European Code against Cancer 4th Edition: Process of reviewing the scientific evidence and revising the recommendations

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ABSTRACT

The European Code Against Cancer is a set of recommendations to give advice on cancer prevention. Its 4th edition is an update of the 3rd edition, from 2003. Working Groups of independent experts from different fields of cancer prevention were appointed to review the recommendations, supported by a Literature Group to provide scientific and technical support in the assessment of the scientific evidence, through systematic reviews of the literature. Common procedures were developed to guide the experts in identifying, retrieving, assessing, interpreting and summarizing the scientific evidence in order to revise the recommendations. The Code strictly followed the concept of providing advice to European Union citizens based on the current best available science. The advice, if followed, would be expected to reduce cancer risk, referring both to avoiding or reducing exposure to carcinogenic agents or changing behaviour related to cancer risk and to participating in medical interventions able to avert specific cancers or their consequences. The information sources and procedures for the review of the scientific evidence are described here in detail. The 12 recommendations of the 4th edition of the European Code Against Cancer were ultimately approved by a Scientific Committee of leading European cancer and public health experts.

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reduce the risk of cancer. To update the scientific evidence to revise the recommendations, common procedures were developed to guide the scientific experts in retrieving, assessing, interpreting and summarizing the evidence. Supplementary information in question-and-answer format, explaining and providing additional information on the 12 recommendations as well as cancer prevention topics not covered in the Code, was developed following the same methodology [1,3].

In the present paper, those procedures are described in detail.

2. General considerations on the methods

2.1. Causality and effectiveness in recommendations for cancer prevention

Recommendations in the Code and corresponding question and answers can be divided into two broader categories, with implications for the required nature and level of evidence. The first type of recommendation focuses on established causes of cancer and risks of developing cancer that people can avoid or reduce. The second type of recommendation deals with medical interventions able to avert specific cancers or their consequences.

Related to the first type of recommendation, the supporting evidence results from the assessment of the causality of associations between exposure and disease. A recommendation to avoid or reduce a given exposure or risk is justified if the available scientific evidence is sufficient to infer a causal association. The Code strictly follows this concept and aims to provide advice to European Union (EU) citizens as recommendations that, if followed, would be expected to reduce cancer risk. This refers both to avoiding or reducing exposure to carcinogenic agents (such as tobacco or ultraviolet radiation [UV]) and to changing behaviour related to cancer risk (such as sedentary behaviour).

Related to the second type of recommendation, the Code aims to provide information on medical interventions that, if followed, reduce the risk of developing or dying from specific cancers. Medical interventions include vaccinations, for instance to prevent viral infection that can ultimately lead to development of cancer [4,5]. Some interventions aim to prevent cancer by early detection or treatment of precancerous lesions, for instance of the cervix [6] or colon and rectum [7]. They may also indicate how to mitigate progression of cancer, such as through detection and treatment of early invasive breast cancer [8].

The supporting evidence for interventions requires evaluation of the efficacy and effectiveness of such defined actions. Like any health intervention, preventive interventions may also have harmful effects. Therefore, careful consideration is given to the balance between the potential benefit and the potential harm before an intervention can be recommended. This applies particularly to recommendations for the general public or large groups of the general population, due to the very large numbers of people exposed to the intervention in order to prevent relatively few cases of disease.

2.2. Process for reviewing the relevant evidence

For the update of the European Code Against Cancer, Working Groups (WGs) of independent scientific experts in different fields of cancer research and prevention were appointed by the European Code Against Cancer scientific secretariat at the International Agency for Research on Cancer (IARC). The six topic-related WGs dealt with: smoking and other forms of tobacco use (Tobacco WG); diet, physical activity, body weight and alcohol (Nutrition WG); environmental, occupational, and pharmaceutical exposures (Environment WG); radiation (Radiation WG); infections and vaccinations (Infections and Vaccinations WG); and cancer screening (Screening WG). The WGs were asked to review the recommendations in the 3rd edition of the Code and to update them if necessary. The recommendations proposed by the WGs were based on a consensus among the experts on the interpretation of the evidence and an appropriate balance between the benefit and risk of following the recommendations. The final form of the recommendations was ultimately approved by a Scientific Committee of leading experts from major European cancer research or public health institutions [1], following an iterative discussion with the WGs.

