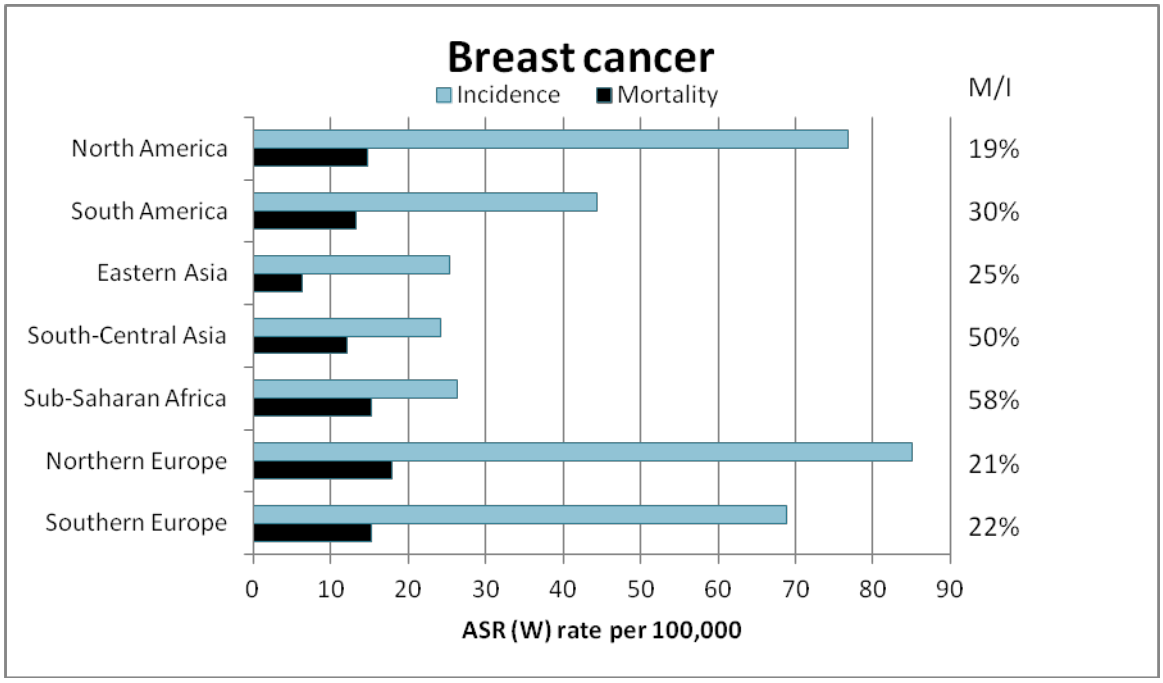


**Figure 2** Lung cancer incidence and mortality rates as age-standardized rate adjusted to the world standard population (ASR (W)) per 100,000 women in seven main regions of the world (from Globocan 2008[5]). M/I, mortality to incidence ratio in percent

