Chapter 5

Epidemiology of Hormone-Associated Cancers as a Reflection of Age

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Abstract

In this chapter we review the epidemiology of hormone-associated cancers (prostate, breast, endometrial, ovarian, pancreatic and thyroid) paying special attention to the variability in the age patterns of cancer incidence rate over populations and time periods. We emphasize the comparative analysis of the age specific incidence rate curves as a valuable source of hypotheses about factors influencing cancer risks in populations in addition to the analysis of the age-adjusted rates.

Introduction

Incidence rates of cancer dramatically increased during the 20th century in the US and globally for all sites combined. According to SEER (The Surveillance, Epidemiology and End Results) program data for 2002-2004, cancer is currently the most common (together with heart disease) adult disorder in the US with the life-time risk approaching 45% in men and 38% in women.[1] Over 22 million people in the world were cancer patients in 2003.[2] The global cancer burden is higher in more developed countries and has increased over time.[2-4] This increase in affluent societies refers to three major causes: population aging, an increase in age-specific cancer incidence rates, particularly at old ages, and an improvement in survival of cancer patients. Among these reasons, the increase in incidence rates is the only factor that could potentially be controlled through the cancer prevention. Understanding factors that are responsible for epidemiological trends in cancer incidence rates is, therefore, of great importance for fostering development of successful cancer prophylactics and decreasing the global cancer burden.

In this chapter we overview typical age patterns, place differences and time trends in the incidence and survival rates for selected hormone-associated cancers, including male prostate, female breast, endometrial and ovarian cancers, pancreatic and thyroid cancers for both sexes. Among those, cancers of the breast and prostate are currently among four most common cancer sites (two others are tumors of the lung and colon) in developed regions of the world, mainly responsible for the higher cancer rates in these regions (Fig. 1).

Specifically, we will concentrate on the age patterns of cancer incidence rate and their variability over populations and time periods. This is because comparing the age specific incidence rate curves often provides more information than it can be extracted from the analyses of the age-adjusted rates alone and is a valuable source of additional hypotheses about causative factors of the observed cancer trends. For instance, a simple look on the age patterns of incidence rates for endometrial and ovarian cancers at different periods of time let us suggest that recent declines

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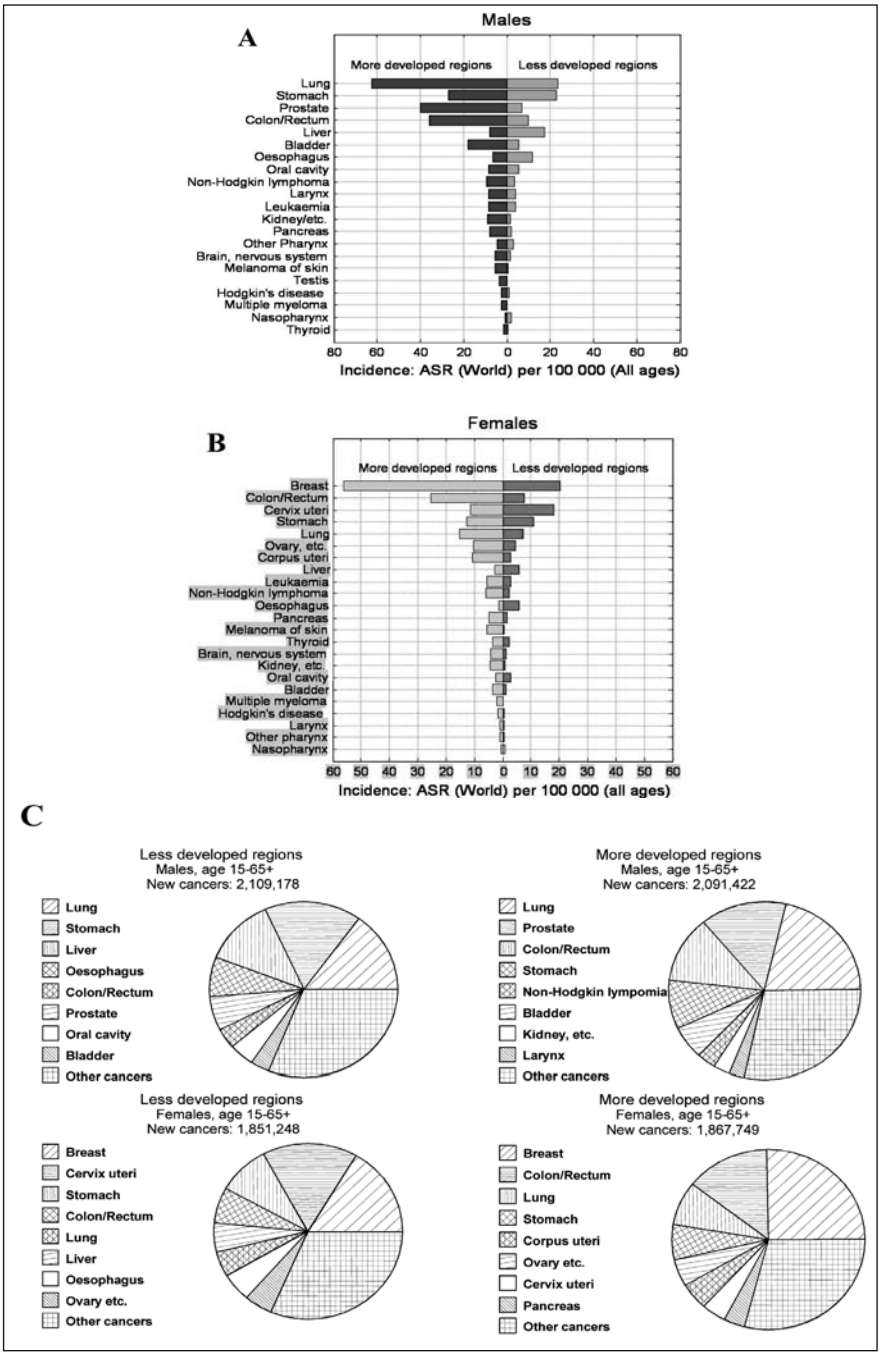

Figure 1. A, B) Age-standardized incidence rates for separate cancer sites in more and less developed regions, by sex. C) Most common adult cancers in more and less developed regions, by sex (GLOBOCAN 1998).[41]

in the age-adjusted rates of these cancers (that seemed consistent) have been driven by fairly different factors (will be discussed below).

