Epidemiological trends of hormone-related cancers in Slovenia

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The incidence of hormone-related cancers tends to be higher in the developed world than in other countries. In Slovenia, six hormone-related cancers (breast, ovarian, endometrial, prostate, testicular, and thyroid) account for a quarter of all cancers. Their incidence goes up each year, breast and prostate cancer in particular. The age at diagnosis is not decreasing for any of the analysed cancer types. The risk of breast cancer is higher in the western part of the country, but no differences in geographical distribution have been observed for other hormone-related cancers. Furthermore, areas polluted with endocrine-disrupting chemicals that affect hormone balance such as PCBs, dioxins, heavy metals, and pesticides, do not seem to involve a greater cancer risk. We know little about how many cancers can be associated with endocrine disruptors, as there are too few reliable exposure studies to support an association.

KEY WORDS: *attributable fraction; cancer burden; endocrine disruptor; hormone-related cancer*

Sex hormones have been associated with breast, ovarian and, endometrium cancers, while their role in prostate and testicular cancers is not as clear (1). The thyroid axis hormones and oestrogens may also take part in the development of thyroid cancer (2). These six cancer types are usually referred to as hormone-related cancers (HRCs) (1-3) because they share the same mechanism of carcinogensis. In addition, there is accumulating evidence that sex hormones also play a role in the aetiology of colorectal (4) and liver cancer (5). Relatively high concentrations of oestrogen receptor are also present in the spleen, while low levels have been detected in the kidney, thymus, skin, and lung (6). However, these cancer types are generally (and in our evaluation) not considered as HRCs (1).

Epidemiological evidence of the association between endogenous and exogenous hormones with cancer comes from a variety of sources: from geographical differences in cancer risk, from migration studies, from time trend analyses of incidence and mortality data and from analytical studies comparing populations being exposed and not being exposed to a selected factor (1-3). Global rates of HRCs have been increasing over the past 40-50 years (3) and are the highest in industrialised countries (7). There is an indication that age at exposure is especially important, as there are periods of greater vulnerability during development (such as foetal and prepubertal exposure) (8).

Endocrine disruptors that are most commonly associated with HRCs are polychlorinated biphenyls (PCBs), dioxins,

some heavy metals, and pesticides (such as DDT and DDE). Table 1 lists the groups of endocrine disruptors associated with HRCs. Many of these association studies are inconclusive because they typically suffer from methodological limitations such as measurement of exposure at wrong time or disregard of combined exposure (2). For example, several organochlorine and organophosphate pesticides have been linked with an increased risk of prostate cancer, especially in occupational studies, but only two pesticides [inorganic arsenic compounds and dioxin TCDD (tetrachlorodibenzo-p-dioxin)] had strong enough evidence to be classified as carcinogenic to humans (IARC Group 1) (1). Five organophosphate pesticides have recently been moved from the IARC Group 3 (not classifiable) to Group 2 (probably carcinogenic to humans), because there is enough evidence that they are carcinogenic in animals. However, evidence from human studies is scarce and inadequate to classify these pesticides as IARC Group 1 (9).

We focused our study on the overall, geographical, and age-specific incidence of six HRCs in Slovenia over the last 50 years. In addition, we put the national statistics in an international context and looked for the reasons for changes in epidemiological indices, paying particular attention to the potential influence of exogenous hormones and hormone-like substances.

Latest research in Slovenia (original data)

Our latest research included 77,271 HRC cases diagnosed in Slovenia between 1961 and 2011, as reported by the Slovenian population-based cancer registry.

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Table 1 *Groups of chemicals associated with hormone-related cancers (adopted from ref. 2)*

	Breast	Endometrium	Ovary	Prostate	Testis	Thyroid
Polychlorinated biphenyls, dioxins, furans	x			x	x	x
Polybrominated diphenyl ethers					x	
DDT/DDE	x	x		x	x	
Pesticides	x		x	x	x	x
Heavy metals	x	x		x		
Bisphenol A, parabens	x	x				x
Phthalates					x	
Pharmaceutical estrogens	x	x	x	x	x	x
Phytoestrogens	x			x		x