A common methodology was developed on how to assess the scientific evidence forming the basis of any recommendation (to avoid or reduce exposure, to change behaviour, or to participate in interventions) and the corresponding questions and answers of additional public health messages [1].

A Literature Group of epidemiologists experienced in systematic review of the scientific literature was established to provide scientific and technical support to the WGs in the identification and analysis of the relevant scientific evidence. In this case, the assessment of the evidence was based on the systematic review of the literature according to the following steps: defining clinical questions, searching the relevant literature, assessing the
Table 1
Correspondence between IARC Monographs and WCRF/AICR reports in overall levels of evidence and whether the evidence was sufficient to consider a recommendation for the European Code against Cancer

<table>
<thead>
<tr>
<th>IARC monographs</th>
<th>WCRF/AICR reports</th>
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<tbody>
<tr>
<td><strong>Sufficient evidence for Code recommendations</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Group 1—carcinogenic to humans</strong></td>
<td>Convincing evidence for causal relationship</td>
</tr>
<tr>
<td>Sufficient evidence of carcinogenicity in humans. Generally required:</td>
<td>Overall evidence strong enough to justify goals and recommendations to reduce cancer incidence. Causal relationship highly unlikely to be modified by new evidence in foreseeable future. Generally required:</td>
</tr>
<tr>
<td>• Several criteria of causality fulfilled [52]</td>
<td>• Evidence from more than one study type and at least two independent cohort studies</td>
</tr>
<tr>
<td>• Strong association (large relative risk)</td>
<td>• No substantial unexplained heterogeneity within or between study types or in different populations regarding presence or absence of association, or direction of effect</td>
</tr>
<tr>
<td>• Replication of results in several studies of same design or with different epidemiological approaches or different exposure conditions</td>
<td>• Good quality studies to confidently exclude the possibility that the observed association results from random or systematic error, including confounding, measurement error, and selection bias</td>
</tr>
<tr>
<td>• Explanation for inconsistent results, if present</td>
<td>• Presence of a plausible biological gradient (“dose–response”) in the association (gradient need not be linear or in same direction across different levels of exposure, so long as this can be explained plausibly)</td>
</tr>
<tr>
<td>• Graded response to exposure (not mandatory)</td>
<td>• Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes</td>
</tr>
<tr>
<td>• Decline in risk after stopping exposure</td>
<td></td>
</tr>
<tr>
<td>Additional factors may increase confidence in causal relationship:</td>
<td></td>
</tr>
<tr>
<td>• Induction of multiple tumour types, temporality</td>
<td></td>
</tr>
<tr>
<td>• Precision of effect estimates</td>
<td></td>
</tr>
<tr>
<td>• Plausibility, coherence of overall database</td>
<td></td>
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<tr>
<td>• Biomarker data</td>
<td></td>
</tr>
<tr>
<td>Exceptionally with less than sufficient evidence of carcinogenicity in humans but with sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans of a relevant mechanism of carcinogenicity</td>
<td></td>
</tr>
<tr>
<td><strong>Not sufficient evidence for Code recommendations</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Group 2A—probably carcinogenic to humans</strong></td>
<td>Limited—suggestive evidence for causal relationship</td>
</tr>
<tr>
<td>Limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals.</td>
<td>Overall evidence too limited for probable or convincing causal judgement, but suggesting direction of effect.</td>
</tr>
<tr>
<td>• In some cases: inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals</td>
<td>• Evidence methodologically flawed or limited in amount, but generally showing a consistent direction of effect</td>
</tr>
<tr>
<td>• Exceptionally: limited evidence of carcinogenicity in humans provides the sole basis for classification</td>
<td>• Recommendations to reduce cancer incidence rarely justified</td>
</tr>
<tr>
<td>• In some cases mechanistic considerations show that agent belongs to a class of agents for which one or more members have been classified in Group 1 or Group 2A</td>
<td>Generally required:</td>
</tr>
<tr>
<td><strong>Group 2B—possibly carcinogenic to humans</strong></td>
<td>• Evidence from at least two independent cohort studies or at least five case–control studies</td>
</tr>
<tr>
<td>Limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals.</td>
<td>• Direction of effect is generally consistent, although some unexplained heterogeneity may be present</td>
</tr>
<tr>
<td>• In some cases: inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals</td>
<td>• Evidence for biological plausibility</td>
</tr>
<tr>
<td>• In some instances: inadequate evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals and supporting evidence from mechanistic and other relevant data</td>
<td></td>
</tr>
<tr>
<td>• In some cases there may only be strong evidence from mechanistic and other relevant data</td>
<td></td>
</tr>
<tr>
<td><strong>Group 3—not classifiable as to its carcinogenicity to humans</strong></td>
<td>Limited—no conclusion</td>
</tr>
<tr>
<td>Inadequate evidence of carcinogenicity in humans and inadequate or limited evidence of carcinogenicity in experimental animals.</td>
<td>Evidence is so limited that no firm conclusion can be made.</td>
</tr>
<tr>
<td>• Exceptionally: inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental studies and strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans</td>
<td>This category represents an entry level, and is intended to allow any exposure for which there are sufficient data to warrant Panel consideration, but where insufficient evidence exists to permit a more definitive grading. This does not necessarily mean a limited quantity of evidence. A body of evidence for a particular exposure might be graded “limited – no conclusion” for a number of reasons. The evidence might be limited by the amount of evidence in terms of the number of studies available, by inconsistency of direction of effect, by poor quality of studies (for example, lack of adjustment for known confounders), or by any combination of these factors</td>
</tr>
<tr>
<td>• Agents that do not fall into any other group are also placed in this category</td>
<td></td>
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</tbody>
</table>
methodological quality of retrieved studies, and preparing evidence tables and summary documents with the most relevant information and the level of evidence about the question posed by the WG members.