Data Sources and Basic Definitions

In this review, we used the data extracted from cancer registries and published by the International Agency for Research on Cancer (IARC), part of the WHO, in the book series Cancer Incidence in Five Continents,[5-7] covering over 200 populations worldwide for the years 1957-2000 and in the monograph series IARC Monographs on the Evaluation of Carcinogenic Risks to Humans.[8,9] We also used statistics on cancer incidence and survival from the National Cancer Institute (NCI) SEER (The Surveillance, Epidemiology and End Results) program[1,10] collecting data from population-based cancer registries covering approximately 26 percent of the US population, as well as from other recognized sources.

The following basic definitions are used in this review. The age-specific cancer incidence rate is defined as the number of new cancer cases (registered for the first time) per 100,000 people in a population of a given age in a particular year or time interval. Age-specific cancer mortality rate stands for the number of cancer deaths per 100,000 people in a population of a given age in a particular year or time interval. The 5-year relative survival from cancer refers to the ratio of the observed survival rate for the patient group to the expected survival rate for persons in the general population similar to the patient group with respect to age, sex, race and calendar year of observation. The 5-year relative survival rate is used to estimate the proportion of cancer patients potentially curable. Because over one-half of all cancers occur in persons 65 years of age and over,[5] many of these individuals die of other causes with no evidence of recurrence of their cancer. The relative survival rate is obtained by adjusting observed survival for the normal life expectancy of the general population of the same age and thus it is an estimate of the chance of surviving the effects of cancer. Cancer burden is broadly characterized by a total number or the proportion of individuals with diagnosed cancer (cancer prevalence) living in general population, no matter when the diagnosis has been made.

Typical Age Patterns of Cancer Incidence and Mortality Rates

There is a prevalent opinion that the shape of the incidence rate curve is a characteristic of a cancer site that is relatively independent on environmental carcinogenicity and best attributed to some intrinsic aspects of a cancer development.[11,12] However, a comparison of incidence rate curves for separate cancer sites over different places and time periods reveals that their shapes substantially vary depending not only on cancer site per se, but also on population and year of study.[5,13] The rates may increase accelerating until very old age (85 and above), or increase almost linearly with age, or manifest decelerated increase with a leveling off at the old ages, or have a wave-like pattern with a peak in middle or late life (see figures in the text as examples). Despite all this variability, the age patterns of overall cancer risk (for all sites combined) do have common features, which include: (i) a peak in early childhood; (ii) the lowest rate in youth; (iii) an increase in the rate, starting at the reproductive period and (iv) the deceleration or decline in cancer rates at the old ages (75 and over) (Fig. 2). These features are recurrent over time and place[5] and can be drawn not only from period data but also from cohort data.[13] The overall cancer mortality rate exhibits a peak at the oldest old ages (90 and over) and then declines, which most probably reflects a decline in the cancer incidence rate observed in earlier years. The mortality peak is lower than the respective peak in the incidence rate and shifts towards older ages (Fig. 2).

Studies of random autopsies from older individuals confirmed diminishing overall cancer risk in advanced years of life.[14,15] Animal experiments revealed remarkable similarity of cancer incidence rate patterns in humans and rodent species—in particular, an intriguing deceleration or decline in overall cancer incidence rate at old ages.[16-18] This is significant finding because it suggests that such deceleration/decline is not simply an artifact of the data and it is unlikely to be due to a diagnostic bias. Two explanations of this phenomenon that are in agreement with both human and animal data have been suggested. First, the differential selection in heterogeneous