Cancer Registry of the Republic of Slovenia (CRS) is one of the oldest population-based cancer registries in the world. Reporting cancer has been mandatory in Slovenia since the CRS's foundation in 1950. Cancer data collection complies with all international standards and covers 100 % of the population (10). Data quality (reliability and completeness) is regularly monitored and published in CRS's annual reports (11). The ratio between mortality and incidence has been stable over the years. The proportion of cases registered based on death certificate only has not exceeded 2 % for several decades. More than 90 % of the registered cases have been confirmed by microscopy. To verify personal information and monitor the vital status of patients, CRS has access to the national population registry, while it updates patient residence data from the national Register of Spatial Units (maintained by the Surveying and Mapping Authority of Slovenia). Population demographics, stratified by gender and five-year age groups, is updated regularly from the Statistical Office of the Republic of Slovenia.

CRS provides information on the incidence, prevalence, and survival of cancer patients. Cancer sites are coded according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD10). Our study has included incidence data on the following HRCs: breast (ICD10: C50; analysed for women only), endometrial (ICD10: C54), ovarian (ICD10: C56 and D39.1 encoding ovarian tumours of borderline malignancy), prostate (ICD10: C61), testicular (ICD10: C62), and thyroid cancer (ICD10: C73). Ovarian tumours of borderline malignancy (D39.1) have been classified separately at the CRS from the year 2001 on, but we've merged both types of ovarian tumour for this analysis.

Incidence rates were age-standardised (ASR) to the European Standard Population using the following formula:

$$ASR = \sum_{i=1}^{17} S_i \frac{N_i}{P_i}$$

where N is the number of cases in the observed population, P is the number of persons in the observed population, S is the number of persons in the standard population and i is a five-year age group. ASRs are presented by the calendar year of diagnosis. The time trends of ASRs for each examined cancer site were analysed using log-linear joinpoint regression (12). The trends were characterised in terms of average annual percent change (APC), assuming a constant rate of the previous year. In addition, a 95 % confidence interval (CI) of APC is reported. To check if the age at cancer onset is decreasing, we calculated age-specific incidence rates for four age groups: 15-39 years, 40-54 years, 55-69 years, and 70 or more years. In addition, we determined the time trend of the median age at diagnosis for all patients younger than 55 at diagnosis.

Review of the latest research results and earlier research in Slovenia

The six HRCs account for almost a quarter of all cancers in the developed countries (including non-melanoma skin cancers). In Europe, their annual age-standardised incidence is 80.4 per 100,000 men and 110.4 per 100,000 women (7). The annual number of new cases and ASR rates for Slovenia is reported in Table 2. With more than 20 % of all cancer cases, breast and prostate cancers are the most common cancers diagnosed in women and men, respectively. Endometrial and ovarian cancers rank 5th to 10th in incidence among women. Testicular cancer is generally rare but is the most common cancer among young and middle-aged men. Thyroid cancer is also relatively uncommon but is approximately four times more frequent in women.