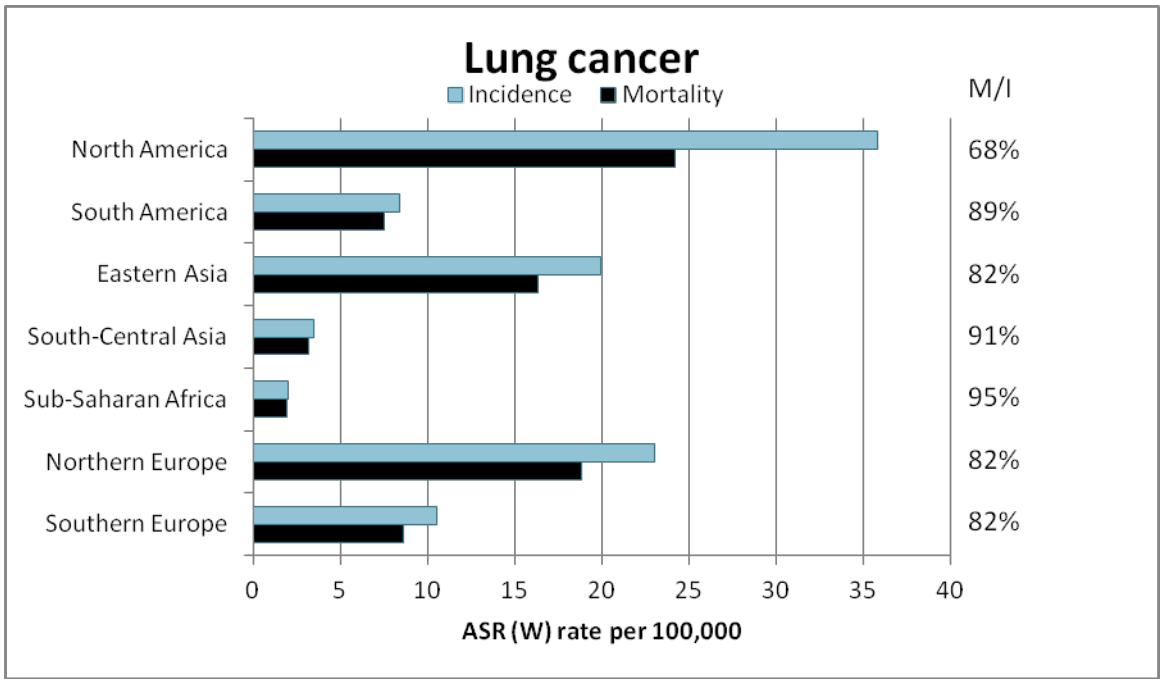


**Figure 3** Colorectal cancer incidence and mortality rates as age-standardized rate adjusted to the world standard population (ASR (W)) per 100,000 women in seven main regions of the world (from Globocan 2008[5]). M/I, mortality to incidence ratio in percent

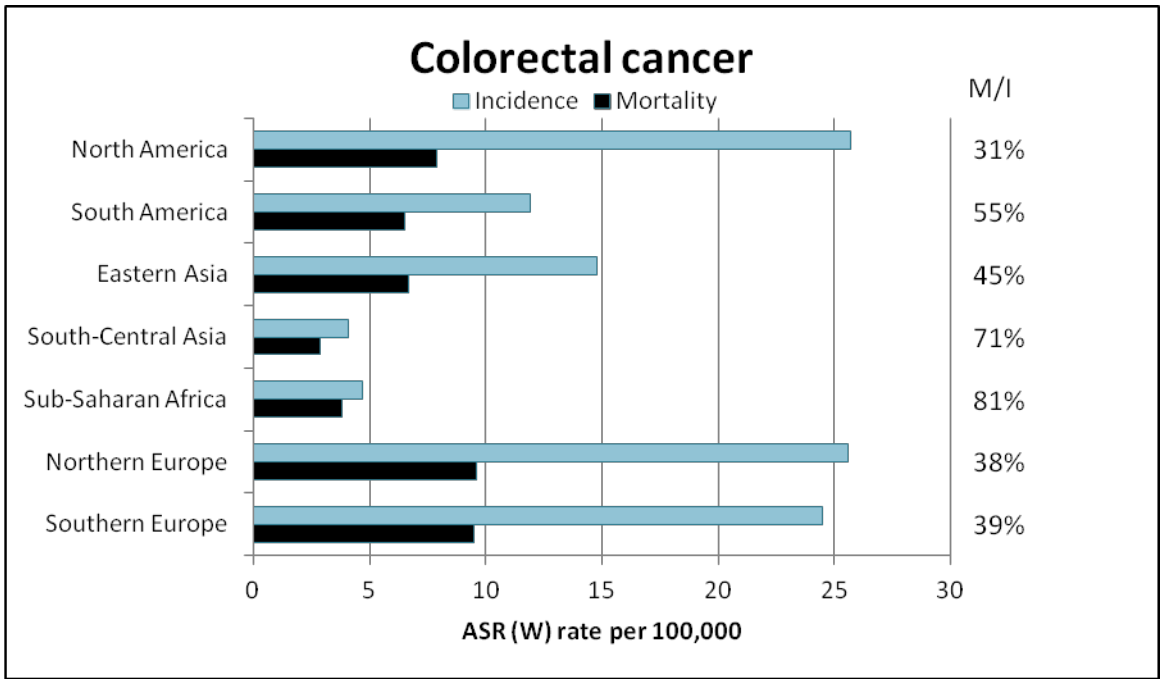


**Figure 4** Cervical cancer incidence and mortality rates as age-standardized rate adjusted to the world standard population (ASR (W)) per 100,000 women in seven main regions of the world (from Globocan 2008[5]). M/I, mortality to incidence ratio in percent