As described in more detail below, it was not the task of WG members to review the totality of scientific evidence, but ensuring the recommendations were based on sufficient scientific evidence for preventing cancer or its consequences, if following them. When sufficient scientific evidence was available from authoritative sources considered as scientifically reliable, they were used as the evidence base for the recommendations. Prerequisite was that these sources were following a rigorous procedure of assessing the scientific evidence, complete and recent.

For confirming evidence on the carcinogenicity to humans, the following sources were defined as fulfilling these criteria:

- the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans (see Section 3.1);
- the Expert Report and Continuous Update Project (CUP) of the World Cancer Research Fund and the American Institute of Cancer Research (WCRF/AICR) (see Section 3.1).

The methods of IARC and WCRF/AICR are similar in their main principles (Table 1): both consider as a primary source of evidence data from human studies, followed by evidence from studies in experimental animals, and mechanistic data. However, the second category in the classification of carcinogenicity differs between the two methods. While WCRF/AICR’s definition for “Probable evidence for causative relationship” refers to “overall evidence strong enough to justify goals and recommendations to reduce cancer incidence, but not as strong as convincing category”; the IARC Monographs’ classification of “Group 2A—probably carcinogenic to humans” indicates “limited evidence of carcinogenicity in humans” (see Table 1).

In the case of the medical interventions, the following authoritative sources were examined:

- the IARC Handbooks of Cancer Prevention (see Section 3.1);
- the World Health Organization (WHO) position papers (see Section 3.1);
- the European Guidelines for Quality Assurance in Cancer Screening (see Section 3.1).

When the systematic reviews provided by those sources were not sufficiently recent, a systematic search of the most recent literature was performed to see whether it would alter the earlier assessment. This applied in particular to some of the questions and answers related to the recommendations.

Below (Section 4), a detailed description is provided of how these procedures for evaluating the evidence were used for each of the 12 individual recommendations.

3. Criteria for updating the evidence

The following criteria for updating the evidence for the recommendations and their corresponding questions and answers were adopted (Fig. 1).