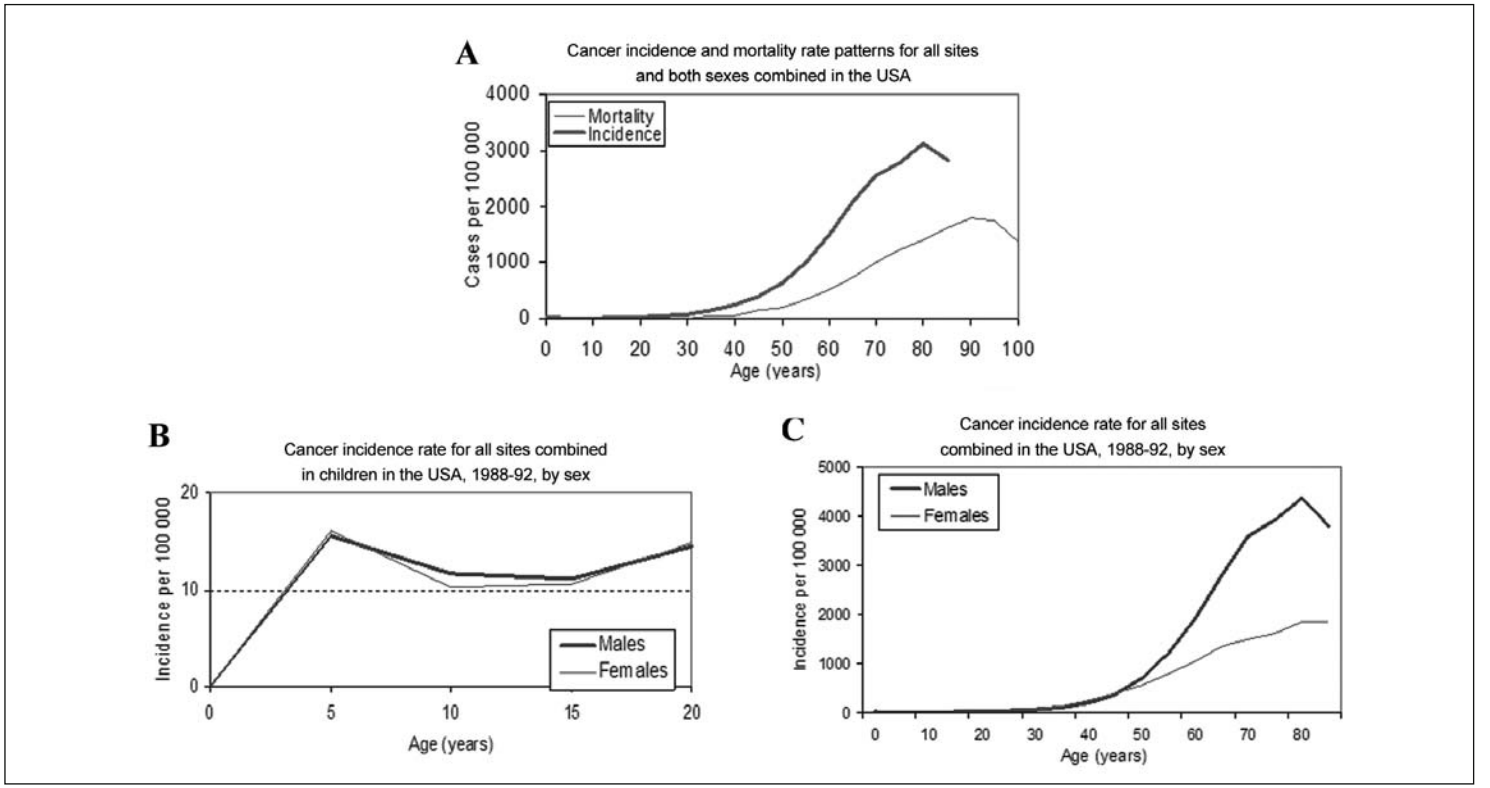

Figure 2. Typical age patterns of overall cancer incidence and mortality rates. Age-specific incidence rates (1988-92), average annual and mortality rate (1990) in the USA (data combined from the sources: IARC, 1997,[6] Health US, 1997,[42] Smith, 1996,[43] Smith, 1999).[44] Figure a is reprinted with permission from: Ukraintseva SV, Yashin AI. Individual aging and cancer risk: How are they related? Demographic Research 2003; 9-8.[21] © 2003 Max-Planck-Gesellschaft.

Table 1. Trends in incidence and patients' survival rates for selected hormone-associated cancers in the US[1,10,40,46]

A. Change in incidence rates between 1950 and 1998 and between 1995 and 2004

Cancer	Change in Incidence Rate 1995-2004 (%)	Change in Incidence Rate 1950-1998 (%)
Prostate	–3	194
Thyroid	53	155
Breast	–8	63
Corpus Uteri	–7	4
Ovary	–13	1
Pancreas	1	14
All cancer sites	–6	60

B. 5-year relative survival rates in 1950 and in 1996-2003

Cancer	5-Year Survival (%) 1996-2003	5-Year Survival (%) 1950
Prostate	99	43
Thyroid	97	80
Breast	90	60
Corpus Uteri	85	72
Ovary	45	30
Pancreas	5	1
All sites	66	35

population may favor the survival of individuals without cancer and increase their share among the elderly that would create the observed decline in the rates.[19] Second, some inherent effects of individual aging may paradoxically oppose cancer development in body and thus contribute to the late deceleration/decline in cancer risk.[17,20,21] For example, the universal decline in rates of basic biological processes in an ageing organism, such as the rates of metabolism and cell proliferation, may contribute to a deceleration of the tumor growth and rates of cancer clinical manifestation at old ages. Metabolic and hormonal changes accompanying ontogenetic transitions in organism (e.g., switching off reproductive function in women) may also play role. Such transitions change the spectrum of internal cancer risk factors, so that it may result in decreasing vulnerability to some cancers (particularly those of female reproductive system, such as ovarian, endometrial and breast cancers) afterwards. For goals of this paper, it is important that the old age decline in cancer risk is a real phenomenon and in case of female hormone associated cancers it could in part be related to the effects of individual aging.[20,21]

Patterns and Trends of Incidence Rates for Hormone Associated Cancers

Prostate Cancer

The age patterns of incidence rate for prostate cancer are typically nonmonotonic with the rate first rapidly increasing during adult life and then declining at the old ages (above 70) (Fig. 3). The low serum testosterone levels as well as elevated estradiol might partially be responsible for the lower risks of prostate cancer in aged men, although results and opinions are not entirely consistent.[22,23]

Both the age-adjusted and age-specific rates of prostate cancer are substantially higher in more developed regions compared to less developed ones (Figs. 1, 3). The rates increased rapidly during