Incidence trends

Figure 1 shows that the incidence of prostate, breast, endometrial, testicular, and thyroid cancers have been on the rise, whereas ovarian cancer has been stable over the investigated 50 years. Average annual percent changes in Table 2 give a better view of the increases in incidence from 1992 to 2011 for each investigated HRC. Prostate cancer clearly leads, followed by thyroid and testicular cancer.
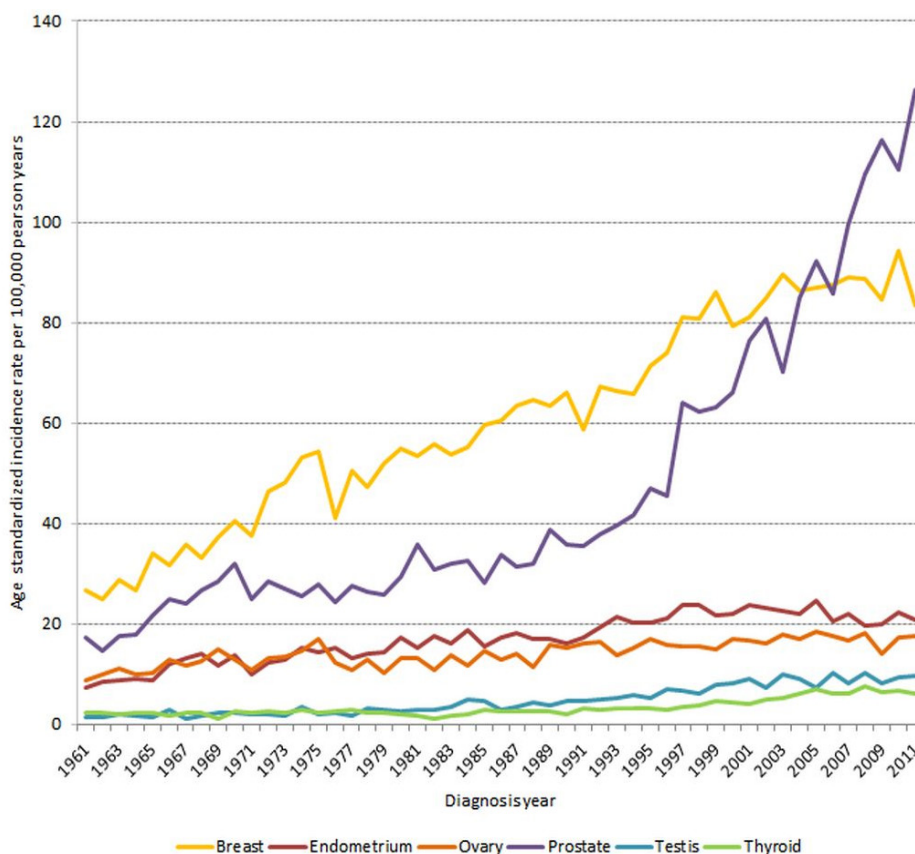
Figure 1 *Age-standardised incidence rates for six hormone-related cancers by calendar year, Slovenia 1961-2011*

Breast cancer incidence, in turn, was the most prominent between 1992 and 1999 (APC: 3.8, CI 2.1;5.5), since which time it has stabilised (APC: 0.5, CI -0.2;1.2). Endometrial cancer incidence has not changed over the last twenty years, and ovarian cancer has shown a rise of only 0.7 % per year.

Age at diagnosis

With the exception of testicular cancer, where the age-specific incidence rates are the highest between 25 and 35 years, all other HRCs develop at a later age, most frequently after the age of 60. Our time-trend analysis of the age at diagnosis did not indicate any earlier cancer onset in recent

years. Figure 2 shows that the incidence of breast, endometrial, and prostate cancers is rising in the population aged 55 and over. Ovarian cancer is dropping in women older than 40, but the trend seems stable in women of younger ages. Thyroid cancer, in turn, shows a comparable increase in age groups up to 69 and a plateau from 70 years up.

For any of the analysed HRCs the median age at diagnosis in patients diagnosed before the age of 55 has not decreased in the last twenty years. On the contrary, it has risen by one year for prostate, testicular, and ovarian cancers (to 51, 33, and 48 years, respectively). As for breast cancer,

Table 2 *Average annual number of new cases (incidence) and age-standardized incidence rates (ASR) for six hormone-related cancers in Slovenia between 2009 and 2011. Average annual percent change of ASR for the six HRCs between 1992 and 2011*

Cancer	Average incidence (2009-2011)	Average ASR (2009-2011)	Annual percent change (95 % CI) (1992-2011)
Breast	1190	88.0	1.5 (1.1;2.0)
Endometrium	305	21.0	0.1 (-0.5;0.7)
Ovary	158	16.3	0.7 (0.1;1.3)
Prostate	1426	117.6	6.4 (5.7;7.1)
Testis	100	9.1	3.4 (2.3;4.5)
Thyroid	150	6.4	5.2 (4.2;6.1)