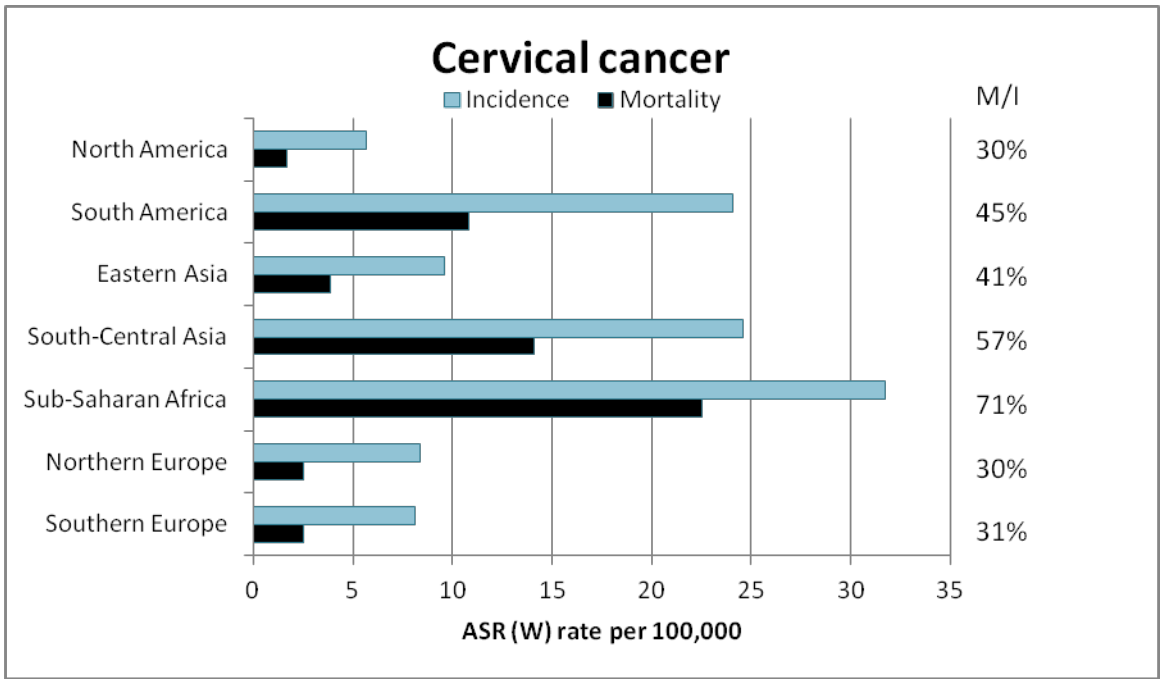


**Figure 5** Endometrial cancer incidence and mortality rates as age-standardized rate adjusted to the world standard population (ASR (W)) per 100,000 women in seven main regions of the world (from Globocan 2008[5]). M/I, mortality to incidence ratio in percent