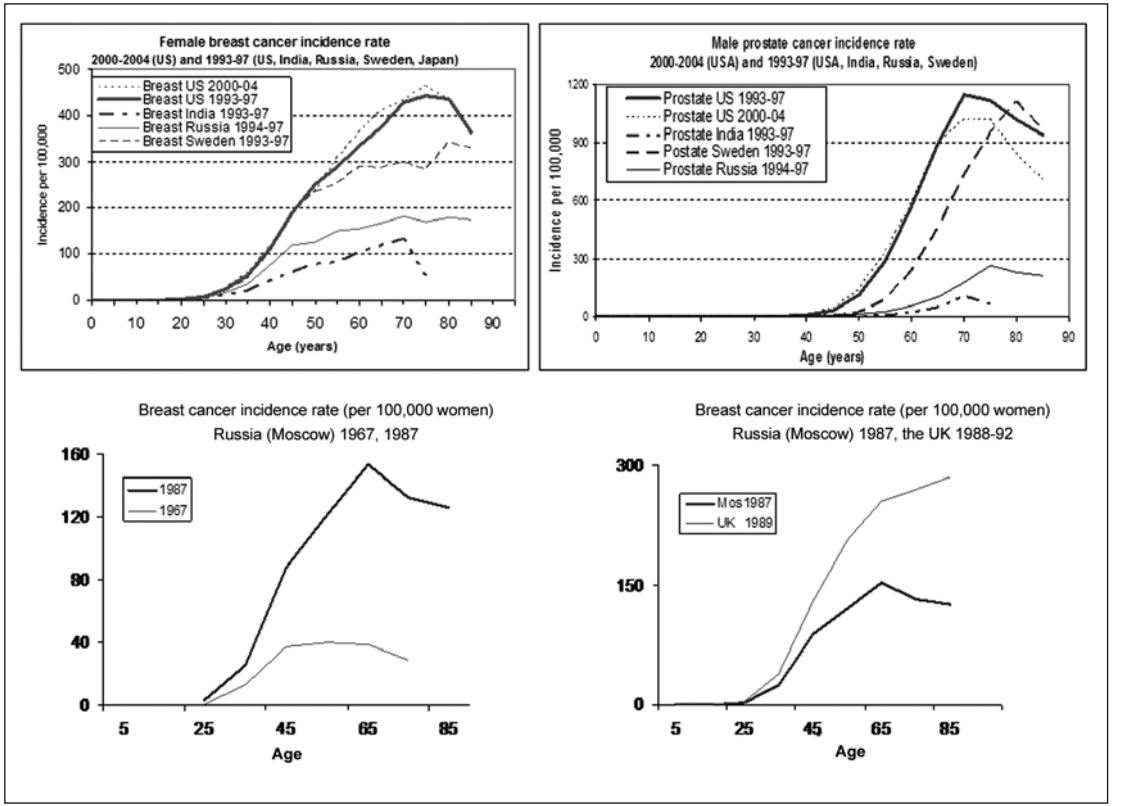

Figure 3. Time and place differences in the age-patterns of incidence rates (average annual) for female breast and male prostate cancers (Aksel and Dvoirin 1991[45]; IARC 1997,[6] IARC 2002[7]; Ries et al 2007[1]).

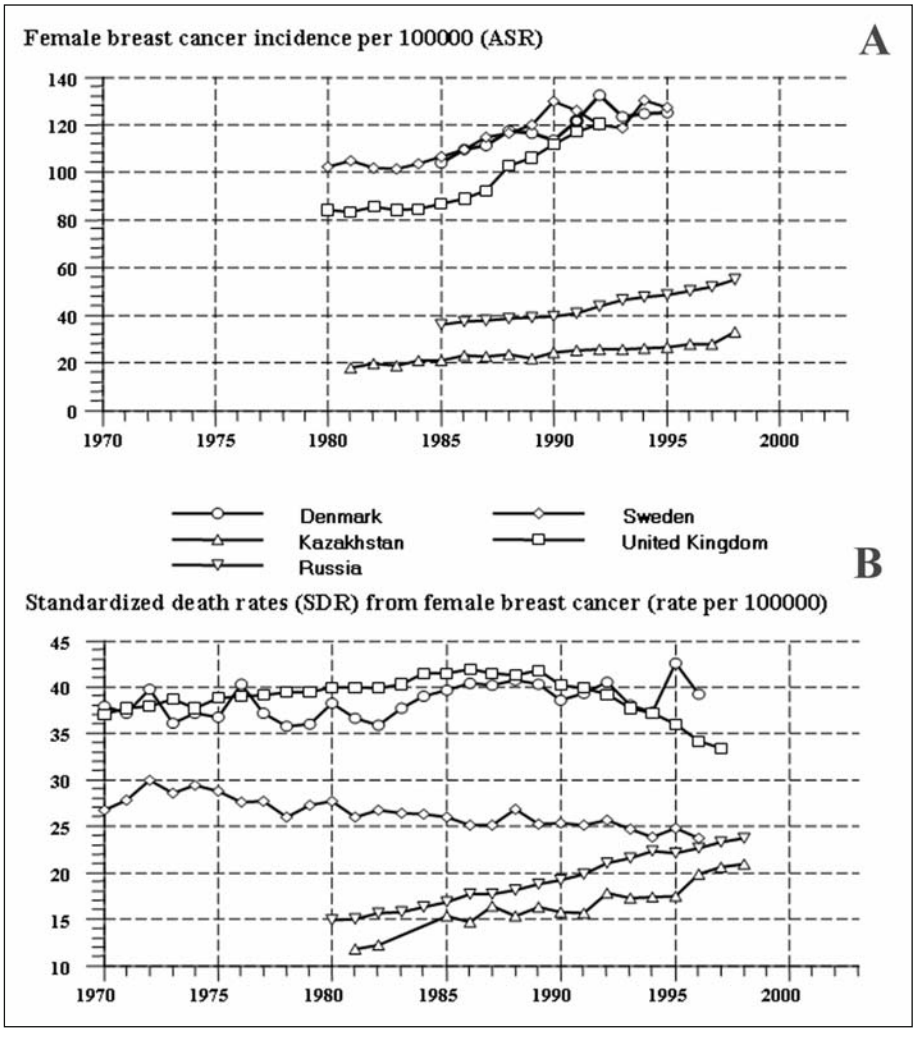

Figure 4. A) Time and place differences in breast cancer age-standardized incidence rates (ASR) (data source: Health for all 2000).[35] The rates are higher in more developed countries (the UK, Sweden, Denmark). B) Time trends and place differences in breast cancer age-standardized death rates (SDR) (Health for all 2000).[35]

second half of 20th century in an association with economic progress and western life style.[1,5] The increase, until recently, was particularly pronounced in the US (Table 1). Exact factors of so dramatic increase in prostate cancer risk remain largely unclear. It could partially be attributed to an increase in early and better detection including that of nonlethal tumors that might be missed from cancer records in the past. Few other factors (both related and not to economic development) have shown a statistically significant association with overall incidence of prostate cancer: African-American race, positive family history, higher tomato products intake (inversely) and alpha-linolenic acid (ALA, the (n-3) fatty acid) in vegetable oils intake.[24,25] Interestingly, high consumption of the ALA is also associated with reduced risk of fatal heart disease.[25] Less statistically supported factors that are associated with the risk of prostate cancer and can also be attributed to western life style

include taller height, higher BMI and high total caloric intake. Some studies suggest that tendency to delayed parenthood might be one more potentially important factor contributing to higher prostate cancer risks in male offspring in developed countries. A higher age of father was associated with an elevated risk of prostate cancer in offspring in the Framingham Study.[26]

