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European Code against Cancer, 4th Edition: Cancer screening☆

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ABSTRACT

In order to update the previous version of the European Code against Cancer and formulate evidence-based recommendations, a systematic search of the literature was performed according to the methodology agreed by the Code Working Groups. Based on the review, the 4th edition of the European Code against Cancer recommends:

"Take part in organized cancer screening programmes for:

- Bowel cancer (men and women)
- Breast cancer (women)
- Cervical cancer (women)."

Organized screening programs are preferable because they provide better conditions to ensure that the Guidelines for Quality Assurance in Screening are followed in order to achieve the greatest benefit with the least harm. Screening is recommended only for those cancers where a demonstrated life-saving effect substantially outweighs the potential harm of examining very large numbers of people who may otherwise never have, or suffer from, these cancers, and when an adequate quality of the screening is achieved. EU citizens are recommended to participate in cancer screening each time an invitation from the national or regional screening program is received and after having read the information materials provided and carefully considered the potential benefits and harms of screening. Screening programs in the European Union vary with respect to the age groups invited and to the

Abbreviations: CI, confidence interval; CIN, cervical intraepithelial neoplasia; CRC, colorectal cancer; DRE, digital rectal examination; ERR, excess relative risk; EU, European Union; EUNICE, European Network for Information on Cancer project; FIT, faecal immunochemical test; FOBT, faecal occult blood test; FS, flexible sigmoidoscopy; gFOBT, guaiac-based faecal occult blood test; HC2, hybrid capture 2; HVP, human papillomavirus; HR, hazard ratio; IARC, International Agency for Research on Cancer; LEEP, loop electrosurgical excision procedure; LSIL, low-grade squamous intraepithelial lesion; OR, odds ratio; PICOS, population, intervention, control, outcome, study design; PCR, polymerase chain reaction; PSA, prostate-specific antigen; RCT, randomized controlled trial; RR, relative risk; SR, systematic review; TC, total colonoscopy; TRUS, transrectal ultrasound; WG, working group.

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interval between invitations, depending on each country's cancer burden, local resources, and the type of screening test used

For colorectal cancer, most programs in the EU invite men and women starting at the age of 50–60 years, and from then on every 2 years if the screening test is the guaiac-based fecal occult blood test or fecal immunochemical test, or every 10 years or more if the screening test is flexible sigmoidoscopy or total colonoscopy. Most programs continue sending invitations to screening up to the age of 70–75 years.

For breast cancer, most programs in the EU invite women starting at the age of 50 years, and not before the age of 40 years, and from then on every 2 years until the age of 70–75 years.

For cervical cancer, if cytology (Pap) testing is used for screening, most programs in the EU invite women starting at the age of 25–30 years and from then on every 3 or 5 years. If human papillomavirus testing is used for screening, most women are invited starting at the age of 35 years (usually not before age 30 years) and from then on every 5 years or more. Irrespective of the test used, women continue participating in screening until the age of 60 or 65 years, and continue beyond this age unless the most recent test results are normal.

1. Introduction

The previous version of the European Code against Cancer [1] recommended citizens to participate in regular screening for those cancers amenable to it. Men and women from 50 years of age were recommended to participate in colorectal screening; women from 25 years of age were recommended to participate in cervical screening, and from 50 years of age to participate in breast screening. All screening programs should have built-in quality control procedures in compliance with the European Union Guidelines for Quality Assurance in Screening [2–4].

In the European Union (EU), colorectal cancer is the third most common cancer and the second leading cause of death due to cancer, with more than 345,000 new cases and 150,000 deaths in 2012. Both men and women are at risk of developing colorectal cancer. About one in 20 people will develop colorectal cancer during their lifetime. About eight out of ten people who are diagnosed with colorectal cancer are older than 60 years. About five out of ten people diagnosed with colorectal cancer will die of the disease; the risk of dying is lower if the cancer is detected at screening [5]. In the EU, breast cancer is the most common cancer and the most common cause of death due to cancer in women, with about 365,000 new cases and 91,000 deaths per year. About one in 10 women will be diagnosed with breast cancer during their lifetime—mostly middle-aged and older women, but younger women can also develop breast cancer. One in four women with breast cancer will die from the disease. Breast cancer in men is rare [5].

In the EU, there were about 34,000 new cases and more than 13,000 deaths due to cervical cancer in 2012. Rates of cervical cancer are particularly high in many of the countries to the east and south that acceded to the EU after 2003; rates of death due to cervical cancer reported in Romania and Lithuania are seven times higher than those in Finland [5]. The extreme differences result primarily from the lack of or inadequate implementation of organized cervical cancer screening programs in many countries that have recently acceded to the EU [6].

The status of cancer screening programs in the EU is described in the first report on implementation of the Council Recommendation on Cancer Screening [6]. In 2007, over 64 million women in the EU were targeted for breast cancer screening programs based on mammography, and approximately 12 million women attended (21 million women were invited by population-based programs rolled out by EU member states). Approximately 146 million women were targeted by cervical cancer screening programs which were running or being established in the EU in 2007, and approximately 32 million women attended (17 million were invited by population-based programs rolled out by EU member states). Approximately 107 million individuals were targeted by colorectal cancer screening programs which were running or being established in the EU in 2007, and approximately 12 million women and men attended (over 8 million were personally invited by population-based programs rolled out by EU member states) [6].

Box 1. European Code against Cancer, 4th edition 2014.

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 programs for:
- Hepatitis B (for newborns)
- Human papillomavirus (HPV) (for girls).

12 Take part in organized cancer screening programs 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.

In order to update the previous version of the European Code against Cancer by formulating evidence-based recommendations, a systematic search of the literature was performed according to the methodology agreed by the Working Groups (WGs) involved in the project [7]. Here, we present the new cancer screening recommendations (see Box 1) and a summary of the evidence retrieved. Based on this evidence, additional information was also provided in the questions and answers section (Q&As) available from the Code website [8].

2. Methods

A literature group composed of experts in systematic reviews was appointed to identify and assess the scientific literature relevant for the Code, adopting the following process (for more details see [7]).

- The Screening WG defined clinical questions according to the PICOS (population, intervention, control, outcome, study design) methodology [7].
- Systematic bibliographic searches were performed on the Cochrane Library, Medline, Embase, and PsycINFO from January 1st 2000 to January 31st 2013. Articles suggested by experts in the field were also considered. If a large amount of literature for a given topic was retrieved, preference was given in the first instance to recently published (since 2007) systematic reviews. If updated systematic reviews addressing the PICOS questions were retrieved, the search for primary studies was limited to those studies published after the last search date of the most recently published systematic review [7].
- The methodological quality of retrieved systematic reviews and primary studies was assessed using criteria extracted from published and validated checklists [7].
- For each clinical questions, evidence tables and summary documents with the most relevant clinical information and the level of evidence were prepared [7]. The evidence was graded according to the levels reported in Table 1.
- Finally, the evidence collected was presented and discussed within the Screening WG [7]. Recommendations were made based on consensus agreement obtained within the group [7].

3. Results

3.1. Recommendations

Taking the evidence into account, the 4th edition of the European Code against Cancer (Box 1) recommends that people:

"Take part in organized cancer screening programmes for:

- Bowel cancer (men and women)
- Breast cancer (women)
- Cervical cancer (women)."

Organized screening programs are recommended because they provide the best conditions to ensure that the European Union Guidelines for Quality Assurance in Screening [2–4] are followed, in order to achieve the greatest benefit with the least harm. Screening is recommended only for those cancers where a demonstrated life-saving effect substantially outweighs the potential harm from examining very large numbers of people who may otherwise never have, or suffer from, these cancers and when adequate quality of the screening is achieved. It is recommended to EU citizens to participate in cancer screening each time an invitation from the national or regional screening program is received and after having read the information materials provided and carefully considered the potential benefits and harms of screening. The WG agreed that the evidence on benefits and harms for screening of other cancers, such as prostate or lung cancer, at the time of the preparation of the Code was not sufficiently available to recommend EU citizens to participate in screening outside research programs, designed for evaluation and implementation purposes. Screening programs in the European Union vary with respect to the age groups invited and to the interval between invitations, depending on each country's cancer burden, local resources, and the type of screening test used.

For colorectal, breast and cervical cancer screening primary test, age and interval between screening tests are reported (see Box 2).

3.2. Scientific justification for the Code recommendations

The evidence on incidence and mortality of screening according to age and intervals between tests, and on side effects of colorectal, breast, and cervical cancer screening is presented here, based on the clinical questions (PICOS) as formulated by the Screening WG. The evidence retrieved on the impact of prostate cancer screening on incidence and mortality is also presented. For clarity, the PICOS used (original ones or simplified forms) are also presented in the paragraphs below (Sections 3.2.1,3.2.2, 3.2.3 and 3.2.4)

3.2.1. Colorectal cancer screening

3.2.1.1. Effectiveness. Is the fecal occult blood test (FOBT) screening offered to the general population effective in reducing colorectal cancer mortality, colorectal cancer incidence, and overall mortality?

The results of a meta-analysis of published RCTs [9] demonstrated that a guaiac-based FOBT (gFOBT) strategy appears to be effective in reducing the colorectal cancer (CRC) mortality in people at average risk, but not in reducing CRC incidence. Combined results from the four eligible RCTs [9] showed that participants allocated to gFOBT screening had a statistically significant 16% reduction in the relative risk of CRC mortality: relative risk (RR), 0.84; 95% confidence interval (95%CI): 0.78–0.90. When adjusted for mean screening attendance in the individual studies, there was a 25% relative mortality reduction (RR, 0.75; 95% CI: 0.66–0.84) for those attending at least one round of screening

Table 1
Grading of levels of evidence.

Level	Type of studies retrieved
I	Multiple randomized controlled trials (RCTs) of reasonable sample size, or their systematic reviews (SRs)
II	One RCT of reasonable sample size, or three or fewer RCTs with small sample size
III	Prospective or retrospective cohort studies or their SRs; diagnostic cross-sectional accuracy studies or their SRs
IV	Retrospective case–control studies or their SRs; time series analysis
V	Case series; before–after studies without a control group, cross-sectional surveys
VI	Expert opinion

Note: when results on side effects and/or benefits were derived from observational studies nested in RCTs, the level of evidence was not reported.

Box 2. Primary test, age and interval between tests for colorectal, breast and cervical screening in organized European programs.

Colorectal cancer screening:

- men and women starting at age 50–60 years,
- and from then on, every 2 years if the screening test is the guaiac-based faecal occult blood test (gFOBT) or the fecal immunochemical test (FIT),
- or every 10 years or more if the screening test is flexible sigmoidoscopy (FS) or colonoscopy (TC).

Most programs continue sending invitations to screening up to age 70–75 years.

Breast cancer screening:

- women starting at age 50 years and not before age of 40 years,
- and from then on, every 2 years until age 70–75 years.

Cervical cancer screening:

- Either cytology (Pap) testing or human papillomavirus (HPV).
- If cytology is used for screening, women starting at age 25–30 years and from then on, every 3 or 5 years.
- If HPV testing is used for screening, women starting at age 35 years (usually not before age 30 years) and from then on, every 5 years.

Irrespective of the test used, women continue participating in screening until the age of 60 or 65 years, and continue beyond this age unless the most recent test results are normal.

using the gFOBT (level of evidence: I). At the time of the literature search there were no studies available of effectiveness of the routine colorectal cancer screening programs with the guaiac-based test.

According to evidence from an RCT, fecal immunochemical test (FIT) screening reduces rectal cancer mortality, and from case–control studies it reduces overall CRC mortality. After 8 years, a significant 32% reduction in rectal cancer mortality but no reduction in colon or overall CRC mortality were found [10]. The following limitations should be considered: follow-up of positive FIT was performed by flexible sigmoidoscopy (FS) instead of total colonoscopy (TC), which may explain the lack of effect in the overall CRC mortality. Furthermore, randomization was not based on individuals but on townships. A significant reduction in CRC mortality was observed in two Japanese case–control studies [11,12], ranging from 52% to 83%, depending on years since last FIT (level of evidence: II–IV). A significant reduction in advanced CRC incidence – odds ratio (OR), 0.54, 95%CI: 0.30–0.99 – was observed in one case–control study when FIT was performed within 3 years before the diagnosis [13] (level of evidence: IV).

Is FIT superior to gFOBT in test performance characteristics?