As explained elsewhere [1], there had to be sufficient scientific evidence that following the recommendation to avoid or reduce exposure to a harmful agent, or to adopt a healthy behaviour, would reduce a person’s risk of developing cancer. The WG made this decision based on:

- whether the exposure was classified as a Group 1 carcinogen ("carcinogenic to humans") in the IARC Monographs, and whether the more recent scientific literature appearing after the Monograph did not alter this assessment [9,10];
- whether the exposure or behaviour was classified as showing strong evidence (convincing or probable causal relationship with the cancer risk) by the Expert Report and Continuous Update Project (CUP) of WCRF/AICR, and whether the more recent scientific literature appearing after the WCRF/AICR reports did not alter this assessment [11,12];
- whether the WG’s own reviews of the most recent scientific literature provided evidence corresponding to a classification of a Group 1 carcinogen by the IARC Monographs or strong evidence by WCRF/AICR.

For the recommendations and questions and answers based on interventions for cancer prevention (e.g. on tobacco cessation, vaccination or screening), evidence on the effectiveness of interventions was retrieved initially from the IARC Handbooks of Cancer Prevention [6,8,13], the WHO position papers [4,5,14], and the European Guidelines for Quality Assurance in Cancer Screening [15–18].

The WG made a recommendation based on whether the systematic literature review conducted by the WG and the Literature Group provided evidence on interventions that the WG members judged to be sufficiently strong.
Fig. 1. Criteria used for grading the evidence of causality and of effectiveness for each recommendation of the 4th edition of the European Code Against Cancer (similarly applied to the questions and answers).
3.1. Description of the authoritative sources of evidence

Comprehensive reviews of the relevant literature have been conducted by IARC in its programme of Monographs on the Evaluation of Carcinogenic Risks to Humans. The programme has been running since 1971, and to date 971 agents have been evaluated and classified as to their carcinogenicity to humans [9,10]. The topics covered by the IARC Monographs are regularly reviewed in international advisory meetings [19]. New Monographs evaluations are also conducted on previously reviewed topics if new evidence indicates the need for an update or a reassessment. Depending on the evidence, the grading may range from strong evidence of carcinogenicity to evidence suggesting lack of carcinogenicity (Table 1). A similar, comprehensive approach to the assessment of causality and cancer risk has been taken by WCRF/AICR in their Second Expert Report “Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective” and the Continuous Update Project [11,12]. For the Report [11], 20 systematic literature reviews, covering 19 cancer sites as well as weight gain and the development of obesity, were commissioned from independent academic research teams [20]. In an extensive consultative process involving the centres participating in the literature reviews, experts from the United Nations and other international organizations, the multidisciplinary panel of experts considered the body of evidence as a whole, in order to reach an overall evaluation of whether a given factor plays a causal role in the development of or protection from cancer in humans.

As stated above, the two methods differ as regards the second category in the classification of carcinogenicity (Table 1).

The IARC Handbooks of Cancer Prevention were launched in 1995 to complement the IARC Monographs’ evaluations of carcinogenic hazards with evaluations of the scientific evidence on the cancer-preventive potential of chemopreventive agents and of primary and secondary prevention interventions. The working procedures and the evaluation scheme of the IARC Handbooks of Cancer Prevention closely mirror those of the IARC Monographs. Interdisciplinary working groups of expert scientists review the published studies and evaluate the weight of the evidence that an agent or activity can prevent cancer [21].

The WHO position papers on hepatitis B virus (HBV) and human papillomavirus (HPV) vaccines belong to a series of regularly updated position papers on vaccines and vaccine combinations against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale immunization programmes. The papers are reviewed by external experts and WHO staff, and reviewed and endorsed by the WHO Strategic Advisory Group of Experts (SAGE) on Immunization. The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) methodology is used to systematically assess the quality of available evidence [22].