Relative 5-year survival of prostate cancer patients has dramatically increased for last 50 years (in the US it now practically approached 100 per cent)[40] in an association with improved diagnostic involving both earlier detection and better detection of nonlethal tumors (Table 1).

Breast Cancer

The age patterns of incidence rate for breast cancer are typically decelerating in middle life and declining at the old ages (Fig. 3). The deceleration/decline may in part be related to slowing down metabolism during aging as well as to ontogenetic hormonal changes in body (e.g., ceasing exposure to internal estrogens at menopause) which may reduce breast cancer rates in late life.[21]

Similar to prostate cancer, the breast cancer rates display clear association with economic progress. The incidence rates are generally higher in more developed countries (Figs. 1, 3, 4).

This excess in risk is most probably related to the factors associated with western life style, such as delayed childbirth or use of hormone replacement therapy (HRT) in menopause. As recent

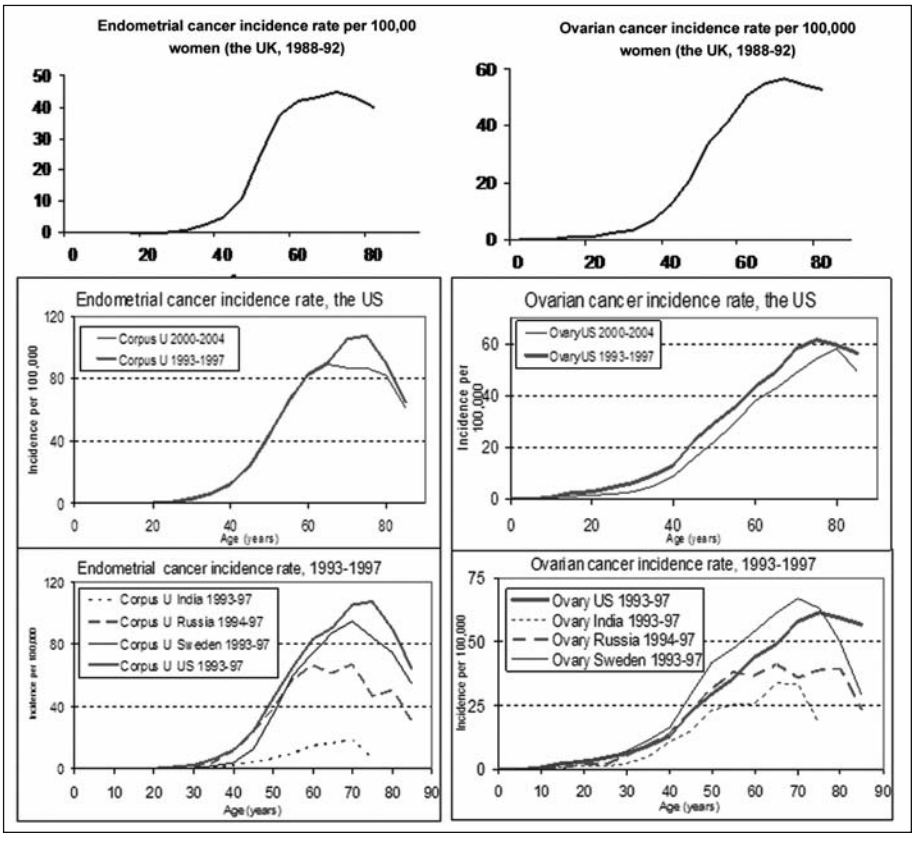

Figure 5. Time and place differences in the age-patterns of incidence rate (average annual) for ovarian and endometrial cancers. The UK, 1988-1992, the US, 1993-1997 and 2000-2004 and different countries, 1993-1997 (data source: IARC 1997,[6] IARC 2002[7]; Ries et al 2007[1]).

studies show, the breast cancer risks rise substantially with age at childbirth for both mothers and female offspring. Women who gave first birth after the age of 35 had a risk increase by 40 percent compared to mothers who experienced their first birth before the age of 20.[27,28] The rate ratios for breast cancer in daughters whose mothers were aged 26 or more years at their birth, relative to women whose mothers were aged 25 years or younger, was 1.3-1.5 in the Framingham Study.[29] Older paternal age may also increase breast cancer risk in female offspring. Women whose fathers were aged 40 or older years at their birth had 1.6-fold increased risk of breast cancer compared with fathers aged less than 30 years.[30]

Another factor, postmenopausal HRT, could contribute to the risk of breast cancer observed primarily at ages over 60. This is particularly true for the US, where postmenopausal HRT was prescribed (until recently) rather often. In a recent study based on SEER data, the notable decline in the rates of new estrogen-receptor-positive breast cancer cases in 2003 was associated with a national-wide reduction in the use of postmenopausal HRT. Age-adjusted incidence rates of breast cancer in women who were 50 years of age or older fell 6.7 percent in the United States in 2003. During this same period, prescriptions for HRT declined rapidly from 61 million prescriptions written in 2001 to 21 million in 2004. This trend followed a highly-discussed 2002 report from the Women's Health Initiative (WHI) study. The latter showed an increased risk of breast cancer and some other disease, such as stroke and pulmonary embolism (but not increased total mortality) among postmenopausal women aged 50-79 (majority were older than 60), who were using HRT including both estrogen and progestin.[31-33] Long-term (but not short-term) exposure to hormonal contraception with estrogens, which is common in developed countries, may also play role in increased risks of breast cancer in premenopausal women. It was shown that premenopausal women who used estrogens during fifteen or more years of life have an increased risk of breast cancer by about 30 percent.[34]