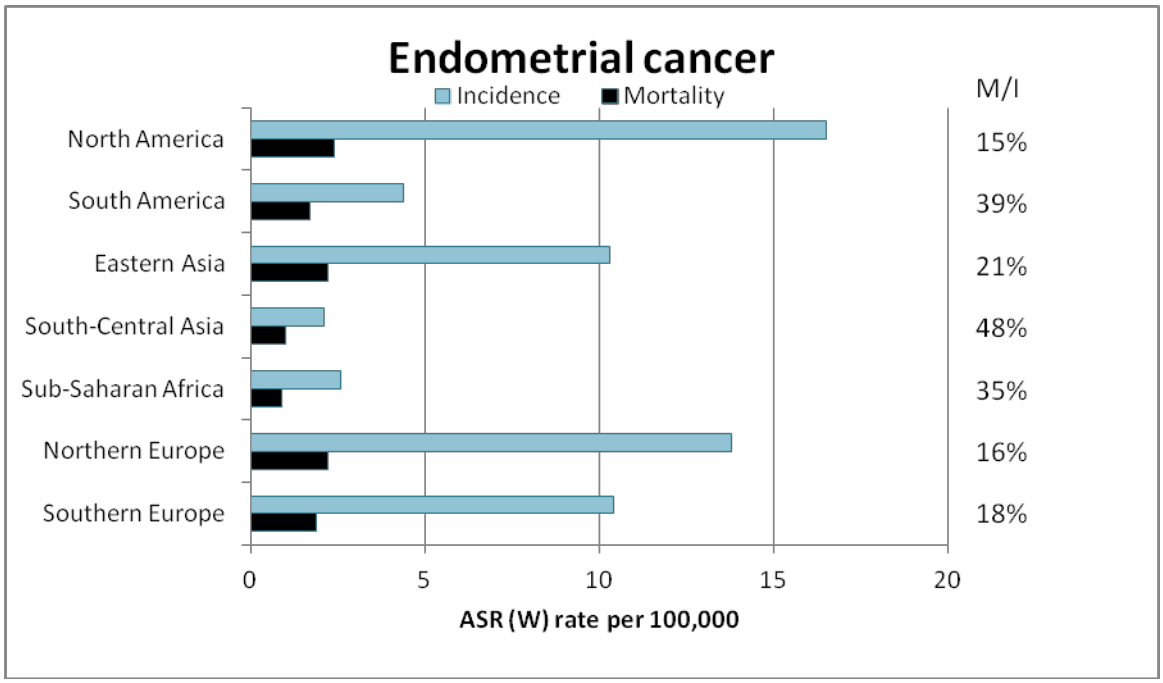
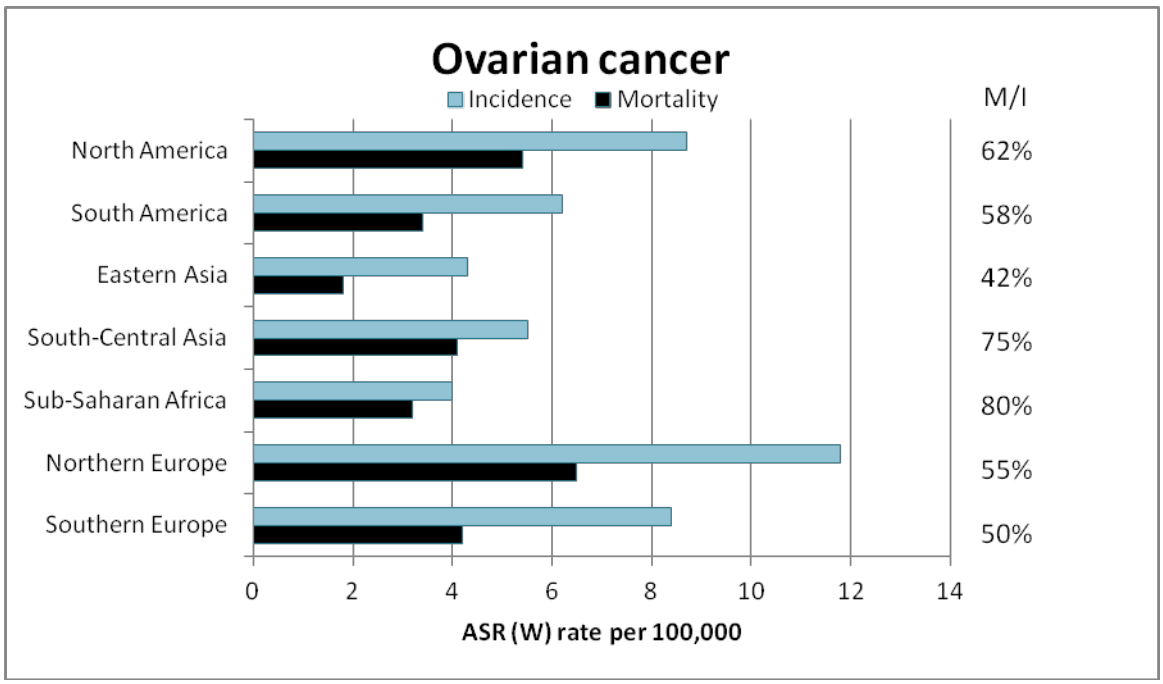
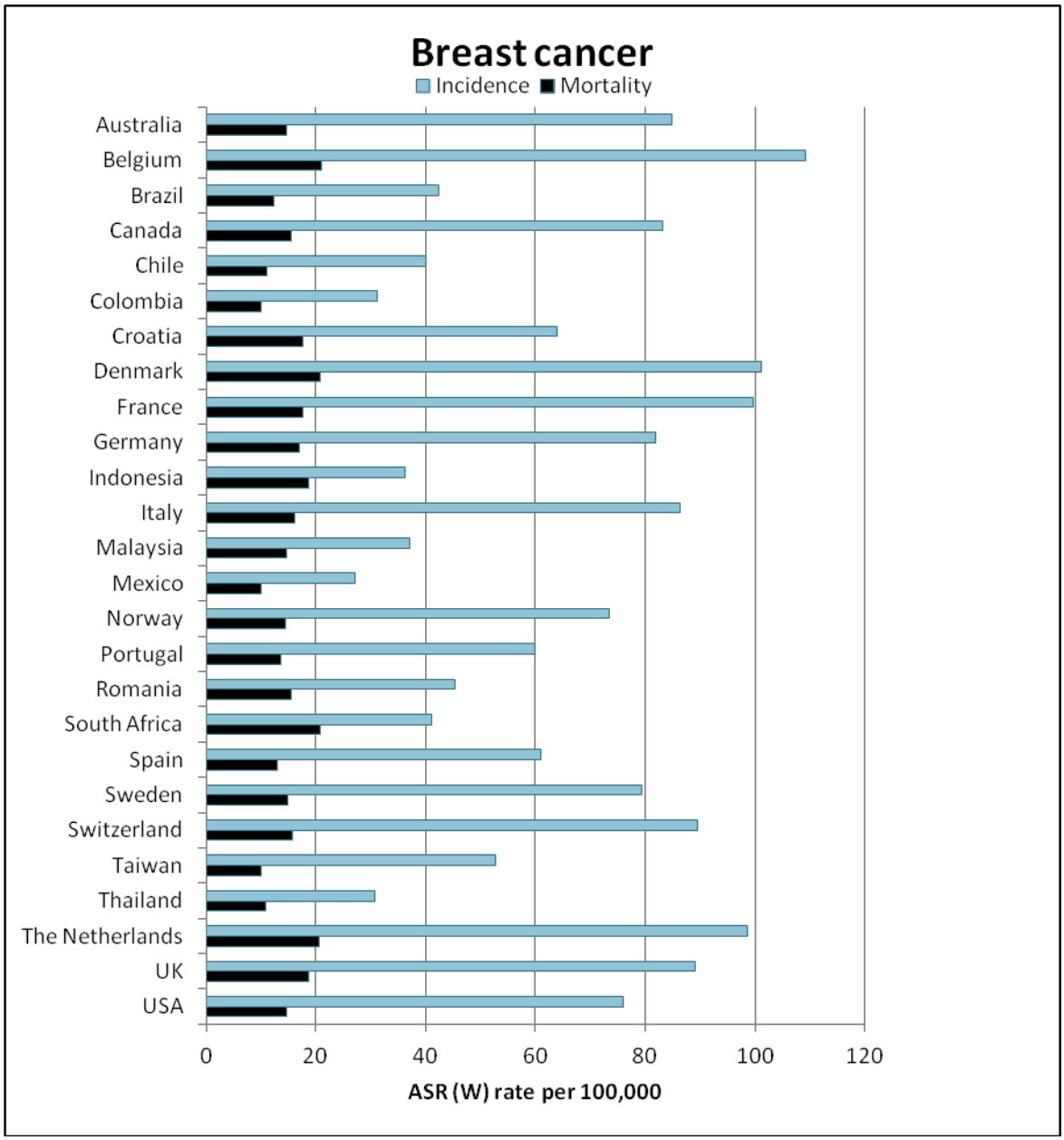