The European Guidelines for Quality Assurance in Cancer Screening have been developed by experts and published by the European Commission. They cover all aspects of colorectal, breast and cervical cancer screening and provide guiding principles and detailed protocols, standards and recommendations that, if followed, ensure that screening services of high quality are provided to the population. Recommendations for breast and cervical cancer screening quality assurance are based on expert consensus [15–17], while recommendations for colorectal cancer screening quality assurance are based on the systematic review of the literature [18].

3.2. Steps undertaken in systematic reviews

The clinical questions initially agreed upon and formulated by the experts of each WG (Supplementary data 1) were developed according to the PICOS method [23–25]:

- P: patients/population characteristics.
- I: intervention on which the question is focused.
- C: comparison intervention/control/reference group.
- O: outcome measure relevant for the clinical question.
- S: study design on which to base the evidence search.

The PICOS components of each prioritized question were used by the Literature Group to define specific keywords used in comprehensive bibliographic searches. Bibliographic searches were performed on the Cochrane Library, Medline, Embase, and PsycINFO for articles appearing between 1/1/2000 and 31/1/2013 using MeSH terms and free text words. Articles suggested by the WG members, if published within the same time period, were added to the literature base. If a large amount of literature for a given topic was retrieved, preference was given in the first instance to systematic reviewed published recently (since 2007). If updated systematic reviews were retrieved addressing the PICOS questions, the search for primary studies was limited to those studies published after the last search date of the most recently published systematic review (e.g. when a systematic review that searched primary studies until February 2006 was retrieved, the Literature Group only searched primary studies published since 2006). Studies fulfilling the inclusion criteria both for study design and for clinical questions published after the deadline 31/1/2013 were considered and included if proposed by the WG members and if they would change the body of evidence. In the case of retrieval of many systematic reviews addressing the same PICOS question, only the “best” systematic reviews were considered. The criteria for selection of the best reviews were: (i) the results of the methodological quality assessment, (ii) the update of the bibliographic search and (iii) the verification that the reviews included the same primary studies (overlapping). The included reviews were therefore those that were most up-to-date, of the highest methodological quality, and included the largest number of primary studies.

The inclusion criteria for primary studies were as follows. For each kind of question (effectiveness, diagnostic accuracy, acceptability and compliance) a hierarchy of the study designs to be considered and inclusion/exclusion criteria was produced by the Literature Group. For studies on effectiveness, randomized controlled trials (RCTs) were considered as the best source of evidence. For studies on diagnostic accuracy, cross-sectional studies with verification by reference standard were considered as the best source of evidence.

The quality assessment of evidence (systematic reviews and primary studies) on the effectiveness of interventions was performed using criteria extracted from published and validated checklists (Supplementary data 2). For each question or group of questions pertaining to the same topic, the Literature Group provided:

- for each included study: an evidence table with the main characteristics of the study (study design, objective of the study, comparisons, participant characteristics, outcome measures, results, methodological quality, level of evidence) (Supplementary data 3)
- a summary document providing a description of the search strategy used for each database, a synthesis of the number, types and characteristics of included studies, the overlapping of primary studies when selecting systematic reviews, the overall methodological quality and the main methodological flaws, their results, the conclusions and the overall level of evidence. (Supplementary data 4).
The following grading of level of evidence was used:

I multiple RCTs of reasonable sample size, or their systematic reviews;
II one RCT of reasonable sample size, or 3 or fewer RCTs with small sample size;
III prospective cohort studies or nested case–control studies, or their systematic reviews; diagnostic cross-sectional accuracy studies or their systematic reviews;
IV retrospective case–control studies or their systematic reviews, time series analysis;
V case series; before–after studies without control group, cross-sectional surveys;
VI expert opinion.