Five-year survival of breast cancer patients varies substantially over populations being generally higher in more developed countries. The best survival rates are currently in the US, where 5-year relative survival approaches 90 per cent (Table 1). The variability in patients' survival can explain diverging trends in cancer mortality among the countries shown on Figure 4. One can see from this figure that while the breast cancer incidence rates increased over time in all the countries compared, mortality from this cancer rose in Russia, Kazakhstan and in less extent, Denmark and declined in Sweden (since 1975) and in the UK (since 1990s). The declining mortality at time of increasing incidence can be explained by a significant improvement in survival of breast cancer patients in the latter countries. It is particularly true for Sweden, where the decline in breast caner mortality is most pronounced, while the incidence rates are among the highest. Respectively, the rise in breast cancer mortality in Russia, Kazakhstan and (less rapidly so) in Denmark most probably reflects an increasing incidence rate on the grounds of relatively poor survival from breast cancer in these countries.[35-37]

Endometrial Cancer

For majority of countries represented in IARC publications[6,7] and also in SEER data,[1] the age pattern of the incidence rate for endometrial (corpus uteri) cancer appears wave-like, with the rate clearly declining at the old ages (above 60) (Fig. 5). Relative stability of this pattern over populations suggests that it may be influenced by ontogenetic factors such as the age-related hormonal changes in a body at menopause, when internal exposure to estrogens ceases. Postmenopausal estrogens are shown to be a risk factor for endometrial cancer. The risk increases with increasing duration of use and decreases with time since last use.[9] One could speculate that ceasing internal exposure to estrogens at menopause would contribute to a decrease in the incidence rates of this cancer later in life in similar way.

The age-adjusted incidence rates of endometrial cancer are in average higher in more developed regions. One reason could again be postmenopausal estrogen therapy that is common in developed countries, while still rare in developing ones. More than 30 case-control studies consistently demonstrated an association between use of postmenopausal estrogens (alone, without progestin)

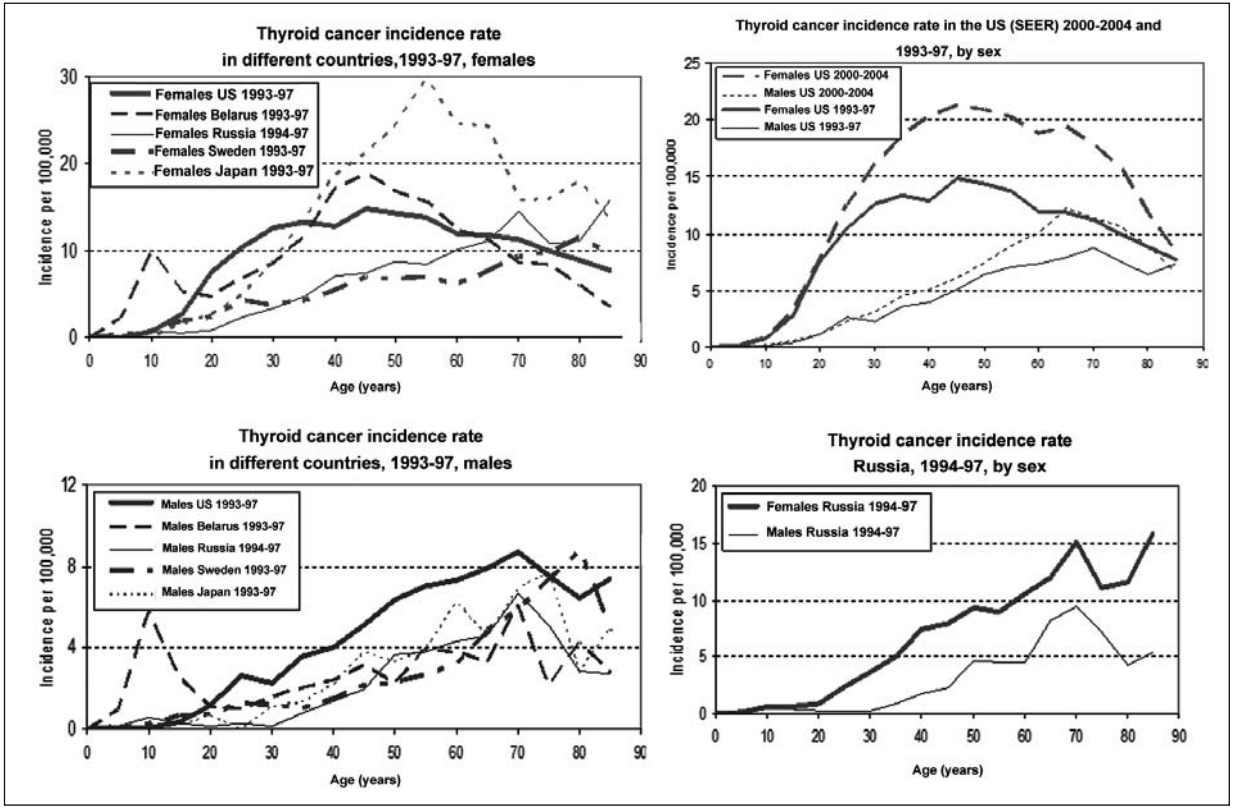

Figure 6. The age-patterns of incidence rates for thyroid cancer in different countries, 1993-97 (average annual), Russia, 1994-97 and the US, 1993-97 and 2000-2004 (average annual) (Ries et al 2007[1]; IARC 2002[7]).

and an increased risk for endometrial cancer.[9] The age-adjusted rates of endometrial cancer were relatively stable in the USA during second half of past century (Table 1); this rate, however, recently declined by about 7 per cent and this decline was almost exclusively attributed to ages above 60. Almost three-fold decline in prescription of postmenopausal HRT (see section on breast cancer for detail) since 2002 might contribute to this trend, similar to that for breast cancer.

