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European Code against Cancer 4th Edition: Medical exposures, including hormone therapy, and cancer☆

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ABSTRACT

The 4th edition of the European Code against Cancer recommends limiting – or avoiding when possible – the use of hormone replacement therapy (HRT) because of the increased risk of cancer, nevertheless acknowledging that prescription of HRT may be indicated under certain medical conditions. Current evidence shows that HRT, generally prescribed as menopausal hormone therapy, is associated with an increased risk of cancers of the breast, endometrium, and ovary, with the risk pattern depending on factors such as the type of therapy (oestrogen-only or combined oestrogen–progestogen), duration of treatment, and initiation according to the time of menopause. Carcinogenicity has also been established for anti-neoplastic agents used in cancer therapy, immunosuppressants, oestrogen–progestogen contraceptives, and tamoxifen. Medical use of ionising radiation, an established carcinogen, can provide major health benefits; however, prudent practices need to be in place, with procedures and techniques providing the needed diagnostic information or therapeutic gain with the lowest possible radiation exposure. For pharmaceutical drugs and medical radiation exposure with convincing evidence on their carcinogenicity, health benefits have to be balanced against the risks; potential increases in long-term cancer risk should be considered in the context of the often substantial and immediate health benefits from diagnosis and/or treatment. Thus, apart from HRT, no general recommendations on reducing cancer risk were given for carcinogenic drugs and medical radiation in the 4th edition of European Code against Cancer. It is crucial that the application of these measures relies on medical expertise and thorough benefit–risk evaluation. This also pertains to cancer-preventive drugs, and self-medication with aspirin or other potential chemopreventive drugs is strongly discouraged because of the possibility of serious, potentially lethal, adverse events.

1. MEDICAL EXPOSURES

1.1. Introduction

The 4th revision of the European Code against Cancer (Box 1) aims to give recommendations to reduce the risk of cancer through personal behavioural changes or participation in organised intervention programmes [1]. In this context, medical exposures differ from recommendations regarding, for example, smoking, sun exposure, or dietary habits, since most medical exposures are not controlled by the individual but administered as diagnostic or therapeutic measures by healthcare professionals. Therefore,

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Box 1. European Code Against Cancer

EUROPEAN CODE AGAINST CANCER

12 ways to reduce your cancer risk

1 Do not smoke. Do not use any form of tobacco.

2 Make your home smoke free. Support smoke-free policies in your workplace.

3 Take action to be a healthy body weight.

4 Be physically active in everyday life. Limit the time you spend sitting.

5 Have a healthy diet:
- Eat plenty of whole grains, pulses, vegetables and fruits.
- Limit high-calorie foods (foods high in sugar or fat) and avoid sugary drinks.
- Avoid processed meat; limit red meat and foods high in salt.

6 If you drink alcohol of any type, limit your intake. Not drinking alcohol is better for cancer prevention.

7 Avoid too much sun, especially for children. Use sun protection. Do not use sunbeds.

8 In the workplace, protect yourself against cancer-causing substances by following health and safety instructions.

9 Find out if you are exposed to radiation from naturally high radon levels in your home. Take action to reduce high radon levels.

10 For women:
- Breastfeeding reduces the mother's cancer risk. If you can, breastfeed your baby.
- Hormone replacement therapy (HRT) increases the risk of certain cancers. Limit use of HRT.

11 Ensure your children take part in vaccination programmes for:
- Hepatitis B (for newborns).
- Human papillomavirus (HPV) (for girls).

12 Take part in organized cancer screening programmes for:
- Bowel cancer (men and women).
- Breast cancer (women).
- Cervical cancer (women).

The European Code against Cancer focuses on actions that individual citizens can take to help prevent cancer. Successful cancer prevention requires these individual actions to be supported by governmental policies and actions.

although the target population for the European Code against Cancer is the general public, guidance on medical exposures should also be directed toward healthcare professionals. A new challenge is the increasing accessibility of drugs through web-based providers, typically without oversight by healthcare professionals or proper instructions for use.

Medical exposures encompass pharmaceutical drugs and the use of ionising radiation in medical diagnostics or therapy. In use of pharmaceutical drugs or ionising radiation, potential increases in the long-term risk of cancer or other adverse effects need to be considered in the context of health benefits – often substantial and immediate – from diagnosis and/or treatment. Chemotherapy and radiotherapy represent classical examples of the need for such careful benefit/risk evaluations, since both types of therapy may induce development of second malignancies, besides their ability to improve survival from the primary cancer being treated. For measures of screening and prevention, the benefit/risk ratio is generally lower than for therapeutic measures: e.g. in the use of X-rays in routine health checks or in the use of tamoxifen for breast cancer prevention. For all new medical interventions, the benefits should be demonstrated by rigorous research, ideally by randomised trials.

The primary objective of the present review was to provide the scientific justification for the recommendation on hormone replacement therapy (HRT), today predominantly prescribed as menopausal hormone therapy (and evaluated as such in the review), for which the Code recommends: "Hormone replacement therapy (HRT) increases the risk of certain cancers. Limit use of HRT". This recommendation is based on unequivocal scientific evidence that HRT is carcinogenic to humans and may induce cancers in female genital organs and breast [2,3]. Although treatment with HRT remains justified under certain medical conditions, the general population should be informed about the cancer risk and avoiding use of HRT outside defined indications. Carcinogenicity has also been established for several other medical exposures, including medications other than HRT and medical use of ionising radiation; however, no general recommendations were given for these measures in the 4th edition of the European Code against Cancer as their use relies on medical expertise and thorough benefit–risk evaluation in each individual.

1.2. Pharmaceutical drugs

A number of drugs used in medical practice have been established as carcinogenic to humans [3]. Some of these drugs – e.g. anti-neoplastic agents – exhibit a high benefit–risk ratio under the approved indications, and continued use of these drugs is endorsed [4]. In contrast, a decision to prescribe and use any drug with established or probable carcinogenicity (e.g. HRT) for non-life-threatening conditions is more problematic [5,6]. Irrespective of drug type and indication, it is imperative to monitor potential long-term carcinogenicity of drugs, because of the limited evidence of carcinogenic potential at the time of licensing. At that time, knowledge of the carcinogenic potential is based almost exclusively on preclinical studies, since the pre-marketing randomised clinical trials with limited sample sizes and follow-up are not well suited to the study of rare outcomes such as cancer, which typically has a long latency period [7–9]. Several drugs have been evaluated for potential cancer-preventive properties: i.e. their ability to interrupt mechanisms or pathways that initiate or accelerate development of cancer [10,11]. Currently, only a few drugs have been approved for cancer preventive therapy: e.g. tamoxifen for women at high risk of breast cancer. However, several drugs are under evaluation as preventive or adjuvant therapies against cancer, including for example aromatase inhibitors, aspirin, metformin, and statins [9].

1.3. Medical exposure to ionising radiation

Since the discovery of x-rays and radioactivity, radiation has been extensively utilised in medicine. Radiation has an important role in both diagnosis and treatment of a wide range of diseases, including cancer. The major medical applications of radiation include radiology, radiotherapy and nuclear medicine. Developments in medical imaging – particularly in computed tomography (CT) and its combinations with other imaging techniques – have led to substantial increases in relatively high-dose X-ray examinations. Medical radiation has become the second most important source of exposure to radiation for an average European citizen, after exposure to radon in homes [12]. To alert health professionals about potentially higher doses received by patients from some of the diagnostic procedures, the European Union Euratom directive 97/43 categorised CT and interventional radiology as procedures that expose patients to high doses of radiation. For illustration, a