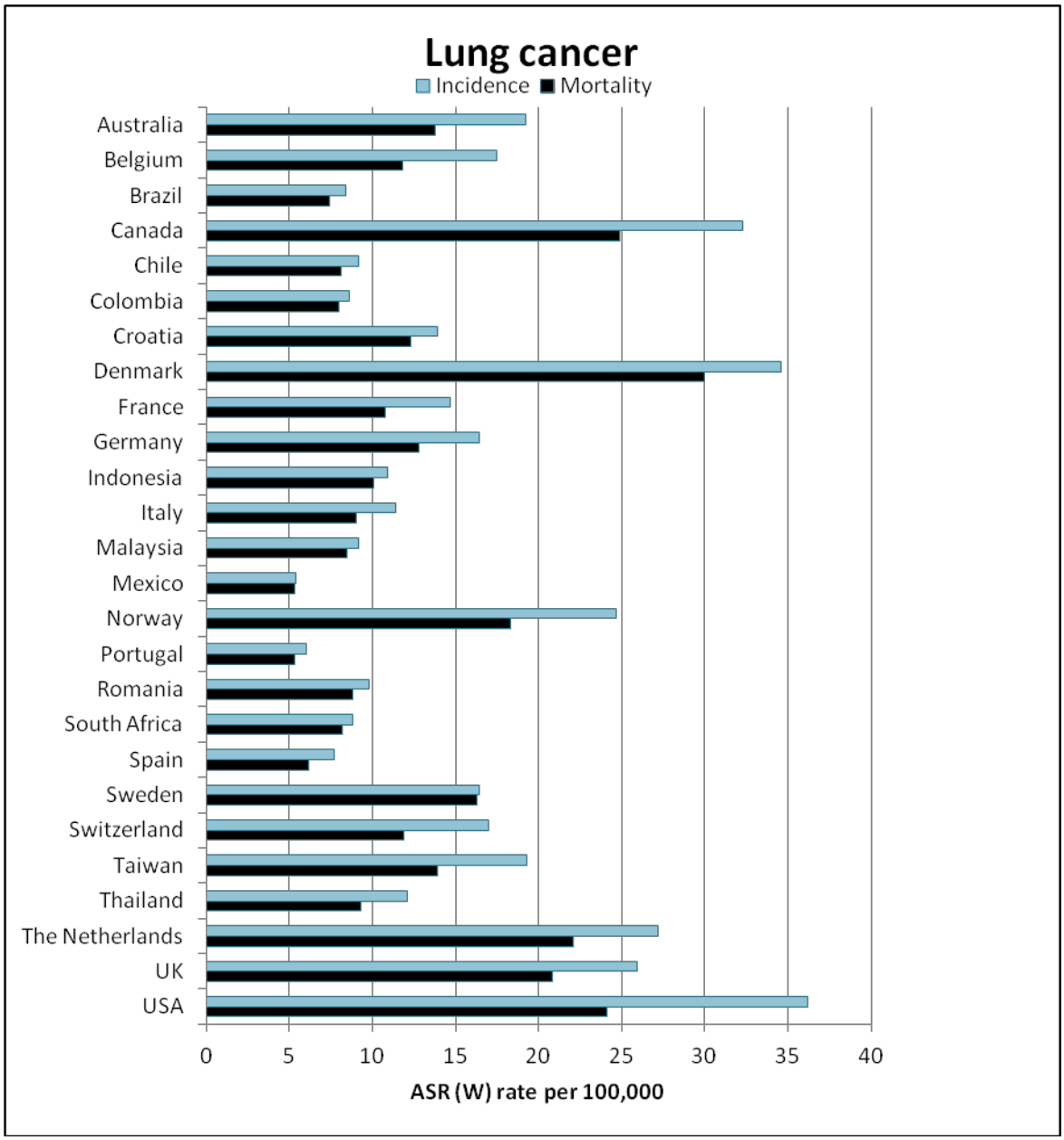
**Figure 6** Ovarian cancer incidence and mortality rates as age-standardized rate adjusted to the world standard population (ASR (W)) per 100,000 women in seven main regions of the world (from Globocan 2008[5]). M/I, mortality to incidence ratio in percent