For last 50 years the relative 5-year survival of endometrial cancer patients increased from 72 to 85 per cent in the US[1,10] and currently it is one of least deadly cancers contributing to both increasing cancer burden and decreasing cancer mortality.

Ovarian Cancer

The age patterns of ovarian cancer are also wave-like and looking similar in different populations (Fig. 5). This indicates a possible role of internal (e.g., ontogenetic) factors in this cancer development. In the US, the age-adjusted rates of ovarian cancer have recently decreased by about 13 per cent (Table 1). Long-term (more than 10 years) postmenopausal HRT with estrogen alone has been associated with an increase in ovarian cancer risk in separate studies,[38] although this problem is controversial and under discussion. Nevertheless, significant reduction in exposure to postmenopausal HRT since 2002 might, in principle, contribute to a decline in the incidence rates of ovarian cancer, similarly to that for breast and endometrial cancers. Note, however, that a simple look on the age specific incidence rate curves from Figure 5 let us suggest that factor responsible for the decrease in ovarian cancer rates is common for all ages at risk, not only for postmenopausal ones. This decrease looks proportional for the different ages and the incidence rate curve for 2000-2004 appears to be parallel shifted in relation to the 1993-1997 curve. Such trend is completely different from that observed for endometrial cancer and, therefore, requires another explanation. It could be for example some formal changes in diagnostic coding or case registration procedure that lead to the proportional decline in ovarian cancer rates. Increased use of combined oral contraceptives during reproductive period is unlikely to be an explanation since the combined contraceptives are protective against both ovarian and endometrial cancers and were shown to affect their rates in similar way.[9]

Ovarian cancer shows intermediate 5-year survival, compared to other hormone associated sites (Table 1). For 50 years, there was only moderate improvement in the survival rates and ovarian cancer continues to be a deadliest one of female reproductive system. Recently, some advances in this cancer treatment were suggested, which may increase the survival rates in forthcoming years (up to 70 per cent, in average); however, early detection of ovarian cancer remains a major problem. While treatment of the first stage is highly successful, with 5-year survival approaching 90 per cent, most cases of ovarian cancer are detected on late stages, which are poorly curable. Major reason is that this cancer produces very few early stage symptoms (almost none are specific) and attempts to establish the efficient screening program have been not successful so far (more details can be found on NCI web site, www.cancer.gov). Finding solid early diagnostic criteria for ovarian cancer is therefore urgent scientific and clinical oncology task.

Thyroid Cancer

Unlike ovarian cancer, the age patterns of the incidence rate for thyroid cancer vary greatly over populations, particularly in females, being sometimes nearly linear, sometimes decelerating with age, or sometimes declining at the old ages (Fig. 6).

One can see from the Figure 6 that the rates of thyroid cancer can be higher or lower in more compared to less developed countries. In other words, there is no definite correlation between this cancer rates and the level of economic development of a country as it is observed for cancers of breast and prostate. In Belarus, a country that has been significantly exposed to radioactive contamination after Chernobyl disaster in 1986 (the vast majority of the radioactive fallout landed in Belarus), one can see ten years later (1993-1997) a clear peak of childhood morbidity at ages around 10, which probably reflects a particularly negative impact of the radioactive exposure in utero. Such peak is absent on incidence rate curves of other countries (Fig. 6). A large incidence peak, however, can be observed in Japanese women at ages between 50 and 60, who were in uterus