Evidence from RCTs directly comparing gFOBT and FIT demonstrates that the sensitivity of FIT for the detection of cancer was significantly higher. The estimated specificity for not having advanced neoplasia and CRC was lower, although not significantly so, for FIT at a cut-off value of 100 ng/mL than that for gFOBT, while it was similar to that of gFOBT with a cut-off value above 100 ng/mL [14–16] (level of evidence: II). Also according to results coming mainly from indirect comparisons in diagnostic cohort and case–control studies, FIT seems to have a higher cross-sectional sensitivity than gFOBT and a similar or lower specificity in detecting CRC, although a meta-analysis of studies has not been performed [17,18] (level of evidence: III). Evidence from multiple population studies [14–16,19–22] and their meta-analyses of RCTs shows that FIT has a higher detection rate than gFOBT for advanced neoplasia and cancer in both the per-protocol and intention-to-treat analyses [23,24] (level of evidence: I). Furthermore, randomized trials have consistently shown that FIT screening is associated with higher uptake than gFOBT screening, presumably because of easier test handling and the need for sampling of feces from only a single bowel movements instead of three repeated movements [16,20,25].

Is FS screening offered to the general population effective in reducing CRC mortality, CRC incidence, and overall mortality?

The results of a meta-analysis of published RCTs demonstrate that an FS-based strategy is effective in reducing the CRC mortality and incidence in average-risk people [26]. When results from five RCTs [27–31] were combined, a statistically significant 28% reduction in the relative risk of CRC mortality (RR, 0.72; 95%CI: 0.65–0.80) was observed in the invited population (intention-to-treat analysis). Among people participating (per-protocol analysis), a 50% reduction in the relative risk was observed among subjects undergoing the examination (RR, 0.50; 95%CI: 0.35–0.64) [26] (level of evidence: I).

When results from four RCTs [27,29–31] were combined, a statistically significant 18% reduction in the relative risk of CRC incidence (RR, 0.82; 95%CI: 0.73–0.91) was observed in the intention-to-treat analysis. In the per-protocol analysis, a statistically significant 32% reduction in the relative risk was observed among subjects undergoing the examination (RR, 0.68; 95%CI: 0.47–0.89) (level of evidence: I).

Is TC screening offered to the general population effective in reducing CRC mortality, CRC incidence, and overall mortality?

Observational evidence exists on the efficacy of TC screening in reducing CRC mortality and incidence [32–43]. Results from RCTs evaluating CRC mortality and incidence as primary endpoints in screening colonoscopy are not available. Results of studies including subjects undergoing at least one colonoscopy, irrespective of a positive or negative result (both subjects undergoing adenoma removal and/or colonoscopic surveillance because of a positive result, and subjects with no adenomas at colonoscopy are included), show a significant mortality and incidence reduction, ranging from 29% to 65%, in the relative risk of CRC mortality, and from 48% to 67% in the relative risk of CRC incidence. Reduction in the overall CRC mortality and incidence is always significant; however, stratification by site suggests that colonoscopy might not be as effective in the proximal colon as in other segments of the colon/rectum (level of evidence: III–IV).

3.2.1.2. Age range and screening interval. What is the optimal age range in which to perform screening with FOBT as the primary screening test, and what is the best time interval for offering screening by FOBT?

In the trials analyzing gFOBT as the primary screening test, the age range of subjects included is 45–80 years. In these trials the observed mortality reduction is significant, and they include analyses of the whole age ranges, with follow-up times varying from 11.7 to 18 years between the trials. None of the RCTs investigating annual or biennial screening gFOBT reported a formal subgroup analysis of efficacy in different age groups [44–47]. Data from the Nottingham trial at 11 years of follow-up showed no difference in CRC mortality rates between subjects older and younger than 65 years [48], but when separate results were reported for age subgroups after a median of 19.5 years, the Nottingham RCT [49] showed that there was a significant reduction in CRC mortality for the age group older than 60 years but not for the age group younger than 60 years (level of evidence: II). No evidence is available on the best age range for FIT screening. Given the similarities between the tests, the age range can be based on the evidence for the optimal age range from gFOBT trials.

The Minnesota trial is the only trial to directly compare annual and biennial screening. Both intervals were found to be effective in reducing CRC mortality, with the benefit from annual screening appearing to be greater than that for biennial screening, although not significantly different [50] (level of evidence: II). Case–control studies suggest that the effect of FIT on colorectal cancer mortality was significant only in those subjects screened within 3 years before the diagnosis, although power may have been an issue for longer intervals [11–13] (level of evidence: II–IV). A population screening study has shown that repeated FIT screening with a 1, 2, or 3-year interval led to a similar diagnostic yield of advanced neoplasia [51].

What is the optimal age range in which to perform screening with FS as the primary screening test, and what is the best time interval for offering screening by FS?

For FS as the primary screening test, no significant differences for any outcome have been observed between ages 55–59, 60–64, and 65–74 years according to the results of the trials in the UK, Italy, and the United States [29–31] (level of evidence: I). According to the results from published RCTs, the reduction in incidence/mortality still remains after 10–11 years of follow-up, and therefore the interval for offering screening could be longer than 10 years (level of evidence: I). In a study in which FS was offered within 5 years of the previous one, no increase in the effect was observed compared to the results of the RCTs offering FS once in a lifetime and with a similar duration of follow-up. [31].

What is the optimal age range in which to perform screening with TC as the primary screening test, and what is the best time interval for offering screening by TC?

Available evidence on the age range for TC as the primary screening test includes subjects ≥50 years and suggests that the impact is lower among elderly people (>75 years). Available evidence on colonoscopy intervals suggests that interval of at least 10 years is sufficient [32–35,40–42] (level of evidence: III–IV).

3.2.1.3. Negative side effects. What is the rate of negative side effects of FOBT screening?

Rates of minor and severe complications

The results of RCTs demonstrate that the FOBT strategy is safe, with no direct adverse effects. Complications in an FOBT program occur from colonoscopies after positive test results [9] (level of evidence: I).

False-positive results

FOBT is associated with false-positive results, leading to anxiety and unnecessary follow-up colonoscopies. The positive predictive value for CRC and advanced adenoma was estimated respectively at 11% and 40% for gFOBT and 9% and 38% for FIT [16], and respectively 10% and 45% for gFOBT and 10% and 53% for FIT [14].

False-negative results

According to the review of 19 diagnostic cross-sectional studies for the diagnosis of all neoplasms (11 cohort studies and eight case–control studies), sensitivity for CRC ranged from 25% to 79% in cohort diagnostic accuracy studies with follow-up [52].

Acceptability, psychological effects

Results on the impact of screening on daily life and levels of anxiety after a positive FOBT result are reported in the review [52] of three RCTs [53–55]. For people with a false-positive FOBT result, the highest anxiety levels occurred after notification of a positive test and before colonoscopy, the lowest one was experienced the day after colonoscopy, and it remained low 1 month later [53]. Among invited people, 46% were worried by the invitation and refused to participate [54]. Among participants, 16% reported being "extremely" worried [54]. Among 54 people with a false-positive FOBT result, 68% reported experiencing distress [55].

What is the rate of negative side effects of FS screening?

Rates of minor and severe complications

Rates of peritonitis-like reaction, glutaraldehyde colitis, allergic reaction to latex gloves, self-limited bleeding, and mild vagal reactions (nausea, feeling faint or feeling dizzy, abdominal pain) from FS range from 0.2% to 0.6%. Rates of hospitalization within 30 days due to serious hemorrhage involving transfusion, or due to perforation, from FS range from 0% to 0.03%. Rates of severe complications with follow-up colonoscopy are about 10 times higher [28,31,56–59].

False-negative results, interval cancers

Prospective follow-ups of negative screening FS in average-risk populations showed that approximately 0.8% of subjects had advanced neoplasia in the distal colon viewed on a second FS conducted 3 years later, and no adenocarcinomas were detected in the distal colon 3 years after a negative screening examination [60,61].

RCTs on long-term impact of FS and interval cancers [31,62] reported a risk of interval distal cancer after a negative FS of 0.07% (33/44,988) after a mean of 11.5 years. In the SCORE trial, among subjects with negative screening examination results the rate of CRC incidence (interval cancers) remained lower than in the control group over the entire follow-up period (Nelson–Aalen cumulative hazard ratio 0.41; 95%CI: 0.32–0.54; 0.21; 95%CI: 0.13–0.32) when considering only distal CRCs [30].

Acceptability, psychological effects

Results from RCTs and studies on patient-reported experiences after FS in a community-based FS screening program show that FS should be considered an acceptable test.

In the context of the UK FS screening trial [56], 80% of participants responding to a questionnaire on the morning after the test reported no pain or only mild pain during the FS screening examination; 3% described the pain as severe. Three months after the FS, 98% were glad that they had had the test, and 97% would, if asked by a friend, encourage them to have the test. In the context of the NORCCAP trial [63], 70% of participants responding to a questionnaire immediately after the FS reported having experienced no pain, and 21% reported experiencing slight pain during the examination. During the PLCO trial [64], 75% said that they would strongly recommend the procedure to their friends; 76% strongly agreed or agreed that the examination did not cause a lot of pain, and 15–25% indicated that they had experienced a lot of pain, great discomfort, or more discomfort than expected. During the SCORE trial [58], 95% of people undergoing FS completed a short questionnaire administered immediately after the test; 60% reported mild discomfort, 23% reported the test to be less painful than expected, and 2% described the pain as the most severe they had ever experienced. In each study, women were more likely to have significant pain or discomfort than men.

What is the rate of negative side effects of TC screening?

Rates of minor and severe complications

Rates of severe complications (death, cardiopulmonary events, bleeding, perforation, other clinically relevant complications) from TC (including complications from polypectomy) reported in three European national screening programs [65–67] and in an ongoing RCT in eight Spanish regions [68] range from 0.06% to 0.5%. Pox 2012 reported also the complication rate in colonoscopies with polypectomy separately from that in colonoscopies without polypectomy (OR, 4.9; 95%CI: 4.6–5.2), and the rate of minor complications (1.9 per 1000).

False-negative results, interval cancers

The miss rate for adenoma ≥10 mm estimated in studies by colonoscopy with segmental unblinding ranges from 0 to 12 per 100 [69–73]. From published data from a colonoscopy-based screening program in Poland [74], it has been observed that after a mean follow-up of 52.1 months, the risk of interval CRCs between screening colonoscopy and scheduled surveillance examination was 0.09% (42/45026).

Acceptability, psychological effects

Results from studies on patient-reported experiences after colonoscopy as the primary screening test [75–81] show that the majority of patients experienced at least moderate discomfort associated with the laxative bowel preparation and perceived it to be the worst part of the colonoscopy [82]. Other reported difficulties were the pre-test fasting and liquid diet, pre-procedural anxiety, worry and anticipation of pain, the instrument insertion, as well as embarrassment with the process, and the length of the procedure that required time away from other duties. In the studies that took pre- and post-test measurements, it appeared that patients experienced less discomfort and pain than expected and/or reduced concerns and anxiety after the procedure [76,79,80]. In all these studies, intravenous sedation was used. When analyzing the results of a 30-day active follow-up among average-risk people undergoing FS, TC, and FIT [83], the proportion of people complaining of serious reactions after bowel preparation (OR, 5.17; 95%CI: 3.70–7.24) or reporting severe pain immediately after the examination (OR, 1.86; 95%CI: 1.47–2.34) was higher for TC than for FS. The most common post-procedural complaints were abdominal distension and pain.

3.2.2. Breast cancer screening

3.2.2.1. Effectiveness. Is mammography screening effective in reducing breast cancer mortality in the general female population at average risk of breast cancer?

Three meta-analyses of RCTs [84–86] found a statistically significant reduction in breast cancer mortality when women of all age ranges between 40 and 74 were considered together (RR, 0.81; 95%CI: 0.74–0.87, nine trials included [84]; RR, 0.82; 95%CI: 0.74–0.91, nine trials included [85]; RR, 0.80; 95%CI: 0.73–0.89, nine trials included [86]). Different meta-analyses include different trials, durations of follow-up, and definitions of outcome. Nevertheless, there is general agreement in their estimates of an approximate 20% reduction in relative risk of breast cancer mortality from invitation to screening (level of evidence: I).