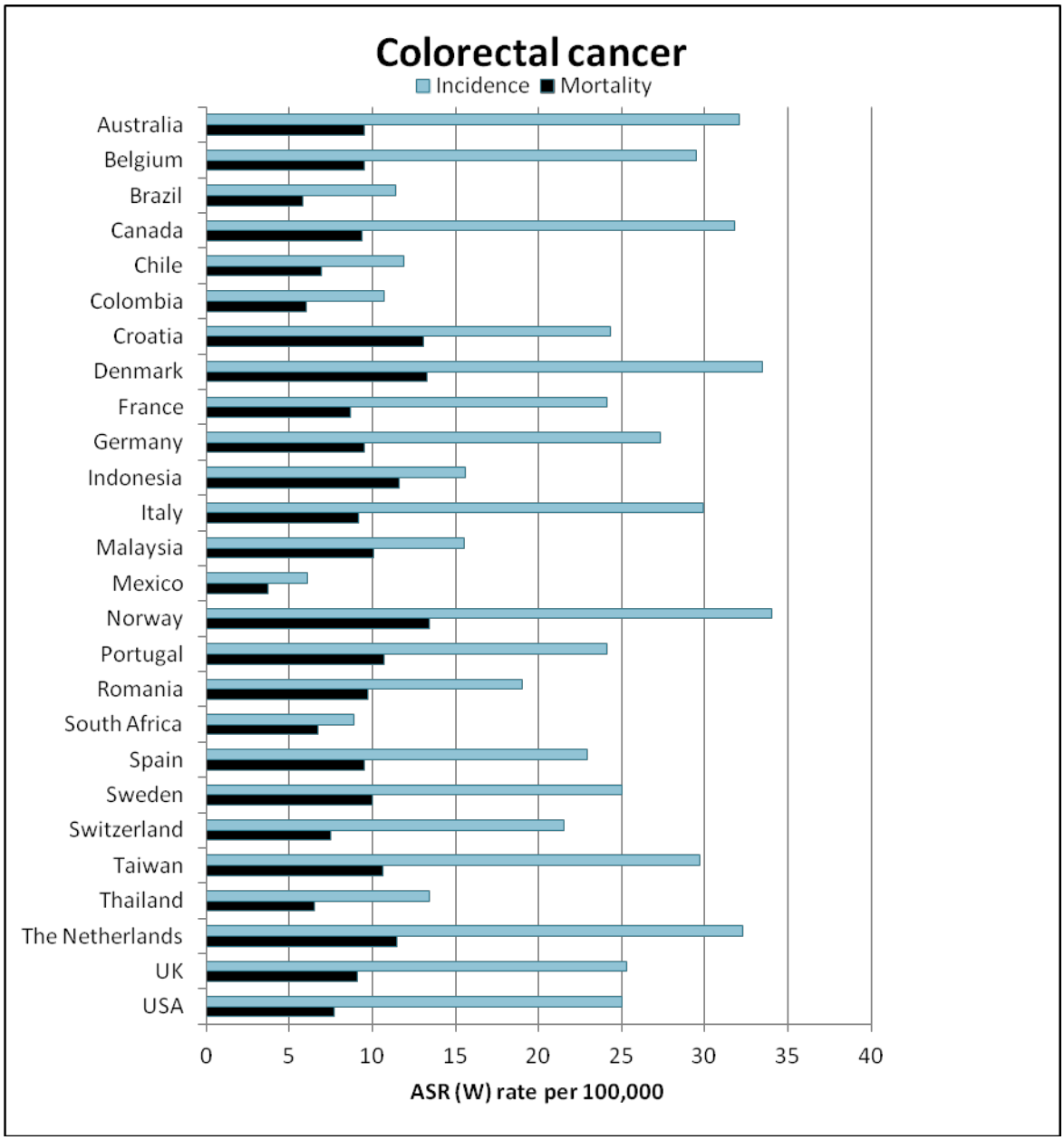
**Supplementary Figure 1** Breast cancer incidence and mortality rates as age-standardized rate adjusted to the world standard population (ASR (W)) per 100,000 women in different countries (from Globocan 2008[5])