ASR: age standardized incidence rate per 100,000 person years (European standard)
CI: confidence interval
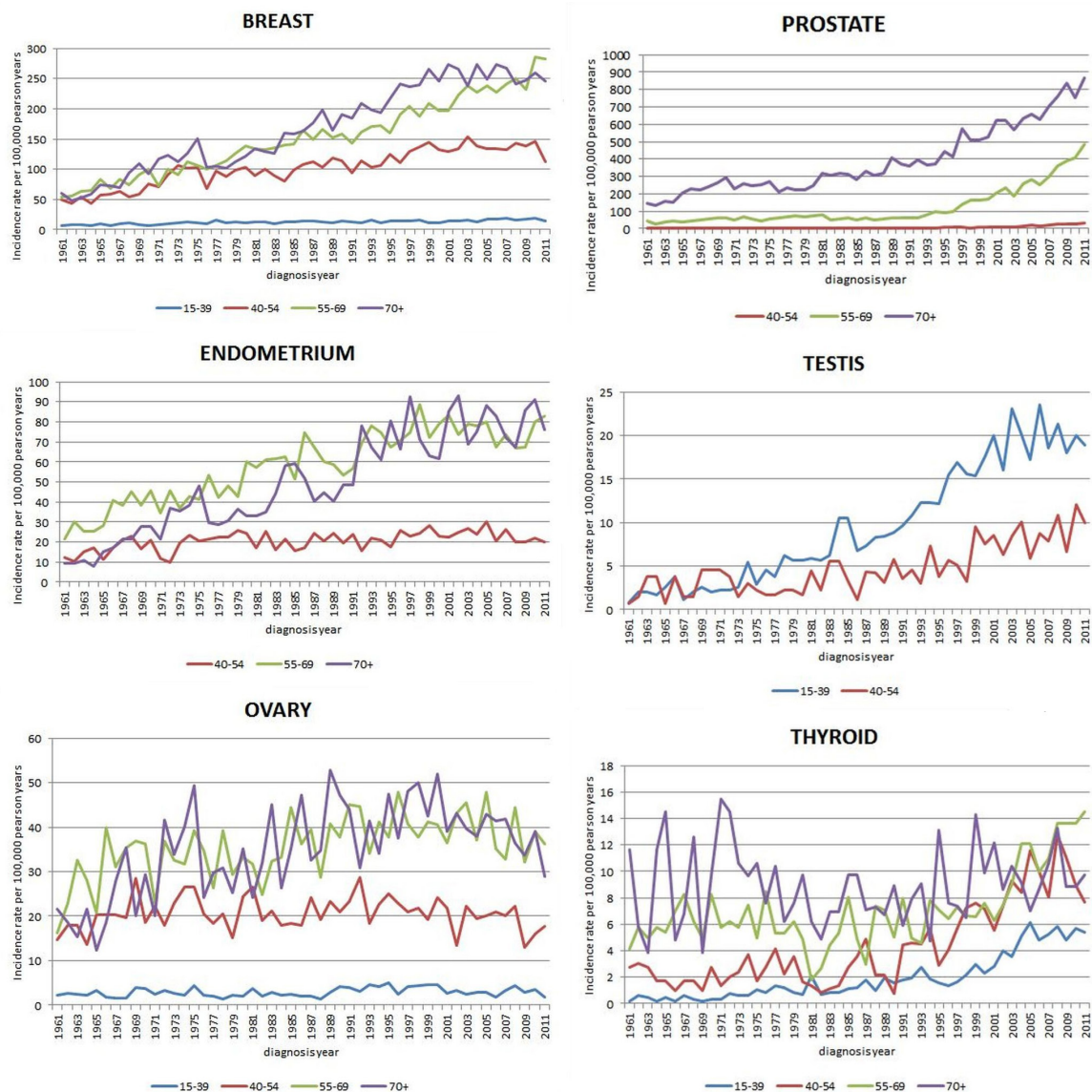
Figure 2 *Age-specific incidence rates for six hormone-related cancers by calendar year, Slovenia 1961-2011*

the median age at diagnosis for patients diagnosed before 55 has been 47 for the last twenty years. In the younger age group, it also has not changed: the median for the groups diagnosed before 35 and before 25 has been 33 and 23 years, respectively.

Geographical distribution

The GLOBOCAN 2012 statistics (7) indicate that the incidence of all HRCs varies significantly worldwide. As a rule, their incidence is higher in the industrial world and remains low in many parts of Asia and Africa. The incidence of prostate, testicular, endometrial, ovarian, and thyroid cancer varies by more than 25-fold across the world's regions. For prostate cancer this variation primarily reflects the differences in the availability of prostate-specific antigen (PSA) screening, but for other cancers the variation may reflect differences in lifestyle and genetic factors, as

described in more detail in Discussion. Variations in breast cancer incidence are smaller (nearly fourfold), with rates ranging from 27 per 100,000 in Middle Africa and Eastern Asia to 96 in Western Europe.