Results from observational studies considering women invited to screening (intention-to-treat analysis) pooled in meta-analyses confirmed the effectiveness of screening in reducing breast cancer mortality [87,88]. The pooled mortality reduction among invited women in seven incidence-based mortality studies was 25% (RR, 0.75, 95%CI: 0.69–0.81), and in seven case–control studies it was 31% (OR, 0.69; 95%CI: 0.57–0.83) [87]. When only women who actually received mammography screening were included in the analysis (per-protocol analysis), the estimate of mortality reduction was significantly higher. Among those actually screened, the pooled mortality reduction in the incidence-based mortality studies was 38% (RR, 0.62; 95%CI: 0.56–0.69) and in the case–control studies it was 48% (OR, 0.52, 95%CI: 0.42–0.65), when adjusted for self-selection [87]. When trend studies were considered, 12 of the 17 trend studies retrieved by Broeders et al. [87] quantified the impact of population-based screening on breast cancer mortality. The estimated reductions in breast cancer mortality ranged from 1% to 9% per year in studies reporting an annual percentage change, and from 28% to 36% in those comparing post- and pre-screening periods over study time periods ranging from 15 to 30 years. [87] (level of evidence: III–IV).

3.2.2.2. Age range and screening interval. What is the optimal age range in which to perform mammography screening for breast cancer, and what is the optimal time interval for such screening?

All meta-analyses of both RCTs [84–86] and observational studies [87,88] of invitation to breast cancer screening found a statistically significant reduction in breast cancer mortality when women of all age ranges between 40 and 74 were considered together (level of evidence: I–III).

When narrower age ranges were considered separately, the reduction in breast cancer mortality was greatest for women in the age range 60–69 years (RR, 0.69, 95%CI: 0.57–0.83, five trials included [85]; RR, 0.68, 95%CI: 0.54–0.87, two trials included [89]) (level of evidence: I). For the age ranges 40–49 and 50–59 years, the reduction in mortality was statistically significant even though it was less than for the age ranges 40–74 (40–49 years: RR, 0.85; 95% CI: 0.75–0.96, eight trials included [85,89]; 50–59 years: RR, 0.82; 95%CI: 0.68–0.98, seven trials included [85], RR, 0.86; 95%CI: 0.75–0.99, six trials included [89]) (level of evidence: I). For women aged 70–74 years, the results indicating a reduction in breast cancer mortality were nearly statistically significant (RR, 0.68; 95%CI: 0.45–1.01, two trials included [85]; RR, 1.12; 95%CI: 0.73–1.72, one trial included [89]) (level of evidence: I).

Results from observational studies and considering different age ranges were reported by Gabe et al. [88] for women younger than 50 years. Four cohort and non-RCT comparative studies reported results separately for women younger than 50 years. In the age range 45–49 years in the UK TEDBC study [90], there was a relative risk of 0.70 (95%CI: 0.57–0.86) for breast cancer mortality in cases diagnosed within 7 and 10 years of entry and a corresponding relative risk of 0.74 (95%CI: 0.64–0.85) for women aged 50–64 years. After adjustment for self-selection bias in women aged 40–49 years, a relative risk of 0.52 (95%CI: 0.40–0.67) was observed in those screened in the study of Tabar et al. [91]. Such a benefit was not observed in the comparative study in women aged 35–49 years in the Netherlands [92], with a relative risk of 0.94 (95%CI: 0.68–1.29) after 16 years of follow-up. In a study of all Swedish counties (except those participating in the randomized studies) [93], the estimated relative risk associated with invitation was 0.91 (95%CI: 0.72–1.15) in women aged 40–49 years (level of evidence: III–IV). A more recent study including all Swedish counties compared breast cancer mortality among women who were invited to service screening at ages 40–49 years (study group) and women in the same age group who were not invited during 1986–2005 (control group). The average follow-up was 16 years. The estimated RR for women who were invited to screening was 0.74 (95%CI, 0.66–0.83), and the RR for women who attended screening was 0.71 (95%CI, 0.62–0.80) [94]

From available evidence on interval cancers, in the age range 40–49 years the proportional incidence (i.e. the interval cancer incidence as a proportion of the underlying breast cancer incidence rate) within 12 months was 43% (95%CI: 30.4%–54.7%) and within 13–24 months it was 67% (95%CI: 55.1–79.8%); the confidence intervals do not overlap [95] (level of evidence: I–III). For the age range 50–59 years, available studies showed a proportion of about 25% within 11 months, and about 50% within 12–23 months; confidence intervals were not reported [96] (level of evidence: II–III).

From available evidence from RCTs on breast cancer mortality, when considering the age range 40–49 years, one RCT estimated a significant reduction in mortality for an interval <24 months. For the age range 50–69 years, a significant reduction in mortality was observed for an interval of 24–33 months, and for the age ranges from 39–69 when the interval was <24 months [85] (level of evidence: I–II).

3.2.2.3. Negative side effects. What is the (cumulative) false-positive rate in the screening age period?

Lynge et al. [96] reported data from 17 national or regional programs: false positives as a percentage of negative/normal results after further non-invasive assessment, after a single screening round, ranged from 0.7% to 17.5% (median 5%). False positives as a percentage of negative/normal results after a

percutaneous biopsy ranged from 0.11% to 1.32% (median: 0.4%) [96]. According to a review of studies performed after 2000 in the context of European mammography screening programs (for a total of 390,000 screened women aged 50–69 years undergoing ten biennial screening tests), the estimated cumulative risk of a false-positive screening result varied from 8% to 21%, and the cumulative risk of an invasive procedure with a benign outcome ranged from 1.8% to 6.3%; the estimated cumulative risk of a false-positive screening result without an invasive procedure was 16.8%, and the risk of undergoing surgical intervention with benign outcome was 0.9% [97]. According to the cross-sectional information collected by the European Network for Information on Cancer project (EUNICE), the proportions of all screening examinations in the programs resulting in needle biopsy were 2.2% for initial screening and 1.1% for subsequent screenings (the rates differed between countries); the corresponding rates of surgical interventions among women without breast cancer were 0.19% and 0.07% [97] (level of evidence: III).

What is the risk of overdiagnosis in the screening process?

The results of the reported systematic reviews of published RCTs or observational studies agreed in demonstrating that a mammography program could cause harm, including the possibility of overdiagnosis. Overdiagnosis is the diagnosis of breast cancer which would never have surfaced as clinically diagnosed cancer during the women's lives, without screening, leading to unnecessary treatment.

Overdiagnosis has been assessed and evaluated in several ways among the systematic reviews and meta-analyses considered, suggesting that the existing phenomenon is difficult to define and determine.

Estimates of risk of over-diagnosis from RCTs are the following: 30% [84], 19% (95%CI 15–23) (when overdiagnosis is defined as excess cancers as a proportion of cancers diagnosed during the active screening period in women invited for screening) and 11% (95%CI 9–12) (when overdiagnosis is defined as excess cancers as a proportion of cancers diagnosed in the long term in women invited for screening) [86].

Estimates of overdiagnosis, expressed as a percentage of the expected incidence in the absence of screening from population-based mammography screening in seven Western European countries (the Netherlands, Italy, Norway, Sweden, Denmark, the UK, and Spain) adjusted for breast cancer risk and lead-time bias are the following: Netherlands, 2.8%; Italy, 4.6% and 1.0%; Denmark, 7.0%; England and Wales, 10% and 3.3%; no reliable estimates were available for Norway, Sweden or Spain. The estimates of risk of overdiagnosis unadjusted or incompletely adjusted for breast cancer risk and lead-time bias ranged from 0% to 54%.

According to the previous considerations, the most plausible estimates of risk of overdiagnosis range from 1% to 10% [98] (level of evidence: I–III).

What about the other harms/negative side effects/adverse effects of mammography screening?

Pain

Mammography is considered an acceptable test. According to the results of the review on screening mammography in women 40–49 years of age by Armstrong 2007, few women agreed that the pain caused by mammography would prevent them from attending future screening. The degree of pain was associated with the stage of menstrual cycle, anxiety, and pre-mammography anticipation of pain [99].

Psychological effects

Brett et al. [100] reviewed 54 studies from 13 countries, and according to these results the negative psychological impact of mammography screening was minimal in women who received a negative result after mammography. Initial anxiety on receipt of the invitation declined at receipt of a clear result after screening. However, the negative psychological impact of a false-positive result appears to be significant prior to the recall appointment, at the recall appointment, and after recall (despite a clear result) [100].

Bond et al. [101] found that having a false-positive screening mammography result can cause breast-cancer-specific distress for up to 3 years, related to the invasiveness of the assessment. In addition, women placed on early recall were also at a greater relative risk of distress. According to results from studies retrieved by Bond et al. [101], women with false-positive mammography results were less likely to return for routine assessment than those with normal ones (RR, 0.97; 95%CI: 0.96–0.98), while according to Brewer et al. [102] the effect was not statistically significant among European women (risk ratio, 0.97; 95%CI: 0.93–1.01). Women who received false-positive results conducted more frequent breast self-examinations and had higher, but apparently not pathologically elevated, levels of distress and anxiety, and thought more about breast cancer than did those with normal results [102].

Overall, the psychological impact of mammography screening is minimal in women who received a negative result after mammography, while it appears to be negative in women who received a false-positive result.

Radiation exposure

Radiation studies have estimated the risk of induced breast cancer due to repeated mammography exposure. These studies have not measured the excess risk of breast cancer directly; instead they model the data from studies assessing radiation effects in other settings. The excess risk of breast cancer induced by radiation depends on the X-ray dose of mammography and the age when starting screening. The risk of breast cancer induced between the ages of 40 and 80 years with annual mammography is 1 per 1000 women. The risk–benefit ratio between 40 and 49 years is one death induced by cancers due to radiation exposure versus three saved lives. For mammography, it is predicted that the excess relative risk (ERR), defined as proportion of RR due solely to radiation exposure (ERR = RR −1), doubles when screening starts at age 40 instead of 50. Other estimates predict that biennial screening starting at age 50 and continuing until age 74 causes 7.7 breast cancers and 1.6 breast cancer deaths per 100,000 women aged 0–100 [103–108] (level of evidence: III, modelling studies).

3.2.2.4. Positive side effects. What is the frequency of mastectomy and breast-conserving surgery for women participating in breast cancer mammography screening?

All cohort studies found that screen-detected breast cancers overall are at an earlier stage and have more favorable tumor characteristics (size, stage, grade) [109–119]. Hofvind et al. [111] found an increased percentage of breast-conserving surgery and a reduced percentage of mastectomies among participating women; Giorgi Rossi et al. [110] found a non-significant reduction in the percentage of mastectomy, and a lower proportion of treatment that was not appropriate for the stage of the disease among invited women. All the other studies found a higher rate of breast-conserving surgery and a reduction in mastectomy compared with cancers detected in women not screened (level of evidence: III).

The following results from population trend studies were retrieved: two studies found a significant decline in the rate of radical mastectomy and an increase in breast-conserving surgery [120,121]. Coburn et al. [122] assessed the rate of breast-conserving surgery and found an increase. Stang et al. [123] found an increase in breast-conserving surgery, while mastectomy rates showed little change over time. Ernst et al. [124,125] and Suhrke et al. [126] did not find a significant increase in breast-conserving surgery or a decline in mastectomy rates (level of evidence: IV).

The retrieved cross-sectional study [127] found that women who underwent mammography screening had smaller tumors,

which resulted in a majority of these patients being able to consider breast conservation as an alternative to mastectomy (level of evidence: V).

All [128–131] but one [132] case series studies found an increase in the rate of breast-conserving surgery and a decrease in the mastectomy rate; in two studies the difference was statistically significant (level of evidence: V).

Overall, most of the studies showed a decrease in the rate of mastectomies and an increase in the rate of breast-conserving surgery among women participating in breast cancer screening.

What are the other positive side-effects of mammography screening in terms of the incidence rates of advanced cancer?

Different study designs give not fully consistent results concerning the impact of breast cancer screening on the incidence of advanced breast cancer. An analysis of the 29-year follow-up data from the Dalarna County component of the Swedish Two-County Trial [133] concluded that the slight proportional deficit in invasive cancers in the active study population at 29 years of follow-up might be due to the detection and removal of carcinoma in situ, and that the long-term reduction in advanced cancers is consistent with the long-term reduction in breast cancer mortality observed in the trial (level of evidence: II).

Two cohort studies [111,112] found that breast cancers detected with screening have favorable tumor characteristics compared with those diagnosed in the pre-screening period and outside the program, and that advanced-stage breast cancer is less common in women invited and participating in the program than in women invited but not participating. A significant and stable decrease in the incidence of late-stage breast cancer was observed from the third year of screening onward, when the ratio of observed to expected incidence rate varied between 0.81 and 0.71 in 700 municipalities, having a total population of 692,824 women aged 55–74 years targeted by organized mammography screening between 1991 and 2005 [134] (level of evidence: III). One cross-sectional study [135] compared the prevalence of advanced cancer detected after 2 years in counties with mammography facilities versus counties without mammography facilities and found a significant association between the absence of in-county mammography facilities and a high probability of diagnosis at a late stage of breast cancer (level of evidence: V).