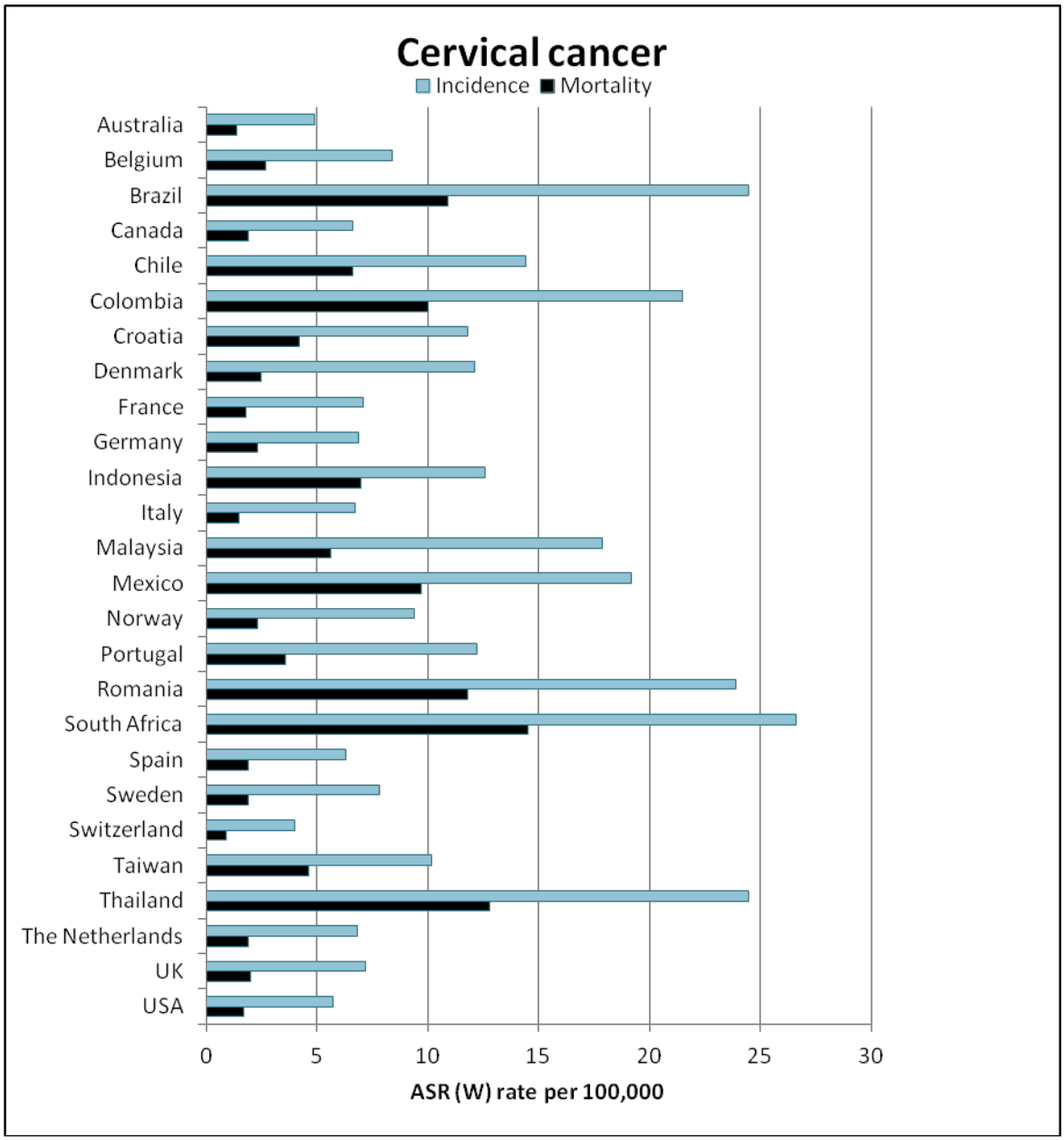
**Supplementary Figure 2** Lung cancer incidence and mortality rates as age-standardized rate adjusted to the world standard population (ASR (W)) per 100,000 women in different countries (from Globocan 2008[5])