HRC incidences do not vary as much between European regions. According to the EUCAN database (13), the variation is the highest for thyroid cancers (over tenfold), with the highest incidence in Austria, Italy, and Lithuania (12-15 per 100,000) and the lowest in Albania, Bosnia and Hercegovina, and Greece (1 per 100,000) (13). Cancer mapping of the Alpine regions (14) shows no geographical variation for endometrial and ovarian cancers. The highest prostate cancer incidence is reported in Austrian communities where PSA testing is extensive, whereas breast cancer incidence is the highest in Italian communities. In an earlier research (15), Zadnik observed variations in breast cancer incidence between Slovenian west and east (highest to

lowest, respectively) (Figure 3). As for other HRCs, we observed no geographical variations.

Recently, we investigated the relationship between cancer burden, environmental pollution and carcinogenic endocrine disruptors (16, 17). The analyses of cancer incidence in Bela krajina, which is heavily polluted with PCBs (16) and of the Celje region, polluted with heavy metals (17) have not established any significant increase in the risk of any HRCs among the population living in these areas.

Risk factors for the development of HRCs include reproductive characteristics associated with oestrogen and other hormones, pharmaceutical hormones, and lifestyle, such as alcohol use and lack of exercise. Below we are going to discuss the reasons that may have led to the rise in HRC burden established in this study, paying particular attention to the potential influence of exogenous hormones and hormone-like substances.

Review of risk factors for HRC development

Female breast cancer

The first to report high incidence of breast cancer in nuns more than three hundred years ago was Bernardo Ramazzini in his *De Morbis Artificum Diatriba* (in chapter "De Nutricum Morbis"), pointing to the association between reproduction and cancer risk. Today we know that breast cancer risk is twice as high in nulliparous women as in the parous women. It is the lowest in women who have given birth at an early age (full term pregnancy) and rises with age (18). In fact, women who give birth at the age 30 or later run a higher risk than nulliparous women.

Furthermore, breast cancer risk drops with breastfeeding. Women who have given birth and breastfed several children over long time run the lowest risk (19, 20).

Menstrual factors are also very important in predicting breast cancer risk. Menarche at an early age and menopause at a later age are associated with the highest risk, presumably due to ovulation activity and changes in endogenous hormonal profiles (21, 22).

Physical activity and obesity may also be related to breast cancer risk. Obesity is associated with higher risk of post-menopausal breast cancer. In premenopausal women obesity-related anovulation seems to reduce the risk, and the conversion of androgens to oestrogens in adipose tissue after menopause seems to increase the risk (1, 21, 23).

Physical activity has been associated with a 23-30 % decrease in breast cancer risk. Some studies have focused on investigating the biological mechanisms mediating this association (23). Physical activity decreases endogenous oestrogens, fat-related insulin resistance, inflammation, and improves adipokine production (leptin and adiponectin) by reducing fat tissue, which are all independently associated with increased breast cancer risk (23, 24). Physical activity also seems to reduce oxidative stress and genomic instability; in postmenopausal women exercise decreases circulating oestrogen levels through weight loss (23-25).

Menopausal hormone replacement therapy has been associated with increased breast cancer risk among post-menopausal women, especially in thin women (26). However, the major risk predictor is the type of hormones used; oestrogen plus progestogen seem to be associated with the highest risk.

Oral contraceptives are associated with increased risk of breast cancer especially among young women, but it falls to baseline after 10 years of discontinuation and is the same as in non-users (26).

According to Barnes et al. (27), the population-attributable risk for non-modifiable breast cancer risk factors (age at menarche, age at menopause, parity, benign breast disease and family history of breast cancer) is 37.2 % for all invasive tumours considered. Among the modifiable risk factors, hormone therapy and physical inactivity contribute the most 19.4 % and 12.8 %, respectively.

Only 3-5 % of breast cancer is due to hereditary predisposition. *BRCA1* and *BRCA2* genes have been identified to be responsible for the majority of hereditary breast cancer. Carriers of germline mutations in *BRCA1/2* genes are at high risk of developing breast and/or ovarian cancer (28, 29). Several moderate and low penetrant genes have also been identified, and their role is still under investigation (29).