Three population trend studies [136–138] with 12, 15, and 32 years of follow-up found a not significant reduction in advanced cancers, or no decline in advanced breast cancer was detected (level of evidence: IV).

Overall, most of the studies found a decrease in the incidence of advanced cancers in populations targeted by organized mammography screening.

3.2.3. Cervical cancer screening

3.2.3.1. Effectiveness. Is screening for cervical cancer effective in reducing cervical cancer incidence and mortality?

Evidence of effectiveness of conventional cytology testing with Papanicolaou staining is derived from observational studies: cohort studies involving follow-up of screened women, case–control studies, as well as time trend studies and ecological or geographical correlation studies [31,39]. Significant reduction in incidence of invasive cancer from cytology testing observed in cohort studies ranged from 80% to 30% [139]. Pooled analysis from case–control studies showed a significant reduction in incidence of 66% (OR, 0.34, 95%CI: 0.31–0.38) [139]. The impact of the reduction was greater in countries that conducted organized screening than in countries that did not (level of evidence: III–IV).

One large cluster-randomized trial provided cervical cancer mortality and incidence outcomes for women with a single lifetime screen – cytology or human papilloma virus (HPV) test – compared with women with no screening history. After 8 years of follow-up, the risk of advanced cervical cancer was 53% significantly lower (HR, 0.47; 95%CI: 0.32–0.69) and cervical cancer mortality was 48% significantly lower (HR, 0.52; 95%CI: 0.33–0.83) among women in the HPV-testing group. No significant reductions in the numbers of advanced cancers or deaths were observed in the cytology-testing group [140] (level of evidence: II).

A recent pooled analysis of follow-up data from four RCTs conducted in Sweden (Swedescreen), the Netherlands (POBASCAM), England (ARTISTIC), and Italy (NTCC) has demonstrated that, compared to cytology, HPV-based screening provides 60–70% greater protection against invasive cervical carcinomas; the respective pooled rate ratio for invasive cervical carcinoma among women with a negative screening test at entry was 0.30 (95%CI 0.15–0.60) [141] (level of evidence: I).

RCTs used different strategies for managing HPV-positive women (by cytology triage or direct referral to colposcopy), and for primary screening using primary HPV testing alone, or in combination with cytology. The biopsy rate was doubled (rate ratio 2.24; 95%CI: 2.09–2.39) in the NTCC trial, where all HPV-positive women were directly referred for colposcopy, while it was not increased in studies using cytological triage (POBASCAM, Swedescreen, ARTISTIC) [141] (level of evidence: I). Co-testing of all women with both HPV and cytology compared with primary HPV testing alone led to increased unnecessary colposcopy [142,143] (level of evidence: I). As the efficacy results were similar, the data support the use of the least extensive strategy (primary HPV screening with triaging by cytology before referral) (level of evidence I).

3.2.3.2. Age range and screening interval. What is the optimal age range in which to perform cervical cancer screening, and what is the best time interval for such screening?

Evidence based on cohort and case–control studies shows that HPV infections and cytological abnormalities among women younger than 25 years are common and transient, whereas cervical intraepithelial neoplasia of grade 3 or worse (CIN3+) is much less common in this group than in women aged 25 years and older [144,145]. Cytology screening in women younger than 25 years has lower detection rates, higher false-positive rates, and lower effectiveness than in older women [146] (level of evidence: III–IV).

HPV testing is more sensitive than cytology [147,148]. HPV testing was substantially more sensitive in detecting CIN2+ than cytology (96.1% versus 53.0%) but less specific (90.7% versus 96.3%). HPV sensitivity was uniformly high at all ages, whereas the sensitivity of cytology was substantially better in women over the age of 50 than in younger women (79.3% versus 59.6%). The specificity of both tests increased with age, but loss in specificity with HPV testing versus cytology is very large at young ages [149]. Specificity of HPV testing can increase by increasing the screening interval [150] or by triaging HPV-positive women with cytology [151].

In pooled data from four RCTs [141] considering age at enrolment, the lowest rate ratio (0.36, 95%CI: 0.14–0.94) was noted in women aged 30–34 years. However, the efficacy of HPV testing did not differ significantly between women aged 30–34 years and those 35 years and older ($P = 0.13$). These results suggest a gain in efficacy with HPV testing, starting at age 30 years (data at younger ages are too sparse to draw conclusions) [141] (level of evidence: I).

When considering age at which to stop screening in an HPV-negative woman, the risk of acquiring a new infection and the long time needed for progression from infection to invasive cancer should be taken into account. In Europe the prevalence of infection by oncogenic HPV types strongly decreases with age up to about age 45; it remains fairly constant after that age [144], and little is known about the age-specific occurrence of new infections. Also, no CIN3 was detected during the second round of screening among

women aged 50–60 years in the HPV group, and five cases of CIN3 were detected in the cytology group [152]. These issues suggest a longer protection of HPV screening at older ages and an earlier age at which to stop screening than with cytology screening [151].

Evidence of reduced risk of cervical cancer after a negative Pap smear result was reported in the IARC multicentre study [153]. The reduction in cumulative incidence of invasive squamous-cell carcinomas of the cervix uteri was reported at 93% when screening every year, 91% when screening every 3 years, and 84% when screening every 5 years, with follow-up among women aged 35–64 years who had at least two previous negative smears [153]. Estimation of the relative risk of carcinoma of the cervix uteri in the Netherlands following a negative screening result, compared with the risk in the absence of screening [154] indicates that almost as much benefit is expected from 3-yearly screening as from annual rescreening among women aged 35–64 years. The same relative risk stratified by age was estimated in England using non-screened women for comparison [155]: among women aged 20–39 years, a 30% risk reduction was observed at 3.5 years; among women aged 40–54 years, a 40% risk reduction was observed at 5 years; and among women aged 55–69 years, a 70% risk reduction was observed at 5 years since the negative test (level of evidence: III–IV).

According to pooled data from the Swedescreen, POBASCAM, ARTISTIC, and NTCC RCTs, when HPV-based screening for cervical cancer was compared with cytology-based cervical screening, the cumulative incidence of invasive cervical carcinoma in women with negative entry tests was 4.6 per 10^5 (95%CI: 1.1–12.1 per 10^5) at 3.5 years and 8.7 per 10^5 (95%CI: 3.3–18.6 per 10^5) at 5.5 years in the HPV-based screening arm; the respective resultsin the cytology-based cervical screening arm were 15.4 per 10^5 (95%CI: 7.9–27.0 per 10^5) at 3.5 years and 36.0 per 10^5 (95%CI: 23.2–53.5 per 10^5) at 5.5 years. The recorded cumulative incidence of cervical cancer was lower 5.5 years after a negative HPV test than 3.5 years after a negative cytology result, indicating that 5-year intervals for HPV screening are safer than 3-year intervals for cytology [141] (level of evidence: I).

Irrespective of the test used, the European guidelines recommend that women continue participating in screening until the age of 60 or 65 years, and beyond this age if the most recent test results are not normal [3].

3.2.3.3. Negative side effects. What is the risk of overdiagnosis in the cervical cancer screening process?

CIN is a pre-invasive lesion, and one out of every four to seven progress to an invasive lesion if not treated. It could be concluded that diagnoses of non-progressive lesions are cases of overdiagnosis, but progressive lesions cannot be distinguished from regressive ones. Results of studies estimating additional overdiagnosis from HPV testing are reported here. Overdiagnosis of regressive lesions has been evaluated in RCTs by comparing the overall detection of regressive lesions in the HPV arm and in the cytology arm up to the second screening round and beyond. No difference between arms in the cumulative incidence of CIN2 and CIN3+ up to the second round in women aged 29–33 years was observed in POBASCAM, the RCT in which the HPV test was applied at the second round [156]. Data from RCTs applying cytology at the second round found different results. In ARTISTIC, overall for women aged 20–64 years non-significant differences in the cumulative detection of regressive lesions were observed [157]; in Swedescreen, no difference in the relative cumulative detection rate of CIN3 was observed, but an increase in CIN2 (HPV versus cytology ratio, 1.56; $P = 0.04$) was found among women aged 32–38 years at recruitment [158,159]. The NTCC trial reported results separately for women aged 25–34 and 35–60 years. A significant increase in regressive lesions in the HPV arm was found. Among women aged 35–60 years, the HPV versus cytology ratio was 1.65 (95%CI: 1.21–2.26) for CIN3 and 1.68 (95%CI: 1.25–2.26) for CIN2. A higher increase was observed in younger women, with a HPV versus cytology ratio of 2.14 (95%CI: 1.28–3.59) for CIN3 when HPV-positive women were directly referred for colposcopy, and of 3.11 (95%CI: 2.20–4.39) for CIN2 with direct referral for colposcopy or with cytological triage for HPV-positive women. [151]. These results suggest overdiagnosis of regressive CIN2 in younger women for HPV-based screening compared with cytology-based screening (level of evidence: II).

What about the other harms/negative side effects/adverse effects of cervical cancer screening?

Performance of HPV testing compared with cytology testing

When data on absolute accuracy of HPV testing from European and North American studies were pooled, the pooled sensitivity was 96% (95%CI: 95–98%), and the pooled specificity was 92% (95% CI: 89–95%). The accuracy values of the hybrid capture 2 (HC2) assay for CIN3+ were similar to those for CIN2+. Of the screened population, 10% (95%CI: 8–12%) were high-risk HPV-positive, 1.4% (95%CI: 1.0–1.9%) had CIN2+, and 0.8% (95%CI: 0.5–1.1%) had CIN3+. The sensitivities of assays based on the polymerase chain reaction (PCR) for high-grade CIN varied widely, but were consistently high and comparable to those of HC2 in studies where the GP5+/6+ primer system was used (94–95%) [160–162].

The sensitivity of HC2, as reported in Ronco et al. [151], was on average 34% (95%CI: 17–52%) and 21% (95%CI: 10–33%) higher than that of cytology at the lowest cytological cut-off for the detection of CIN2+ and CIN3+, respectively. The relative sensitivity was higher when compared with cytology at the cut-off for the detection of low-grade squamous intraepithelial lesions or worse (LSIL+). The specificity of HC2 was significantly lower than that of cytology, with a ratio of 0.97 (95%CI: 0.96–0.97) and 0.92 (95%CI: 0.89–0.95), considering the cut-offs for atypical squamous cells of undetermined significance or worse (ASC-US+) and LSIL+, respectively. PCR was also more sensitive and less specific than cytology for detecting CIN2+ (ratios: 1.25; 95%CI: 1.08–1.45 and 0.97; 95%CI: 0.94–1.00).

Numbers of colposcopies needed to detect 1 case of disease

To compare the potential harms of the various strategies, Patanwala et al. [163] calculated the numbers of women who would need to undergo colposcopy to detect one case of disease from round 1 (CIN2+ and CIN3+, respectively) of the NTCCS, Indian, ARTISTIC, POBASCAM, and Finnish trials. For detection of CIN2+, significantly higher numbers of colposcopies were needed in the HPV arm in the Indian trial [140], the NTCCS phase I trial in women aged 35–60 years [152], and the ARTISTIC trial [157], whereas significantly higher numbers of colposcopies were needed in the cytology arm in the Finnish trial [164]. For detection of CIN3+, significantly higher numbers of colposcopies were needed in the HPV arm in the NTCCS phase I trial in women aged 35–60 years [152] and in the ARTISTIC trial [157]. For the Indian study [140], which reported cervical cancer rather than CIN3+ as an outcome, the numbers of colposcopies needed to detect one case of cervical cancer were 27.7 and 14.8 for the HPV-based and cytology-based groups, respectively; this difference was statistically significant ($P < 0.0001$). In the ARTISTIC trial, significantly higher numbers of colposcopies were needed in the HPV co-testing arm for detection of CIN3+ in round 1, but this did not result in increased sensitivity. The calculated number of colposcopies needed likely underestimates the true number of colposcopies needed, because it reflects the initial test positivity rate and does not include subsequent colposcopies resulting from increased surveillance in women who remain HPV-positive over time [163].