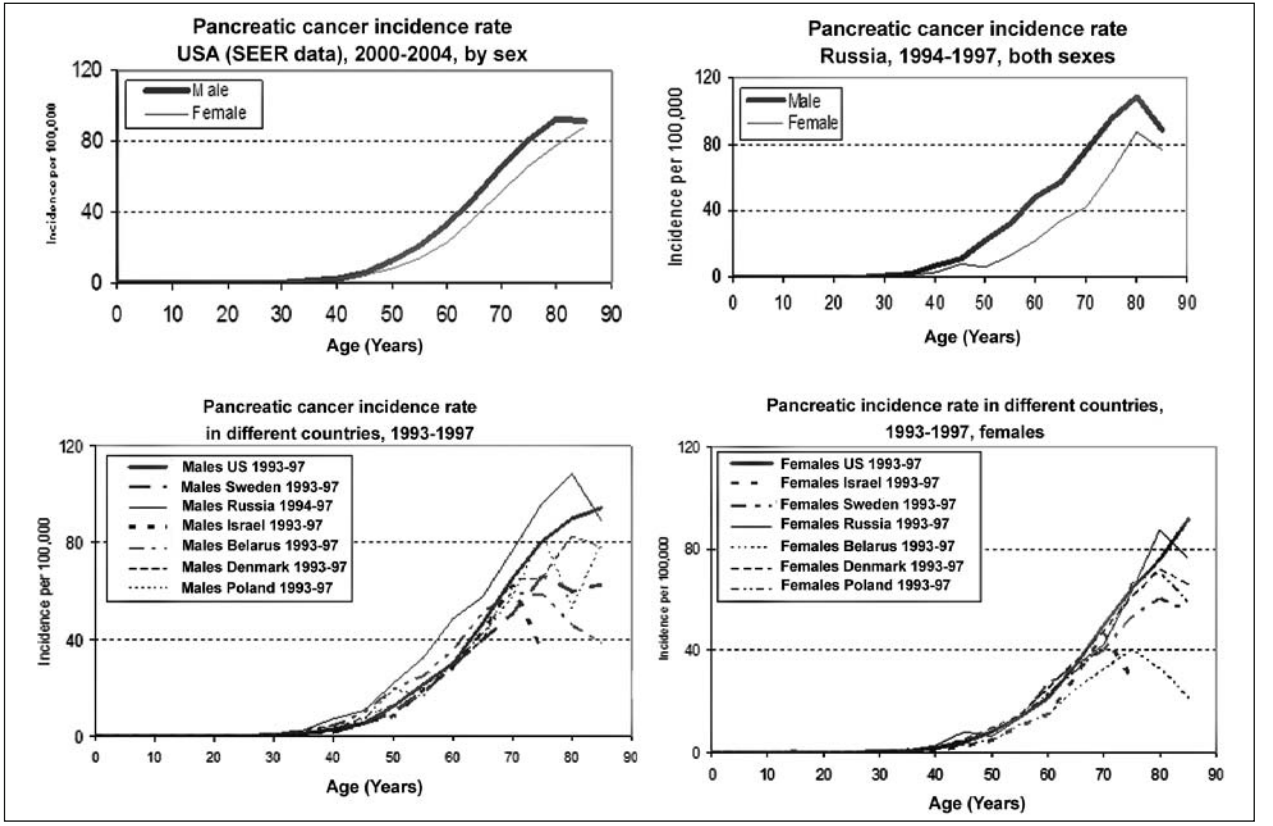

Figure 7. The age-patterns and place differences in the incidence rates (average annual) of pancreatic cancer (Ries et al 2007[1]; IARC 2002 [7]).

or young children at time of atomic bombings of Hiroshima and Nagasaki. All this indicates that the age-specific risks of thyroid cancer are greatly influenced by local exposure factors (such as radioactive contamination) and less related to a level of economic development of a country.

Thyroid cancer manifests substantial increase in the incidence rate over time in the US, particularly in females (Table 1, Fig. 6), which probably reflects increasing exposure to factors affecting thyroid vulnerability (for instance, it might be a rise in rates of sporadic goiter linked to spread of lithium treatment for depression, or other factors). Relative 5-year survival of thyroid cancer patients has been one of the best among all cancers since long time: Even in the 1950s this survival approached 80 per cent; nowadays it is nearly a hundred per cent (Table 1).

Pancreatic Cancer

The age patterns of the incidence rate for this cancer are similar for males and females. The incidence rate increases with age until old ages (70+) with the rate that is similar in very different populations (such as the US and Russia) (Fig. 7). These notable similarities suggest that development of pancreatic cancer could be considerably influenced by universal aging-associated changes in a body (which are common for different populations and sexes). Exposures to oxidative stress that accumulate their effects in organism with age or aging-associated insulin resistance might be among these factors.

The age-adjusted incidence rates for pancreatic cancer are generally higher in more developed regions (Fig. 1); contemporary epidemic of diabetes in affluent societies might contribute to this excess. The rates, however, not so dramatically increased in 20th century as it was for some other sites, including prostate, thyroid and breast (IARC 1965-2002[5]; Table 1). The rates of pancreatic cancer have recently stabilized in the US (Table 1, Fig. 7).

5-year relative survival for pancreatic cancer is poorest among the all mentioned cancers (Table 1). It is practically not cured, implying that current diagnostic and treatment strategies for this cancer are not adequate and need fundamental revision. Pancreatic cancer is often missed during routine examination and diagnosed too late due to lack of early symptoms. Even more important is that tumors are very resistant to standard chemotherapy or radiation. One forthcoming option might be novel therapies that target the pancreatic cancer stem cells which have recently been suggested to be mainly responsible for the tumor resistance to conventional treatment.[39]

Conclusions

In this chapter we reviewed typical features of the epidemiology of hormone-associated cancers emphasizing comparison of the age specific incidence rate curves as a valuable source of hypotheses about factors influencing cancer risks. Here the findings are briefly summarized.

Typical Features of the Age Patterns of Cancer Incidence Rate

Typical age patterns of the incidence rate for cancers of the breast, prostate, ovary and endometrium are wave-like, that is, nonmonotonic. Such patterns can be observed over different populations and time periods and also seen in laboratory animals.[5,16-18,21] Differential selection in heterogeneous populations as well as factors of individual aging (such as slow down of metabolism or hormonal changes in an aging body) may play a role in these patterns.[19-21] Thyroid cancer manifests substantial variability of the incidence rate patterns over populations suggesting a predominant contribution of local exposure factors to this cancer risk. Comparing the incidence rate curves for pancreatic cancer allows for assumption that this cancer risk can be influenced by some universal age associated changes in a body that are common for both sexes.

An Association between Cancer Risk and Economic Progress

Age-standardized cancer incidence rates for all sites combined show a clear association with economic progress. The rates are higher in more developed countries and until recently increased over time.[1,5] This is also true for some (but not all) hormone-associated cancers. These cancers substantially vary in their susceptibility to factors associated with economic prosperity and western life style: cancers of the breast, endometrium and prostate display the highest vulnerability to such factors, while cancers of the thyroid and pancreas appear to be least dependent on those.

The incidence rates of female hormone-associated cancers recently declined in the US[1,40] (Table 1). In case of breast and endometrial cancers, this decline can be attributed to reducing exposure to HRT in postmenopausal women; in case of ovarian cancer it is probably related to different factor(s).

Continuing increase of thyroid cancer rates in the US may reflect increasing population exposure to factors affecting thyroid vulnerability, particularly in females.

Variability in Survival of Cancer Patients

The relative 5-years survival of cancer patients greatly improved over last 50 years for most hormone-associated cancers, including thyroid, prostate, breast and endometrial, so that these cancers are nowadays among the least deadly ones (Table 1). Pancreatic cancer does not fit this positive trend and continues to be among the deadliest human malignancies (in both sexes) suggesting that current diagnostic and treatment strategies are not adequately addressing the nature of this cancer. Ovarian cancer shows intermediate survival, with only slight progress happened for past 50 years. It continues to be a most fatal female cancer urgently requiring development of more effective diagnostic and treatment tools.

Acknowledgements

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