Endometrial cancer

Hormones play an important role in the aetiology of endometrial cancer, which is believed to arise from oestrogen stimulation that is unopposed by progestins (1). More than 80 % of cases of endometrial cancers are oestrogen-related. Obesity and menopausal hormone therapy are strong risk predictors, as well as early age at menarche, late age at menopause, and nulliparity. Oral contraceptives are associated with a long-lasting decrease in endometrial cancer risk only if they contain progestogen in addition to oestrogen (30). Unopposed oestrogen use in hormone replacement therapy is associated with a remarkably high risk (two to tenfold increase) which depends on the duration of use and the woman's body mass (higher in thin women) (31). Obesity is associated with annovulatory cycles in premenopausal women, so the endometrial tissue receives continuous stimulation. In post-menopausal women, the concentration of endogenous oestrogens increases in obese women. Endogenous oestrogens are mainly the product of androgen aromatisation in the fat tissue. Furthermore, excess weight is associated with insulin resistance and chronically elevated insulin concentration and increased concentrations of sex steroids (32) - all these factors are associated with higher endometrial cancer risk. Higher risk is also observed in patients with type 1 and type 2 diabetes. Other clinical features are also associated with higher risk such as polycystic ovary
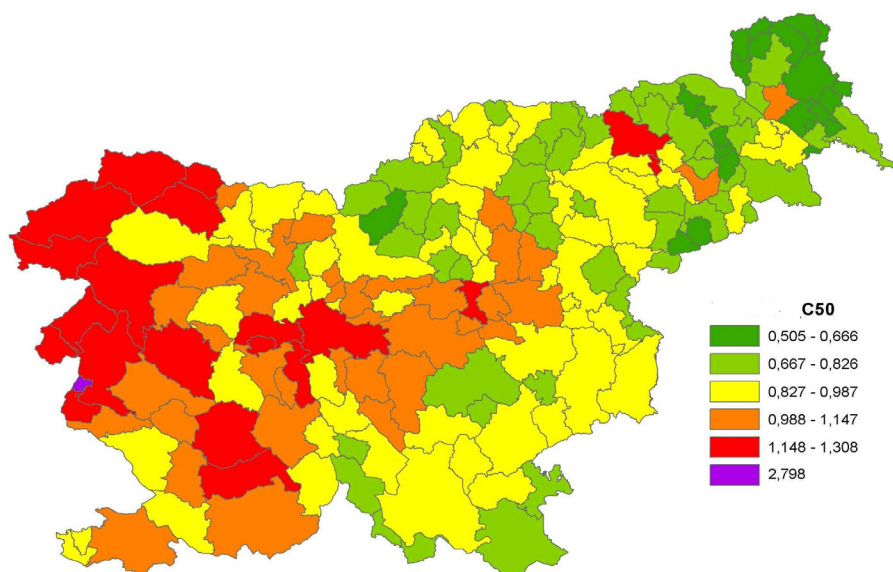
Figure 3 *Relative risks of breast cancer by municipalities, Slovenia 1995-2002 (15)*

syndrome (associated with increased blood androgen levels), infertility, amenorrhea, hirsutism, and tamoxifen therapy (twofold increase compared to non-users) (1).

Two to five percent of endometrial cancers are associated with hereditary syndromes such as Lynch (most frequent), Muir-Torre, Cowden, and the *BRCA1* syndrome. Patients with Lynch syndrome who carry germline mutations in mismatch repair genes (mostly *MLH1, MSH2, MSH6*) face a 40-60 % lifetime risk of endometrial cancer (1).

Ovarian cancer

Nulliparity and infertility are well-known risk factors for ovarian cancers. Another predictor of some types of ovarian cancers (clear cell and endometroid cancers) is endometriosis (33). Beside hormonal factors (elevated gonadotropin levels), some irritants (talc, asbestos) seem to increase the risk of ovarian cancer.

The risk, however, drops with suppressed ovulation (by pregnancy or oral contraceptives; both lower pituitary gonadotropins) (34, 35). Substantially reduced risks have been observed in women who had simple hysterectomy or tubal ligation. While reduced ovulation is known to diminish the risk, it does not explain all of the identified risk factors. Latest research points to hormonal and immunological factors (36).