Potential harms related to diagnosis and treatment of CIN

Risks of colposcopy and cervical biopsy include pain, bleeding, infection, failure to diagnose (inadequate sampling), and cost to the patient (e.g. time off work and psychological impact). Results from the TOMBOLA study [165], comparing cytological

surveillance versus immediate colposcopy referral, indicated similar proportions of women with depression in the surveillance and immediate colposcopy groups at 6 weeks after the procedure, although women in the surveillance group were more likely to be anxious (13.4% versus 7.9%; $P < 0.001$). Significantly lower proportions of women in the surveillance group reported any pain (15.0% versus 38.9%; $P < 0.001$), bleeding (17.2% versus 46.9%; $P < 0.001$), or discharge (8.6% versus 34.2%; $P < 0.001$), compared with women in the immediate colposcopy arm. An observational study within the TOMBOLA cohort [166] reported pain, bleeding, or discharge at 6 weeks among 14–18% of women aged 20–59 years with colposcopy and no biopsy. Of those who had colposcopic biopsy, 53% reported pain, 79% reported bleeding, and 46% reported discharge. For women who had the loop electrosurgical excision procedure (LEEP), these proportions were 67%, 87%, and 63%, respectively. The duration of bleeding and discharge was longer for women treated by LEEP than women in the other groups reporting these symptoms (level of evidence: II–III).

Potential harms of treatment of CIN include immediate, short-term, and long-term risks

Cold-knife conization was significantly associated with preterm delivery (<37 weeks: eight studies; RR, 2.59; 95%CI: 1.80–3.72), low birth weight (<2500 g: four studies; RR, 2.53; 95%CI: 1.19–5.36), and cesarean delivery (four studies; RR, 3.17; 95%CI: 1.07–9.40), but no increase in perinatal mortality was seen [167]. LEEP was also significantly associated with preterm delivery (eight studies; RR, 1.7; 95%CI: 1.24–2.35), low birth weight (six studies; RR, 1.82; 95%CI: 1.09–3.06), and premature rupture of membranes (three studies; RR, 2.69; 95%CI: 1.62–4.46), but not with cesarean delivery or perinatal mortality. Similar effects on preterm delivery were noted for laser conization, but these were not statistically significant. No increased risk of adverse obstetric outcomes was detected among women who underwent laser ablation (level of evidence: III).

A 2008 review of excisional or ablative therapies found that cold-knife conization was associated with an increased risk of preterm birth (<30 weeks: four studies; RR, 5.33; 95%CI: 1.63–17.40; <34 weeks: five studies; RR, 2.78; 95%CI: 1.72–4.51), low birth weight (<2000 g: one study; RR, 2.86; 95%CI: 1.37–5.97), and perinatal mortality (seven studies; RR, 2.87; 95%CI: 1.42–5.81) [168]. LEEP was not associated with an increased risk of perinatal mortality, preterm birth (<32–34 weeks), or preterm labor (<28–30 weeks). One included study evaluated the impact of LEEP on low birth weight and found no significant increased risk of low birth weight (<2000 or 1500 g). Ablative procedures (two studies of cryotherapy and four of laser ablation) were not associated with an increased risk of preterm birth, perinatal mortality, or low birth weight.

One large retrospective United States cohort study found no increased risk of preterm birth associated with LEEP [169] (level of evidence: III).

3.2.4. Effectiveness of prostate cancer screening

Is PSA testing for prostate cancer screening effective in reducing prostate cancer mortality and overall mortality for the male population at average risk by age range?

To date, five RCTs (the Quebec study, the Stockholm study, the Norrkoping study, the European Randomized Study of Screening for Prostate Cancer [ERSPC], and the United States Prostate, Lung, Colorectal and Ovarian [PLCO] Cancer Screening Trial) comparing mass screening for prostate cancer to no screening have assessed the efficacy of screening men for prostate cancer in reducing prostate cancer-specific and all-cause mortality.

The Quebec study recruited men aged 45–80 years in Canada, providing annual screening with combination digital rectal examination (DRE) and prostate-specific antigen (PSA) testing. Participants were followed up over an 11-year period. The cut-off for biopsy was PSA >3.0 ng/mL [170]. The Stockholm study recruited men aged 55–70 years in Sweden for a one-time screening using DRE, PSA, and transrectal ultrasound (TRUS). Participants were followed up over a 15-year period. The cut-off for biopsy was PSA >10.0 ng/mL, with repeat TRUS performed for PSA >7.0 ng/mL [171]. The Norrkoping study recruited men aged 50–69 years in Sweden and screened every 3 years. During the initial phase of the study, only DRE was offered; however, the screening regimen later evolved to include both DRE and PSA testing. Participants were followed up over a 20-year period. The cut-off for biopsy was PSA >4.0 ng/mL [172]. The PLCO study recruited men aged 55–74 years in the United States for annual screening with DRE and PSA. Participants were followed up over a 10–13-year period. Patients were advised for diagnostic evaluation when PSA exceeded 4.0 ng/mL [173]. The ERSPC recruited men aged 50–74 years across nine European countries. Screening regimens varied across participating sites, with cut-off values for biopsy ranging from PSA >2.5, to 3.0, 4.0, and 10.0 ng/mL. The screening interval in six of the sites was 4 years [174].

The methodological quality of the RCTs was assessed for the risk of bias by Ilic et al. [175]. The Quebec, Stockholm, and Norrkoping trials were assessed as having a high risk of bias. The ERSPC and the PLCO Cancer Screening Trial were assessed as having a low risk of bias, but provided contradictory results. The ERSPC reported a significant reduction in prostate-cancer-specific mortality (RR, 0.84; 95%CI: 0.73–0.95) [174]; the PLCO study concluded that there was no significant benefit (RR, 1.15; 95%CI: 0.86–1.54) [173].

However, high risk of contamination (45% of the control group had PSA opportunistic screening in the 3 years preceding randomization, and 52% during the time period of the last round of screening in the intervention arm) and high level of loss to follow-up (43%) in the PLCO study suggest the likelihood of contamination and selection bias. In conclusion, one RCT of good quality showed an overall significant reduction in prostate cancer-specific mortality, that was higher when considering the core age group (55–69 years) of the study and those aged 65–69 years; however results from the other available RCTs at high risk of bias are in the opposite direction (level of evidence: II).

4. Conclusions

According to the evidence retrieved on the incidence and mortality of screening according to age and intervals between tests, and on side effects of colorectal, breast, and cervical cancer screening, the 4th edition of the European Code against Cancer recommends that men and women take part in organized cancer screening programs for colorectal cancer and that women take part in organized cancer screening programs for breast and cervical cancer.

Organized screening programs are recommended, in order to achieve the greatest benefit with the least harm. Screening is recommended only for those cancers where a demonstrated life-saving effect substantially outweighs the potential harm of examining very large numbers of people who may otherwise never have, or suffer from, these cancers. Screening programs are expected to provide routine factual evidence of the balance between benefits and harms. The WG agreed that the of evidence on benefits and harms for screening of other cancers, such as prostate or lung cancers, at the time of the preparation of the Code was not sufficiently available to recommend EU citizens to participate in screening outside research programs, designed for evaluation and implementation purposes.

Conflicts of interest

Wendy Atkin has received significant non-monetary research support from Eiken Chemicals for reagents and lease of a machine

for processing immunochemical fecal occult blood tests. The support is ongoing and the monetary equivalent to the in-kind support received will total less than £80,000.

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References

[1] P. Boyle, P. Autier, H. Bartelink, J. Baselga, P. Boffetta, J. Burn, et al., European Code against Cancer and scientific justification: third version (2003), Ann. Oncol. 14 (2003) 973–1005.
[2] European Commission. European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis, in: N. Perry, M. Broeders, C. de Wolf (Eds.), 4th edition, Luxembourg: Office for Official Publications of the European Communities, 2006.
[3] M. Arbyn, A. Anttila, J. Jordan, G. Ronco, U. Schenck, N. Segnan, et al., European Guidelines for Quality Assurance on Cervical Cancer Screening, 2nd edition, European Community, Brussels; Office for Official Publications of the European Communities, Luxembourg, 2008.
[4] European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis, in: N. Segnan, J. Patnick, L. von Karsa (Eds.), 1st edition, European Commission, Publications Office of the European Union, Luxembourg, 2010.
[5] J. Ferlay, I. Soerjomataram, M. Ervik, R. Dikshit, S. Eser, C. Mathers, et al., GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet], France: International Agency for Research on Cancer, Lyon, 2013. accessed on day/month/year http://globocan.iarc.fr.
[6] L. von Karsa, A. Anttila, G. Ronco, A. Ponti, N. Malila, M. Arbyn, et al., Cancer screening in the European Union, Report on the Implementation of the Council Recommendation on cancer screening—First Report, European Communities, Luxembourg, 2008. http://ec.europa.eu/health/ph_determinants/genetics/documents/cancer_screening.pdf.
[7] S. Minozzi, P. Armaroli, C. Espina, P. Villain, M. Wiseman, J. Schüz, et al., European Code against Cancer 4th Edition: process of reviewing the scientific evidence and revising the recommendations, Cancer Epidemiol 39 (2015) S11–S19.
[8] IARC, The European Code against Cancer. Available from: http://cancer-code-europe.iarc.fr.
[9] P. Hewitson, P. Glasziou, L. Irwig, B. Towler, E. Watson, Screening for colorectal cancer using the faecal occult blood test, Hemoccult, Cochrane Database Syst. Rev. (2007) CD001216.
[10] S. Zheng, K. Chen, X. Liu, X. Ma, H. Yu, K. Chen, et al., Cluster randomization trial of sequence mass screening for colorectal cancer, Dis. Colon Rectum 46 (2003) 51–58.
[11] H. Saito, Y. Soma, J. Koeda, T. Wada, H. Kawaguchi, T. Sobue, et al., Reduction in risk of mortality from colorectal cancer by fecal occult blood screening with immunochemical hemagglutination test. A case-control study, Int. J. Cancer 61 (1995) 465–469.
[12] H. Saito, Y. Soma, M. Nakajima, J. Koeda, H. Kawaguchi, R. Kakizaki, et al., A case-control study evaluating occult blood screening for colorectal cancer with hemoccult test and an immunochemical hemagglutination test, Oncol. Rep. 7 (2000) 815–819.
[13] M. Nakajima, H. Saito, Y. Soma, T. Sobue, M. Tanaka, A. Munakata, Prevention of advanced colorectal cancer by screening using the immunochemical faecal occult blood test: a case-control study, Br. J. Cancer 89 (2003) 23–28.
[14] L. Hol, J.A. Wilschut, M. van Ballegooijen, A.J. van Vuuren, H. van der Valk, J.C. Reijerink, et al., Screening for colorectal cancer: random comparison of guaiac and immunochemical faecal occult blood testing at different cut-off levels, Br. J. Cancer 100 (2009) 1103–1110.
[15] Z. Levi, S. Birkenfeld, A. Vilkin, M. Bar-Chana, I. Lifshitz, M. Chared, et al., A higher detection rate for colorectal cancer and advanced adenomatous polyp for screening with immunochemical fecal occult blood test than guaiac fecal occult blood test, despite lower compliance rate A prospective, controlled, feasibility study, Int. J. Cancer 128 (2011) 2415–2424.
[16] L.G. van Rossum, A.F. van Rijn, R.J. Laheij, M.G. van Oijen, P. Fockens, H.H. van Krieken, et al., Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population, Gastroenterology 135 (2008) 82–90.
[17] J.A. Burch, K. Soares-Weiser, D.J. St John, S. Duffy, S. Smith, J. Kleijnen, et al., Diagnostic accuracy of faecal occult blood tests used in screening for colorectal cancer: a systematic review, J. Med. Screen. 14 (2007) 132–137.
[18] E.P. Whitlock, J.S. Lin, E. Liles, T.L. Beil, R. Fu, Screening for colorectal cancer: a targeted, updated systematic review for the U.S. Preventive Services Task Force, Ann. Intern. Med. 149 (2008) 638–658.
[19] A. Federici, P. Giorgi Rossi, P. Borgia, F. Bartolozzi, S. Farchi, G. Gausticchi, The immunochemical faecal occult blood test leads to higher compliance than the guaiac for colorectal cancer screening programmes: a cluster randomized controlled trial, J. Med. Screen. 12 (2005) 83–88.
[20] L. Hol, M.E. van Leerdam, M. van Ballegooijen, A.J. van Vuuren, H. van Dekken, J.C. Reijerink, et al., Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy, Gut 59 (2010) 62–68.
[21] K. Hughes, B. Leggett, C. Del Mar, J. Croese, S. Fairley, J. Masson, et al., Guaiac versus immunochemical tests: faecal occult blood test screening for colorectal cancer in a rural community, Aust. N. Z. J. Public Health 29 (2005) 358–364.
[22] C.W. Ko, J.A. Dominitz, T.D. Nguyen, Fecal occult blood testing in a general medical clinic: comparison between guaiac-based and immunochemical-based tests, Am. J. Med. 115 (2003) 111–114.
[23] C. Hassan, P. Giorgi Rossi, L. Camilloni, D.K. Rex, B. Jimenez-Cendales, E. Ferroni, et al., Meta-analysis: adherence to colorectal cancer screening and the detection rate for advanced neoplasia, according to the type of screening test, Aliment. Pharmacol. Ther. 36 (2012) 929–940.
[24] M.M. Zhu, X.T. Xu, F. Nie, J.L. Tong, S.D. Xiao, Z.H. Ran, Comparison of immunochemical and guaiac-based fecal occult blood test in screening and surveillance for advanced colorectal neoplasms: a meta-analysis, J. Dig. Dis. 11 (2010) 148–160.
[25] R.M. Hoffman, S. Steel, E.F. Yee, L. Massie, R.M. Schrader, G.H. Murata, Colorectal cancer screening adherence is higher with fecal immunochemical tests than guaiac-based fecal occult blood tests: a randomized, controlled trial, Prev. Med. 50 (2010) 297–299.
[26] B.J. Elmunzer, R.A. Hayward, P.S. Schoenfeld, S.D. Saini, A. Deshpande, A.K. Waljee, Effect of flexible sigmoidoscopy-based screening on incidence and mortality of colorectal cancer: a systematic review and meta-analysis of randomized controlled trials, PLoS Med. 9 (2012) e1001352.
[27] E. Thiis-Evensen, G.S. Hoff, J. Sauar, F. Langmark, B.M. Majak, M.H. Vatn, Population-based surveillance by colonoscopy: effect on the incidence of colorectal cancer: Telemark Polyp Study I, Scand. J. Gastroenterol. 34 (1999) 414–420.
[28] G. Hoff, T. Grotmol, E. Skovlund, M. Bretthauer, Norwegian colorectal cancer prevention study G. Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial, BMJ 338 (2009) b1846.
[29] W.S. Atkin, R. Edwards, I. Kralj-Hans, K. Wooldrage, A.R. Hart, J.M. Northover, et al., Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial, Lancet 375 (2010) 1624–1633.
[30] N. Segnan, P. Armaroli, L. Bonelli, M. Risio, S. Sciallero, M. Zappa, et al., Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian randomized controlled trial—SCORE, J. Natl. Cancer Inst. 103 (2011) 1310–1322.
[31] R.E. Schoen, P.F. Pinsky, J.L. Weissfeld, L.A. Yokochi, T. Church, A.O. Laiyemo, et al., Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy, N. Engl. J. Med. 366 (2012) 2345–2357.
[32] N.N. Baxter, M.A. Goldwasser, L.F. Paszat, R. Saskin, D.R. Urbach, L. Rabeneck, Association of colonoscopy and death from colorectal cancer, Ann. Intern. Med. 150 (2009) 1–8.
[33] H. Brenner, U. Haug, V. Arndt, C. Stegmaier, L. Altenhofen, M. Hoffmeister, Low risk of colorectal cancer and advanced adenomas more than 10 years after negative colonoscopy, Gastroenterology 138 (2010) 870–876.
[34] H. Brenner, M. Hoffmeister, V. Arndt, C. Stegmaier, L. Altenhofen, U. Haug, Protection from right- and left-sided colorectal neoplasms after colonoscopy: population-based study, J. Natl. Cancer Inst. 102 (2010) 89–95.
[35] H. Brenner, J. Chang-Claude, C.M. Seiler, A. Rickert, M. Hoffmeister, Protection from colorectal cancer after colonoscopy: a population-based, case-control study, Ann. Intern Med. 154 (2011) 22–30.
[36] F. Citarda, G. Tomaselli, R. Capocaccia, S. Barcherini, M. Crespi, Italian Multicentre Study G. Efficacy in standard clinical practice of colonoscopic polypectomy in reducing colorectal cancer incidence, Gut 48 (2001) 812–815.
[37] C.J. Kahi, T.F. Imperiale, B.E. Juliar, D.K. Rex, Effect of screening colonoscopy on colorectal cancer incidence and mortality, Clin. Gastroenterol. Hepatol. 7 (2009) 770–775 quiz 11.
[38] J. Lakoff, L.F. Paszat, R. Saskin, L. Rabeneck, Risk of developing proximal versus distal colorectal cancer after a negative colonoscopy: a population-based study, Clin. Gastroenterol. Hepatol. 6 (2008) 1117–1121 quiz 064.
[39] L. Rabeneck, L.F. Paszat, R. Saskin, T.A. Stukel, Association between colonoscopy rates and colorectal cancer mortality, Am. J. Gastroenterol. 105 (2010) 1627–1632.
[40] H. Singh, Z. Nugent, A.A. Demers, E.V. Kliewer, S.M. Mahmud, C.N. Bernstein, The reduction in colorectal cancer mortality after colonoscopy varies by site of the cancer, Gastroenterology 139 (2010) 1128–1137.