4. Sources of evidence

For each of the 12 recommendations and their corresponding questions and answers, the applied methodology and the sources of evidence were the following:

“1. Do not smoke. Do not use any form of tobacco.”
Evidence on the causal association between smoking and cancer was assessed as convincing for the haematopoietic system (specifically, myeloid leukaemia), for cancers of the cervix, colorectum, kidney, larynx, liver, lung, nasal cavity and paranasal sinus, oesophagus, oral cavity, ovary, pancreas, pharynx (naso-, oro-, and hypopharynx), stomach, ureter, and urinary bladder, and for hepatoblastoma (in the children of smokers), as extensively documented in the IARC Monographs [10,26,27]. Evidence on the causal association between smokeless tobacco overall and cancer was assessed as convincing for cancers of the oesophagus, oral cavity, and pancreas, from the IARC Monographs [10,27,28] and relevant studies suggested by the WG members [29].

Evidence on the reduction in risk of cancer and of cancer death after smoking cessation was based on the work reported in the IARC Handbooks of Cancer Prevention Volume 11 [13] and on evidence from milestone studies with recently reported follow-up [29], while the effectiveness of interventions to stop smoking was assessed using 10 clinical PICOS-based questions (Supplementary data 1) for systematic literature searches [3,29].

“2. Make your home smoke free. Support smoke-free policies in your workplace.”
Evidence on the causal association between second-hand tobacco smoke and cancer was assessed as convincing for lung cancer, from the IARC Monographs [10,26,27].
Evidence on the effectiveness of smoke-free policies in reducing exposure to second-hand tobacco smoke in different environments, including voluntary smoking restrictions in the residential home, was assessed from the IARC Handbooks of Cancer Prevention Volume 13 [30] and relevant consistent studies suggested by the WG members [29].

“3. Take action to be a healthy body weight.”
Evidence on the causal association between excess body weight and cancer was assessed and updated as convincing for cancers of the breast (postmenopausal), colorectum, endometrium, gall bladder, kidney, oesophagus, ovary, pancreas and prostate (advanced), from WCRF/AICR Continuous Update Project (CUP) [11,12,31], the IARC Handbooks of Cancer Prevention [32] and relevant studies suggested by the WG members [33].

“4. Be physically active in everyday life. Limit the time you spend sitting.”
Evidence on the protective association between physical activity and cancer was assessed and updated as convincing for colorectal cancers and endometrial cancers, from WCRF/AICR CUP [11,12], the IARC Handbooks of Cancer Prevention [32] and relevant studies suggested by the WG members [34].

Evidence that a sedentary lifestyle causes weight gain, overweight, and obesity was assessed as convincing by the WCRF/AICR Panel [11].

“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.”

Evidence on the protective association between dietary fibre and colorectal cancer was assessed and updated as convincing, from the WCRF/AICR CUP [12] and relevant studies suggested by the WG members [35].

Evidence that diets rich in high-calorie foods, such as fatty and sugary foods, and in sugary beverages lead to excess calorie intake and promote obesity, and in turn lead to an increased risk of cancer, was assessed as convincing by the WCRF/AICR [35].

Evidence on the causal association between high intakes of red meat and processed meat and colorectal cancer was assessed and updated as convincing by the WCRF/AICR CUP [12].

Evidence on the association between salt intake and stomach cancer was assessed from the WCRF/AICR [11] and relevant recent studies suggested by the WG members [35], to conclude the evidence to be strong enough to justify the recommendation.

“6. If you drink alcohol of any type, limit your intake. Not drinking alcohol is better for cancer prevention.”
Evidence on the causal association between alcohol and cancer was assessed as convincing for cancers of the colon, female breast, larynx, liver, oesophagus, oral cavity, pharynx, and rectum, from the IARC Monographs [36], the WCRF/AICR CUP [37,38] and relevant studies suggested by the WG members [39].

“7. Avoid too much sun, especially for children. Use sun protection. Do not use sunbeds.”
Evidence on the causal association between exposure to UVR and cancer was assessed as convincing for all types of skin cancer, from the IARC Monographs [40] and relevant studies suggested by the WG members [41]. Evidence on the causal association between UVR-emitting devices (e.g. sunbeds) and skin cancer was assessed as convincing by the IARC Monographs for UVR [40] and was confirmed by a recent systematic review and meta-analysis [41].

Evidence on limiting exposure to UVR or sunlight and possible resulting vitamin D deficiency was assessed by systematic literature review based on 1 clinical PICOS-based question (Supplementary data 1) [3].