A very important risk factor is family history, since it accounts for about 10 % of cases. The risk increases threefold when two or more first-degree relatives have been diagnosed with ovarian cancer. Furthermore, women who carry germline mutations in *BRCA1/2* genes and women with Lynch syndrome have a 30-70 % lifetime risk of developing ovarian cancer (37, 38).

Prostate cancer

Epidemiological studies, numerous as they are, seem to have failed to pinpoint all the causes of prostate cancer. We know that the risk increases with age, and is race and family history related (1). About 25 % of men with prostate cancer have a known family history of this cancer (39). Furthermore, in a twin cohort study (40) 42 % of prostate cancer cases were inheritable.

For a number of other probable exogenous risk factors such as alcohol, smoking, vasectomy, body mass index, exposure to certain chemicals in the workplace, the connection to prostate cancer has been evaluated but not confirmed. Agricultural workers have been identified as having a higher risk of prostate cancers, most probably because of their exposure to pesticides (1).

Among protective factors stand out specific diets such as those rich in carotenoid lycopene (41) or phytoestrogens that have been associated with lower incidence of prostate cancer in Asia (42).

Sex hormones are undoubtedly involved in the aetiology of prostate cancer, but the mechanism is still unclear. Epidemiological studies have ruled out the association with serum testosterone (1). It is most likely that changes in the metabolism or transfer of hormones on the cellular level are involved in prostate cancer development. Pharmacological inhibitors of 5-alpha reductase lower the risk (43) whereas insulin-like growth factor seems to increase it (1).

The enormous increase in the incidence of prostate cancer in the developed countries in the last twenty years has mainly been attributed to the intensive use of screening with the PSA. PSA screening has increased the detection of all prostate cancers, including indolent prostate cancers. It has nearly doubled the diagnosis of prostate cancer but has also reduced its mortality by 20 % (44). However, the

question is not whether it is effective in reducing mortality, but whether it does more harm than good. Compared to breast cancer screening in women PSA screening involves a significantly greater risk of overdiagnosis, unnecessary treatment, and eventually, lower quality of life in overdiagnosed patients.

Testicular cancer

Testicular cancer is, in most cases, a germ cell neoplasm. The incidence of testicular cancer rises with adolescence, and hormonal factors clearly play a role in its aetiology. The diagnosis peaks in the twenties and thirties. There is a variety of other factors that increase cancer risk, including height, subfertility, and exposure to endocrine disruptors. Some risk factors also involve exposure to hormones *in utero* (cryptorchidism, hypospadias, inguinal hernia, low birth weight, short gestational age, and being a twin) or to endogenous hormones (45). Established risk factors for testicular germ cell tumours also include a prior testicular germ cell tumour, a family history of germ cell tumour and various inter-sex syndromes (46, 47). There are very interesting migrant studies that suggest environmental and dietary factors. For example, the incidence of testicular cancer in Finland is half that in Sweden. Furthermore, the second generation Finnish migrants to Sweden face the same testicular cancer incidence as the Swedish population (48).

A small minority of testicular cancers, as in other cancers, appear to be familiar, with approximately 2 % of patients having an affected family member. Men with a first-degree relative with testicular cancer run a three to ten times higher risk of being diagnosed with the disease (46).

Thyroid cancer

Thyroid cancer is not as common, but its incidence has been increasing worldwide. This trend may be associated with improved screening and detection, the detection of papillary microcarcinoma in particular (49, 50).

Exposure to ionising radiation, especially in childhood (as it predisposes for papillary thyroid cancer) is among the well-known high risk factors for thyroid cancer. About 5 % of patients develop thyroid cancer due to radiation exposure (1, 50).

The distribution between genders is strikingly uneven, as the cancer affects women three to times more often than men (50) for reasons that may be related to hormones but are far from clear. An association between female hormonal and reproductive factors as drivers for thyroid cancer development has been shown *in vitro* but has not been confirmed in population-based analyses (51, 52).

According to population-based studies, thyroid cancer might also be moderately associated with height and body mass index in both genders (51). A rare clinical condition - acromegaly (caused by an overproduction of growth hormone) is also associated with increased risk of thyroid cancer. It is also known that thyroid cancer development is strongly associated with a history of benign nodules/adenoma or goitre. Furthermore, iodine deficiency may induce benign thyroid conditions that predispose for thyroid cancer, but it is still unclear to what extent dietary iodine intake might serve as a risk predictor (51).