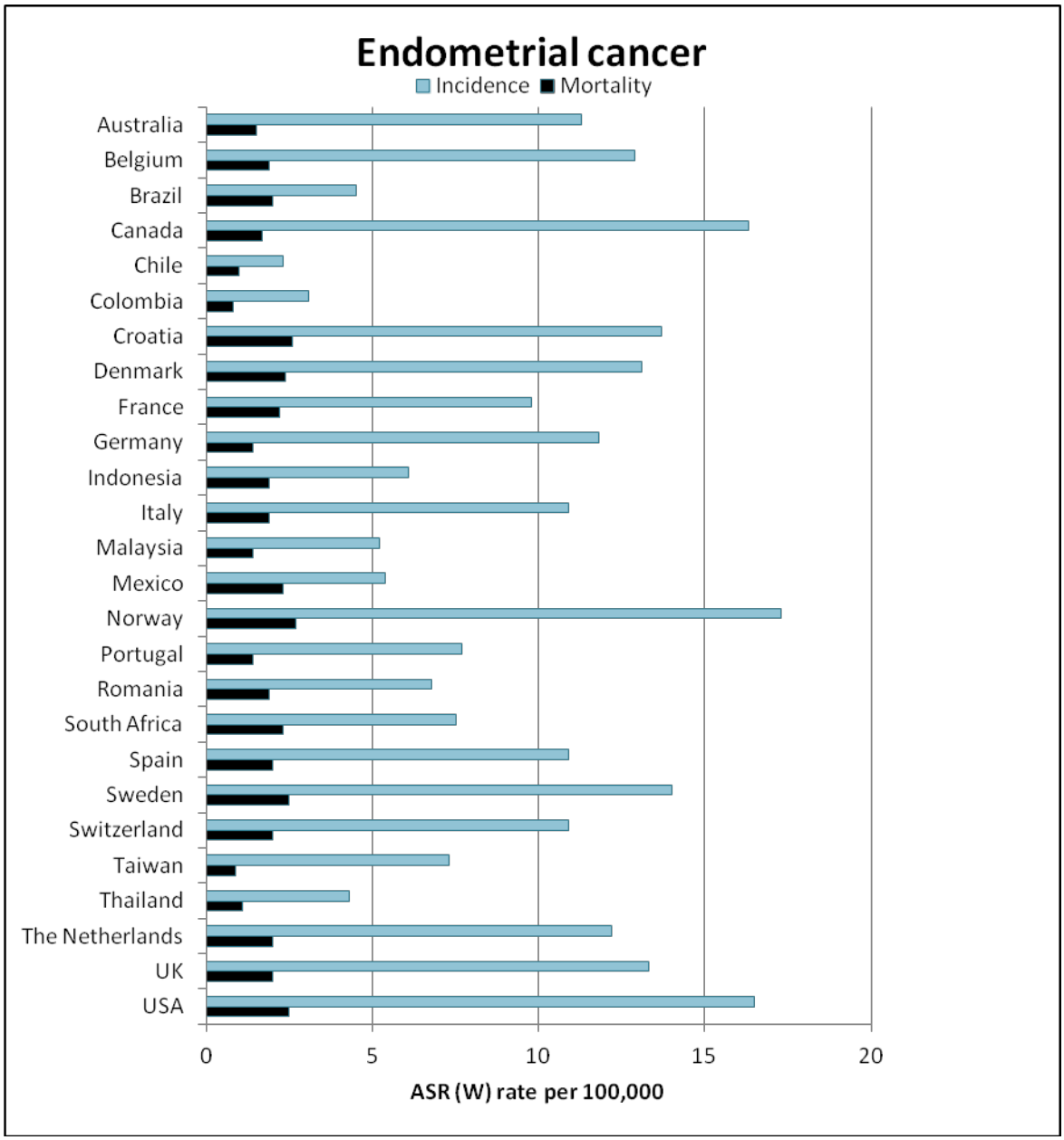
**Supplementary Figure 3** Colorectal cancer incidence and mortality rates as age-standardized rate adjusted to the world standard population (ASR (W)) per 100,000 women in different countries (from Globocan 2008[5])



**Supplementary Figure 4** Cervical cancer incidence and mortality rates as age-standardized rate adjusted to the world standard population (ASR (W)) per 100,000 women in different countries (from Globocan 2008[5])



**Supplementary Figure 5** Endometrial cancer incidence and mortality rates as age-standardized rate adjusted to the world standard population (ASR (W)) per 100,000 women in different countries (from Globocan 2008[5])



**Supplementary Figure 6** Ovarian cancer incidence and mortality rates as age-standardized rate adjusted to the world standard population (ASR (W)) per 100.000 women in different countries (from Globocan 2008[5])