[41] H. Singh, Z. Nugent, S.M. Mahmud, A.A. Demers, C.N. Bernstein, Predictors of colorectal cancer after negative colonoscopy: a population-based study, Am. J. Gastroenterol. 105 (2010) 663–673 quiz 74.
[42] A.G. Zauber, S.J. Winawer, M.J. O'Brien, I. Lansdorp-Vogelaar, M. van Ballegooijen, B.F. Hankey, et al., Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths, N. Engl. J. Med. 366 (2012) 687–696.
[43] S.J. Winawer, A.G. Zauber, M.N. Ho, M.J. O'Brien, L.S. Gottlieb, S.S. Sternberg, et al., Prevention of colorectal cancer by colonoscopic polypectomy: The National Polyp Study Workgroup, N. Engl. J. Med. 329 (1993) 1977–1981.
[44] J.D. Hardcastle, J.O. Chamberlain, M.H. Robinson, S.M. Moss, S.S. Amar, T.W. Balfour, et al., Randomised controlled trial of faecal-occult-blood screening for colorectal cancer, Lancet 348 (1996) 1472–1477.
[45] O. Kronborg, C. Fenger, J. Olsen, O.D. Jorgensen, O. Sondergaard, Randomised study of screening for colorectal cancer with faecal-occult-blood test, Lancet 348 (1996) 1467–1471.
[46] E. Lindholm, H. Brevinge, E. Haglind, Survival benefit in a randomized clinical trial of faecal occult blood screening for colorectal cancer, Br. J. Surg. 95 (2008) 1029–1036.
[47] J.S. Mandel, J.H. Bond, T.R. Church, D.C. Snover, G.M. Bradley, L.M. Schuman, et al., Reducing mortality from colorectal cancer by screening for fecal occult blood: Minnesota Colon Cancer Control study, N. Engl. J. Med. 328 (1993) 1365–1371.
[48] J.H. Scholefield, S. Moss, F. Sufi, C.M. Mangham, J.D. Hardcastle, Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial, Gut 50 (2002) 840–844.
[49] J.H. Scholefield, S.M. Moss, C.M. Mangham, D.K. Whynes, J.D. Hardcastle, Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up, Gut 61 (2012) 1036–1040.
[50] J.S. Mandel, T.R. Church, F. Ederer, J.H. Bond, Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood, J. Natl. Cancer Inst. 91 (1999) 434–437.
[51] A.H. van Roon, S.L. Goede, M. van Ballegooijen, A.J. van Vuuren, C.W. Looman, K. Biermann, et al., Random comparison of repeated faecal immunochemical testing at different intervals for population-based colorectal cancer screening, Gut 62 (2013) 409–415.
[52] K. Soares-Weiser, J. Burch, S. Duffy, J. St John, S. Smith, M. Westwood, et al., Diagnostic accuracy and cost-effectiveness of faecal occult blood tests (FOBT) used in screening for colorectal cancer: a systematic review, Database Abstr. Rev. Eff. 2 (2007) 221.
[53] M.A. Parker, M.H. Robinson, J.H. Scholefield, J.D. Hardcastle, Psychiatric morbidity and screening for colorectal cancer, J. Med. Screen. 9 (2002) 7–10.
[54] E. Lindholm, B. Berglund, J. Kewenter, E. Haglind, Worry associated with screening for colorectal carcinomas, Scand. J. Gastroenterol. 32 (1997) 238–245.
[55] D. Mant, R. Fitzpatrick, A. Hogg, A. Fuller, A. Farmer, J. Verne, et al., Experiences of patients with false positive results from colorectal cancer screening, Br. J. Gen. Pract. 40 (1990) 423–425.
[56] W.S. Atkin, C.F. Cook, J. Cuzick, R. Edwards, J.M. Northover, J. Wardle, et al., Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial, Lancet 359 (2002) 1291–1300.
[57] G. Gondal, T. Grotmol, B. Hofstad, M. Bretthauer, T.J. Eide, G. Hoff, The Norwegian Colorectal Cancer Prevention (NORCCAP) screening study: baseline findings and implementations for clinical work-up in age groups 50–64 years, Scand. J. Gastroenterol. 38 (2003) 635–642.
[58] N. Segnan, C. Senore, B. Andreoni, H. Aste, L. Bonelli, C. Crosta, et al., Baseline findings of the Italian multicenter randomized controlled trial of once-only sigmoidoscopy–SCORE, J. Natl. Cancer Inst. 94 (2002) 1763–1772.
[59] N. Segnan, C. Senore, B. Andreoni, A. Arrigoni, L. Bisanti, A. Cardelli, et al., Randomized trial of different screening strategies for colorectal cancer: patient response and detection rates, J. Natl. Cancer Inst. 97 (2005) 347–357.
[60] R.E. Schoen, P.F. Pinsky, J.L. Weissfeld, R.S. Bresalier, T. Church, P. Prorok, et al., Results of repeat sigmoidoscopy 3 years after a negative examination, JAMA 290 (2003) 41–48.
[61] C.A. Burke, K. Elder, R. Lopez, Screening for colorectal cancer with flexible sigmoidoscopy: is a 5-yr interval appropriate? A comparison of the detection of neoplasia 3 yr versus 5 yr after a normal examination, Am. J. Gastroenterol. 101 (2006) 1329–1332.
[62] R.E. Schoen, P.F. Pinsky, J.L. Weissfeld, L.A. Yokochi, T. Church, A.O. Laiyemo, et al., Colorectal cancers not detected by screening flexible sigmoidoscopy in the prostate, lung, colorectal, and ovarian cancer screening trial, Gastrointest. Endosc. 75 (2012) 612–620.
[63] I.K. Larsen, T. Grotmol, M. Bretthauer, G. Gondal, G. Huppertz-Hauss, B. Hofstad, et al., Continuous evaluation of patient satisfaction in endoscopy centres, Scand. J. Gastroenterol. 37 (2002) 850–855.
[64] R.E. Schoen, J.L. Weissfeld, N.J. Bowen, G. Switzer, A. Baum, Patient satisfaction with screening flexible sigmoidoscopy, Arch. Intern. Med. 160 (2000) 1790–1796.
[65] M. Ferlitsch, K. Reinhart, S. Pramhas, C. Wiener, O. Gal, C. Bannert, et al., Sex-specific prevalence of adenomas, advanced adenomas, and colorectal cancer in individuals undergoing screening colonoscopy, JAMA 306 (2011) 1352–1358.
[66] C.P. Pox, L. Altenhofen, H. Brenner, A. Theilmeier, D. Von Stillfried, W. Schmiegel, Efficacy of a nationwide screening colonoscopy program for colorectal cancer, Gastroenterology 142 (2012) 1460–1467 e2.
[67] J. Regula, M. Rupinski, E. Kraszewska, M. Polkowski, J. Pachlewski, J. Orlowska, et al., Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia, N. Engl. J. Med. 355 (2006) 1863–1872.
[68] E. Quintero, A. Castells, L. Bujanda, J. Cubiella, D. Salas, A. Lanas, et al., Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening, N. Engl. J. Med. 366 (2012) 697–706.
[69] A. Graser, P. Stieber, D. Nagel, C. Schafer, D. Horst, C.R. Becker, et al., Comparison of CT colonography, colonoscopy, sigmoidoscopy and faecal occult blood tests for the detection of advanced adenoma in an average risk population, Gut 58 (2009) 241–248.
[70] C.D. Johnson, J.G. Fletcher, R.L. MacCarty, J.N. Mandrekar, W.S. Harmsen, P.J. Limburg, et al., Effect of slice thickness and primary 2D versus 3D virtual dissection on colorectal lesion detection at CT colonography in 452 asymptomatic adults, Am. J. Roentgenol. 189 (2007) 672–680.
[71] C.D. Johnson, M.H. Chen, A.Y. Toledano, J.P. Heiken, A. Dachman, M.D. Kuo, et al., Accuracy of CT colonography for detection of large adenomas and cancers, N. Engl. J. Med. 359 (2008) 1207–1217.
[72] Y.S. Kim, N. Kim, S.H. Kim, M.J. Park, S.H. Lim, J.Y. Yim, et al., The efficacy of intravenous contrast-enhanced 16-raw multidetector CT colonography for detecting patients with colorectal polyps in an asymptomatic population in Korea, J. Clin. Gastroenterol. 42 (2008) 791–798.
[73] P.J. Pickhardt, J.R. Choi, I. Hwang, J.A. Butler, M.L. Puckett, H.A. Hildebrandt, et al., Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults, N. Engl. J. Med. 349 (2003) 2191–2200.
[74] M.F. Kaminski, J. Regula, E. Kraszewska, M. Polkowski, U. Wojciechowska, J. Didkowska, et al., Quality indicators for colonoscopy and the risk of interval cancer, N. Engl. J. Med. 362 (2010) 1795–1803.
[75] H.B. Bosworth, D.C. Rockey, E.K. Paulson, D. Niedzwiecki, W. Davis, L.L. Sanders, et al., Prospective comparison of patient experience with colon imaging tests, Am. J. Med. 119 (2006) 791–799.
[76] A. Condon, L. Graff, L. Elliot, A. Ilnyckyj, Acceptance of colonoscopy requires more than test tolerance, Can. J. Gastroenterol. 22 (2008) 41–47.
[77] T.M. Gluecker, C.D. Johnson, W.S. Harmsen, K.P. Offord, A.M. Harris, L.A. Wilson, et al., Colorectal cancer screening with CT colonography, colonoscopy, and double-contrast barium enema examination: prospective assessment of patient perceptions and preferences, Radiology 227 (2003) 378–384.
[78] F.B. Nicholson, M.G. Korman, Acceptance of flexible sigmoidoscopy and colonoscopy for screening and surveillance in colorectal cancer prevention, J. Med. Screen. 12 (2005) 89–95.
[79] S.L. Ristvedt, E.G. McFarland, L.B. Weinstock, E.P. Thyssen, Patient preferences for CT colonography, conventional colonoscopy, and bowel preparation, Am. J. Gastroenterol. 98 (2003) 578–585.
[80] R.E. van Gelder, E. Birnie, J. Florie, M.P. Schutter, J.F. Bartelsman, P. Snel, et al., CT colonography and colonoscopy: assessment of patient preference in a 5-week follow-up study, Radiology 233 (2004) 328–337.
[81] Multicentre Australian Colorectal-neoplasia Screening G, A comparison of colorectal neoplasia screening tests: a multicentre community-based study of the impact of consumer choice, Med. J. Aust. 184 (2006) 546–550.
[82] S.A. McLachlan, A. Clements, J. Austoker, Patients' experiences and reported barriers to colonoscopy in the screening context—a systematic review of the literature, Patient Educ. Couns. 86 (2012) 137–146.
[83] C. Senore, A. Ederle, A. Fantin, B. Andreoni, L. Bisanti, G. Grazzini, et al., Acceptability and side-effects of colonoscopy and sigmoidoscopy in a screening setting, J. Med. Screen. 18 (2011) 128–134.
[84] P.C. Gotzsche, K.J. Jorgensen, Screening for breast cancer with mammography, Cochrane Database Syst Rev. 6 (2013) CD001877.
[85] D. Fitzpatrick-Lewis, N. Hodgson, D. Ciliska, Breast Cancer Screening, McMaster University, Hamilton, Ontario, Canada, 2011.
[86] Independent UKPoBCS, The benefits and harms of breast cancer screening: an independent review, Lancet 380 (2012) 1778–1786.
[87] M. Broeders, S. Moss, L. Nystrom, S. Njor, H. Jonsson, E. Paap, et al., The impact of mammographic screening on breast cancer mortality in Europe: a review of observational studies, J. Med. Screen. 19 (Suppl. 1) (2012) 14–25.
[88] R. Gabe, S.W. Duffy, Evaluation of service screening mammography in practice: the impact on breast cancer mortality, Ann. Oncol. 16 (Suppl. 2) (2005) 53–62.
[89] H.D. Nelson, K. Tyne, A. Naik, C. Bougatsos, B.K. Chan, L. Humphrey, et al., Screening for breast cancer: an update for the U.S. Preventive Services Task Force, Ann. Intern. Med. 151 (727–737) (2009) W237–W242.
[90] S.M. Moss, 16-year mortality from breast cancer in the UK Trial of Early Detection of Breast Cancer, Lancet 353 (1999) 1909–1914.
[91] L. Tabar, M.F. Yen, B. Vitak, H.H. Chen, R.A. Smith, S.W. Duffy, Mammography service screening and mortality in breast cancer patients: 20-year follow-up before and after introduction of screening, Lancet 361 (2003) 1405–1410.
[92] P.G. Peer, J.M. Werre, M. Mravunac, J.H. Hendriks, R. Holland, A.L. Verbeek, Effect on breast cancer mortality of biennial mammographic screening of women under age 50, Int. J. Cancer 60 (1995) 808–811.
[93] H. Jonsson, S. Tornberg, L. Nystrom, P. Lenner, Service screening with mammography in Sweden—evaluation of effects of screening on breast cancer mortality in age group 40–49 years, Acta Oncol. 39 (2000) 617–623.
[94] B.N. Hellquist, S.W. Duffy, S. Abdsaleh, L. Bjorneld, P. Bordas, L. Tabar, et al., Effectiveness of population-based service screening with mammography for women ages 40 to 49 years: evaluation of the Swedish Mammography Screening in Young Women (SCRY) cohort, Cancer 117 (2011) 714–722.