“8. In the workplace, protect yourself against cancer-causing substances by following health and safety instructions.”
Evidence on the causal association between 44 chemical exposures in the workplace and cancer (including cancers of the larynx, liver, lung, nasopharynx, ovary, stomach, and urinary bladder, as well as non-melanoma skin cancer, leukaemia and lymphoma, mesothelioma, and sinonasal cancer) was assessed as convincing, from the IARC Monographs [10] and relevant studies suggested by the WG members [42].

“9. Find out if you are exposed to radiation from naturally high radon levels in your home. Take action to reduce high radon levels.”
Evidence on the causal association between radon and lung cancer was assessed as convincing, from the IARC Monographs [40].

International guidance on radon concentration levels and practical methods for reducing high radon levels have been assessed by WHO [43], the International Commission on Radiological Protection (ICRP) [44] and relevant studies suggested by the WG members [45].

“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.”

Evidence on the protective association between breastfeeding and breast cancer was assessed and updated as convincing, from the WCRF/AICR CUP [12,46] and relevant studies suggested by the WG members [47]. Evidence on duration of breastfeeding, the protective effect of breastfeeding on breast cancer risk, and the effect of breastfeeding on women’s weight was assessed from systematic literature searches based on 2 clinical PICOS-based questions (Supplementary data 1) [3,47].

Evidence on the causal association between HRT and cancer was assessed as convincing for cancers of the breast, endometrium, and ovary, based on the IARC Monographs [10,48] and relevant studies suggested by the WG members on the basis of an updated literature review [49].

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

Evidence on the causal association between cancer and exposure to HBV and HPV has been assessed by the IARC Monographs Programme [9].

The effectiveness and safety of HBV vaccine assessed in the latest WHO position paper [14] was updated with systematic literature searches based on 1 clinical PICOS-based question (Supplementary data 1) to identify systematic reviews and individual studies [3,50].

The efficacy and safety of HPV vaccines assessed in the WHO position papers [4,5] were updated with systematic literature searches based on 3 clinical PICOS-based questions (Supplementary data 1) to identify systematic reviews on the efficacy and safety of HPV vaccines in women, and to identify RCTs on the efficacy and safety of HPV vaccines in men [3,50].

Evidence on the causal association between cancer and exposure to hepatitis C virus (HCV), human immunodeficiency virus (HIV) and Helicobacter pylori (H. pylori) has been assessed by the IARC Monographs Programme [9]. HCV, H. pylori and HIV were not part of any of the recommendations of the Code but are part of the infection-related questions and answers. Evidence was retrieved on the effectiveness of persistent HBV infection treatment, of persistent HCV infection treatment, and of antiretroviral treatment in HIV with systematic literature searches based on 3 clinical PICOS-based questions (Supplementary data 1) [3,50].

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

For colorectal, cervical, breast, and prostate cancer screening, the evidence was retrieved initially from the IARC Handbooks of Cancer Prevention [6,8] and the European Guidelines for Quality Assurance in Cancer Screening published between 2003 and January 2013 [15–18]. A systematic update of the evidence on impact on mortality/incidence, age, interval and optimal test, further benefits and harms was performed to support the recommendations using systematic literature searches based on 38 clinical PICOS-based questions (Supplementary data 1) [3,51].

5. Conclusions

The described methodology was consistently followed by the WGs to review and update the evidence supporting the recommendations in the 4th edition of the European Code Against Cancer and their related questions and answers. The recommendations were proposed by the WGs and ultimately approved by the Scientific Committee [1].

The objective of the methodology for reviewing and updating the European Code Against Cancer was to adopt a unified approach for evaluating the causes of cancer and the effectiveness of interventions in order to ensure that the recommendations were as robust and authoritative as possible.

Further work based on a systematic and possibly continuous process of updating will be needed in the future; recent systematic reviews of the scientific evidence from this project or elsewhere could provide a basis for the timely updating of the recommendations or other parts of the Code.

Conflict of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jcanep.2015.08.014.

References