There are several rare inherited conditions (familial adenomatous polyposis syndrome, Cowden syndrome, Werner syndrome) that are associated with different types of thyroid cancer (53). When investigating medullary thyroid cancers only, about 25 % occur as part of the multiple endocrine neoplasia type 2 (MEN2) syndrome (54). MEN2 syndrome is caused by germline mutation in the *RET* protooncogene and is involved in phaeochromocytoma, hyperparathyroidism, and medullary thyroid carcinoma. *RET* protooncogene mutation analysis therefore enables predictive testing and genotype-based tailored prophylactic treatment and serves as a role model of personalised medicine, since medullary thyroid cancers as part of MEN 2 may be prevented by early prophylactic resection of the thyroid gland.

As for non-syndromic thyroid cancer, it is estimated that around 10 % of all non-medullary thyroid cancers are hereditary, since first-degree relatives of patients with thyroid cancer run a ten times higher risk of thyroid cancer than the general population (53).

The influence of risk factors on the burden of HRCs in Slovenia

Risk factors for HRC are heterogeneous and are predominantly associated with our lifestyle, reproductive factors, or genetic characteristics. They can have opposite effects in different cancers; oral hormonal contraception increases the risk of breast cancer but decreases the risk of ovarian cancer. Even though the prevalence of HRC risk factors has been poorly investigated in Slovenia, we have enough information to explain, at least in part, the spatial distribution of breast cancer risk (risk is higher in the western part of the country) and the rapid rise in breast and prostate cancer incidence. Several studies of the reproductive factors in Slovenia (55-57) indicate that nulliparity and late first birth (which are both more prevalent in the west of the country) could be responsible for higher breast cancer risk in that part of the country. Reproductive risk factors in Slovenia are also central to the understanding of the increase in breast cancer incidence. The average age at first delivery and the nulliparity are increasing, and Slovenian women today have on average fewer children than earlier generations (15). The dramatic rise in prostate cancer incidence, in turn, is owed to dramatic rise in detection thanks to prostate-specific antigen (PSA) screening, which has been part of regular check-ups since the early 1990s (58).

Although reproductive and genetic factors play a major role in the carcinogenesis of HRCs, the contribution of

environmental chemicals cannot be dismissed. Endocrine disruptors seem to be involved in carcinogenesis through the same mechanisms as natural hormones. At the moment, however, we do not know how many of the newly diagnosed cancers are associated with endocrine disruptors. Further research should focus on assessing exposure and individual susceptibility, as well as latency and critical exposure windows. In the meantime, public health policies promote a precautionary approach to reasonably reduce exposure to endocrine-disrupting chemicals.

Conflict of interest

The authors declare no conflict of interests regarding the publication of this paper.

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Epidemiološki trendi hormonsko odvisnih rakov

Spolni hormoni so znan in pomemben nevarnostni dejavnik rakov na dojki, jajčniku in endometriju, medtem ko je njihova vloga pri rakih prostate in mod verjetna, a manj raziskana. Vpletenost hormonov v kancerogenezo se nakazuje tudi pri raku ščitnice. Predvidevamo, da se po enakih mehanizmih kot telesu lastni hormoni v nastanek raka vpletajo tudi hormonski motilci. Rake hormonsko odzivnih tkiv najpogosteje povezujemo z izpostavljenostjo PCB-jem in dioksinom, DDT/DDE ter nekaterim težkim kovinam in pesticidom. Incidenca hormonsko odvisnih rakov je največja v državah razvitega sveta. V Sloveniji predstavljajo hormonsko odvisni raki četrtino vseh rakov; njihovo število se z izjemo raka jajčnikov vsak leto veča. Tveganje raka dojk je že več desetletij večje na zahodu države, medtem ko pri ostalih lokacijah med območij ne opažamo pomembnih razlik. Hormonskim motilcem pripisljivega deleža rakov trenutno ni mogoče določiti, saj imamo verodostojnih raziskav pri izpostavljenih, predvsem v kritičnih razvojnih obdobjih, premalo.

KLJUČNE BESEDE: *dejavniki tveganja; geografska razporeditev; hormonski motilec; incidenčni trendi; pripisljiv delež*