[95] R. Taylor, A. Page, D. Bampton, J. Estoesta, M. Rickard, Age-specific interval breast cancers in New South Wales and meta-analysis of studies of women aged 40–49 years, J. Med. Screen. 11 (2004) 199–206.
[96] E. Lynge, A.H. Olsen, J. Fracheboud, J. Patnick, Reporting of performance indicators of mammography screening in Europe, Eur. J. Cancer Prev. 12 (2003) 213–222.
[97] S. Hofvind, A. Ponti, J. Patnick, N. Ascunce, S. Njor, M. Broeders, et al., False-positive results in mammographic screening for breast cancer in Europe: a literature review and survey of service screening programmes, J. Med. Screen. 19 (Suppl. 1) (2012) 57–66.
[98] D. Puliti, S.W. Duffy, G. Miccinesi, H. de Koning, E. Lynge, M. Zappa, et al., Over-diagnosis in mammographic screening for breast cancer in Europe: a literature review, J. Med. Screen. 19 (Suppl. 1) (2012) 42–56.
[99] K. Armstrong, E. Moye, S. Williams, J.A. Berlin, E.E. Reynolds, Screening mammography in women 40 to 49 years of age: a systematic review for the American College of Physicians, Ann. Intern. Med. 146 (2007) 516–526.
[100] J. Brett, C. Bankhead, B. Henderson, E. Watson, J. Austoker, The psychological impact of mammographic screening. A systematic review, Psycho-Oncol. 14 (2005) 917–938.
[101] M. Bond, T. Pavey, K. Welch, C. Cooper, R. Garside, S. Dean, et al., Systematic review of the psychological consequences of false-positive screening mammograms, Health Technol. Assess. 17 (2013) 1–170 v-vi.
[102] N.T. Brewer, T. Salz, S.E. Lillie, Systematic review: the long-term effects of false-positive mammograms, Ann. Intern. Med. 146 (2007) 502–510.
[103] H. Bijwaard, A. Brenner, F. Dekkers, T. van Dillen, C.E. Land, J.D. Boice Jr, Breast cancer risk from different mammography screening practices, Radiat. Res. 174 (2010) 367–376.
[104] R. de Gelder, G. Draisma, E.A. Heijnsdijk, H.J. de Koning, Population-based mammography screening below age 50: balancing radiation-induced vs prevented breast cancer deaths, Br. J. Cancer 104 (2011) 1214–1220.
[105] R.E. Hendrick, Radiation doses and cancer risks from breast imaging studies, Radiology 257 (2010) 246–253.
[106] G.J. Heyes, A.J. Mill, M.W. Charles, Mammography-oncogenecity at low doses, J. Radiol. Prot. 29 (2009) A123–32.
[107] M.K. O'Connor, H. Li, D.J. Rhodes, C.B. Hruska, C.B. Clancy, R.J. Vetter, Comparison of radiation exposure and associated radiation-induced cancer risks from mammography and molecular imaging of the breast, Med. Phys. 37 (2010) 6187–6198.
[108] M.J. Yaffe, J.G. Mainprize, Risk of radiation-induced breast cancer from mammographic screening, Radiology 258 (2011) 98–105.
[109] R.J. Barth Jr., G.R. Gibson, P.A. Carney, L.A. Mott, R.D. Becher, S.P. Poplack, Detection of breast cancer on screening mammography allows patients to be treated with less-toxic therapy, Am. J. Roentgenol. 184 (2005) 324–329.
[110] P. Giorgi Rossi, F. Chini, A. Barca, D. Baiocchi, A. Federici, S. Farchi, et al., Efficacy of disease management profiles: the mammographic screening program of Lazio, Tumori 94 (2008) 297–303.
[111] S. Hofvind, C.I. Lee, J.G. Elmore, Stage-specific breast cancer incidence rates among participants and non-participants of a population-based mammographic screening program, Breast Cancer Res. Treat. 135 (2012) 291–299.
[112] S. Hofvind, P. Skaane, Stage distribution of breast cancer diagnosed before and after implementation of population-based mammographic screening, RoFo: Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin 184 (2012) 437–442.
[113] H.G. Kaplan, J.A. Malmgren, Disease-specific survival in patient-detected breast cancer, Clinical Breast Cancer 7 (2006) 133–140.
[114] J.A. Malmgren, J. Parikh, M.K. Atwood, H.G. Kaplan, Impact of mammography detection on the course of breast cancer in women aged 40–49 years, Radiology 262 (2012) 797–806.
[115] J.A. Perez-Fidalgo, J. Miranda, I. Chirivella, J. Ibanez, B. Bermejo, C. Pons, et al., Impact of a mammography screening programme on the breast cancer population of the Region of Valencia (Spain), Clin. Transl. Oncol. 10 (2008) 745–752.
[116] N. Samnakay, J. Tinning, A. Ives, P. Willsher, S. Archer, E. Wylie, et al., Rates for mastectomy are lower in women attending a breast-screening programme, ANZ J. Surg. 75 (2005) 936–939.
[117] A.J. Spillane, C.W. Kennedy, D.J. Gillett, H.L. Carmalt, N.C. Janu, M.T. Rickard, et al., Screen-detected breast cancer compared to symptomatic presentation: an analysis of surgical treatment and end-points of effective mammographic screening, ANZ J. Surg. 71 (2001) 398–402.
[118] P.M. Walsh, P. McCarron, R.J. Middleton, H. Comber, A.T. Gavin, L. Murray, Influence of mammographic screening on trends in breast-conserving surgery in Ireland, Eur. J. Cancer Prev. 15 (2006) 138–148.
[119] M. Zorzi, D. Puliti, M. Vettorazzi, V. De Lisi, F. Falcini, M. Federico, et al., Mastectomy rates are decreasing in the era of service screening: a population-based study in Italy (1997–2001), Br. J. Cancer 95 (2006) 1265–1268.
[120] M.D. Crawford, A.V. Biankin, M.T. Rickard, M.J. Coleman, R. West, F.W. Niesche, et al., The operative management of screen-detected breast cancers, Aust. N. Z. J. Surg. 70 (2000) 168–173.
[121] E. Paci, S.W. Duffy, D. Giorgi, M. Zappa, E. Crocetti, V. Vezzosi, et al., Are breast cancer screening programmes increasing rates of mastectomy? Observational study, BMJ 325 (2002) 418.
[122] N.G. Coburn, B. Cady, J.P. Fulton, C. Law, M.A. Chung, Improving size, lymph node metastatic rate, breast conservation, and mortality of invasive breast cancer in Rhode Island women, a well-screened population, Breast Cancer Res. Treat. 135 (2012) 831–837.
[123] A. Stang, V. Kaab-Sanyal, H.W. Hense, N. Becker, O. Kuss, Effect of mammography screening on surgical treatment for breast cancer: a nationwide analysis of hospitalization rates in Germany 2005–2009, Eur. J. Epidemiol. 28 (2013) 689–696.
[124] M.F. Ernst, A.C. Voogd, J.W. Coebergh, O.J. Repelaer van Driel, J.A. Roukema, The introduction of mammographical screening has had little effect on the trend in breast-conserving surgery: a population-based study in Southeast Netherlands, Eur. J. Cancer 37 (2001) 2435–2440.
[125] M.F. Ernst, A.C. Voogd, J.W.W. Coebergh, J.A. Roukema, An improved prognosis and a more favourable stage of the tumour in patients with invasive breast carcinoma following the introduction of the breast cancer screening programme in Tilburg: betere prognose en gunstiger tumorstadium bij patienten met invasief mammacarcinoom na de introductie van het bevolkingsonderzoek op borstkanker in Tilburg, Ned. Tijdschr. Geneeskd. 148 (2004) 378–382.
[126] P. Suhrke, J. Maehlen, E. Schlichting, K.J. Jorgensen, P.C. Gotzsche, P.H. Zahl, Effect of mammography screening on surgical treatment for breast cancer in Norway: comparative analysis of cancer registry data, BMJ 343 (2011) d4692.
[127] G.M. Freedman, P.R. Anderson, L.J. Goldstein, A.L. Hanlon, M.E. Cianfrocca, M. M. Millenson, et al., Routine mammography is associated with earlier stage disease and greater eligibility for breast conservation in breast carcinoma patients age 40 years and older, Cancer 98 (2003) 918–925.
[128] A.J. Coldman, N. Phillips, C. Speers, A retrospective study of the effect of participation in screening mammography on the use of chemotherapy and breast conserving surgery, Int. J. Cancer 120 (2007) 2185–2190.
[129] A.W. Leung, J. Mak, P.S. Cheung, R.J. Epstein, Clinicopathological correlates in a cohort of Hong Kong breast cancer patients presenting with screen-detected or symptomatic disease, Hong Kong Med. J. 13 (2007) 194–198.
[130] P. Meijnen, J.L. Peterse, H.S. Oldenburg, L.A. Woerdeman, E.J. Rutgers, Changing patterns in diagnosis and treatment of ductal carcinoma in situ of the breast, Eur. J. Surg. Oncol. 31 (2005) 833–839.
[131] I. Palka, G. Kelemen, K. Ormandi, G. Lazar, T. Nyari, L. Thurzo, et al., Tumor characteristics in screen-detected and symptomatic breast cancers, Pathol. Oncol. Res. 14 (2008) 161–167.
[132] T.K. Yau, I.S. Soong, H. Sze, C.W. Choi, M.W. Yeung, W.T. Ng, et al., Trends and patterns of breast conservation treatment in Hong Kong: 1994–2007, Int. J. Radiat. Oncol., Biol., Phys. 74 (2009) 98–103.
[133] A.M. Yen, S.W. Duffy, T.H. Chen, L.S. Chen, S.Y. Chiu, J.C. Fann, et al., Long-term incidence of breast cancer by trial arm in one county of the Swedish Two-County Trial of mammographic screening, Cancer 118 (2012) 5728–5732.
[134] F. Foca, S. Mancini, L. Bucchi, D. Puliti, M. Zappa, C. Naldoni, et al., Decreasing incidence of late-stage breast cancer after the introduction of organized mammography screening in Italy, Cancer 119 (2013) 2022–2028.
[135] L.S. Elting, C.D. Cooksley, B.N. Bekele, S.H. Giordano, Y.C. Shih, K.K. Lovell, et al., Mammography capacity impact on screening rates and breast cancer stage at diagnosis, Am. J. Prev. Med. 37 (2009) 102–108.
[136] P. Autier, M. Boniol, The incidence of advanced breast cancer in the West Midlands, United Kingdom, Eur. J. Cancer Prev. 21 (2012) 217–221.
[137] A. Bleyer, H.G. Welch, Effect of three decades of screening mammography on breast-cancer incidence, N. Engl. J. Med. 367 (2012) 1998–2005.
[138] J. Nederend, L.E. Duijm, A.C. Voogd, J.H. Groenewoud, F.H. Jansen, M.W. Louwman, Trends in incidence and detection of advanced breast cancer at biennial screening mammography in The Netherlands: a population based study, Breast Cancer Res. 14 (2012) R10.
[139] Strategies IWGotEoCP, Cervix Cancer Screening. IARC Handbooks of Cancer Prevention No. 10, IARC, Lyon, 2005.
[140] R. Sankaranarayanan, B.M. Nene, S.S. Shastri, K. Jayant, R. Muwonge, A.M. Budukh, et al., HPV screening for cervical cancer in rural India, N. Engl. J. Med. 360 (2009) 1385–1394.
[141] G. Ronco, J. Dillner, K.M. Elfstrom, S. Tunesi, P.J. Snijders, M. Arbyn, et al., Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials, Lancet 383 (2014) 524–532.
[142] G. Ronco, N. Segnan, P. Giorgi-Rossi, M. Zappa, G.P. Casadei, F. Carozzi, et al., Human papillomavirus testing and liquid-based cytology: results at recruitment from the new technologies for cervical cancer randomized controlled trial, J. NatL. Cancer Inst. 98 (2006) 765–774.
[143] G. Ronco, P. Giorgi-Rossi, F. Carozzi, M. Confortini, P. Dalla Palma, A. Del Mistro, et al., Results at recruitment from a randomized controlled trial comparing human papillomavirus testing alone with conventional cytology as the primary cervical cancer screening test, J. Natl. Cancer Inst. 100 (2008) 492–501.
[144] H. De Vuyst, G. Clifford, N. Li, S. Franceschi, HPV infection in Europe, Eur. J. Cancer 45 (2009) 2632–2639.
[145] C.B. Woodman, S. Collins, H. Winter, A. Bailey, J. Ellis, P. Prior, et al., Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study, Lancet 357 (2001) 1831–1836.
[146] K.K. Vesco, E.P. Whitlock, M. Eder, J. Lin, B.U. Burda, C.A. Senger, R.S. Holmes, R. Fu, S. Zuber, Screening for Cervical Cancer: A Systematic Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 86. AHRQ Publication No. 11-05156-EF-1, Agency for Healthcare Research and Quality, Rockville, MD, 2011.
[147] M. Arbyn, G. Ronco, C.J. Meijer, P. Naucler, Trials comparing cytology with human papillomavirus screening, Lancet Oncol. 10 (2009) 935–936.

[148] J. Cuzick, M. Arbyn, R. Sankaranarayanan, V. Tsu, G. Ronco, M.H. Mayrand, et al., Overview of human papillomavirus-based and other novel options for cervical cancer screening in developed and developing countries, Vaccine 26 (Suppl. 10) (2008) K29–41.
[149] J. Cuzick, M.H. Mayrand, G. Ronco, P. Snijders, J. Wardle, Chapter 10: new dimensions in cervical cancer screening, Vaccine 24 (Suppl. 3:S3) (2006) 90–97.
[150] J.J. Kim, T.C. Wright, S.J. Goldie, Cost-effectiveness of human papillomavirus DNA testing in the United Kingdom, The Netherlands, France, and Italy, J. Natl. Cancer Inst. 97 (2005) 888–895.
[151] G. Ronco, A. Biggeri, M. Confortini, C. Naldoni, N. Segnan, M. Sideri, et al., Health technology assessment report: HPV DNA based primary screening for cervical cancer precursors, Epidemiol. Prev. 36 (2012) e1–72.
[152] G. Ronco, P. Giorgi-Rossi, F. Carozzi, M. Confortini, P. Dalla Palma, A. Del Mistro, et al., Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial, Lancet Oncol. 11 (2010) 249–257.
[153] Screening for squamous cervical cancer: duration of low risk after negative results of cervical cytology and its implication for screening policies. IARC Working Group on evaluation of cervical cancer screening programmes. Br. Med. J. (Clin. Res. Ed.) 1986, 293 (September (6548)), 659–664.
[154] M.E. van den Akker-van Marle, M. van Ballegooijen, J.D. Habbema, Low risk of cervical cancer during a long period after negative screening in the Netherlands, Br. J. Cancer 88 (2003) 1054–1057.
[155] P. Sasieni, J. Adams, J. Cuzick, Benefit of cervical screening at different ages: evidence from the UK audit of screening histories, Br. J. Cancer 89 (2003) 88–93.
[156] D.C. Rijkaart, J. Berkhof, L. Rozendaal, F.J. van Kemenade, N.W. Bulkmans, D.A. Heideman, et al., Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial, Lancet Oncol. 13 (2012) 78–88.
[157] H.C. Kitchener, M. Almonte, C. Thomson, P. Wheeler, A. Sargent, B. Stoykova, et al., HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial, Lancet Oncol. 10 (2009) 672–682.
[158] P. Naucler, W. Ryd, S. Tornberg, A. Strand, G. Wadell, K. Elfgren, et al., Human papillomavirus and Papanicolaou tests to screen for cervical cancer, N. Engl. J. Med. 357 (2007) 1589–1597.
[159] P. Naucler, W. Ryd, S. Tornberg, A. Strand, G. Wadell, K. Elfgren, et al., Efficacy of HPV DNA testing with cytology triage and/or repeat HPV DNA testing in primary cervical cancer screening, J. Natl. Cancer Inst. 101 (2009) 88–99.
[160] M. Arbyn, G. Ronco, A. Anttila, C.J. Meijer, M. Poljak, G. Ogilvie, et al., Evidence regarding human papillomavirus testing in secondary prevention of cervical cancer, Vaccine 30 (Suppl. 5) (2012) F88–99.
[161] S. Bulk, N.W. Bulkmans, J. Berkhof, L. Rozendaal, A.J. Boeke, R.H. Verheijen, et al., Risk of high-grade cervical intra-epithelial neoplasia based on cytology and high-risk HPV testing at baseline and at 6-months, Int. J. Cancer 121 (2007) 361–367.
[162] A. Schneider, H. Hoyer, B. Lotz, S. Leistritza, R. Kuhne-Heid, I. Nindl, et al., Screening for high-grade cervical intra-epithelial neoplasia and cancer by testing for high-risk HPV, routine cytology or colposcopy, Int. J. Cancer 89 (2000) 529–534.
[163] I.Y. Patanwala, H.M. Bauer, J. Miyamoto, I.U. Park, M.J. Huchko, K.K. Smith-McCune, A systematic review of randomized trials assessing human papillomavirus testing in cervical cancer screening, Am. J. Obstet. Gynecol. 208 (2013) 343–353.
[164] M. Leinonen, P. Nieminen, L. Kotaniemi-Talonen, N. Malila, J. Tarkkanen, P. Laurila, et al., Age-specific evaluation of primary human papillomavirus screening vs conventional cytology in a randomized setting, J. Natl. Cancer Inst. 101 (2009) 1612–1623.
[165] T. Group, Cytological surveillance compared with immediate referral for colposcopy in management of women with low grade cervical abnormalities: multicentre randomised controlled trial, BMJ 339 (2009) b2546.
[166] T. Group, L. Sharp, S. Cotton, C. Cochran, N. Gray, J. Little, et al., After-effects reported by women following colposcopy, cervical biopsies and LLETZ: results from the TOMBOLA trial, BJOG 116 (2009) 1506–1514.
[167] M. Kyrgiou, G. Koliopoulos, P. Martin-Hirsch, M. Arbyn, W. Prendiville, E. Paraskevaidis, Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis, Lancet 367 (2006) 489–498.
[168] M. Arbyn, M. Kyrgiou, C. Simoens, A.O. Raifu, G. Koliopoulos, P. Martin-Hirsch, et al., Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis, BMJ 337 (2008) a1284.
[169] C.L. Werner, J.Y. Lo, T. Heffernan, W.F. Griffith, D.D. McIntire, K.J. Leveno, Loop electrosurgical excision procedure and risk of preterm birth, Obstet. Gynecol. 115 (2010) 605–608.
[170] F. Labrie, B. Candas, L. Cusan, J.L. Gomez, A. Belanger, G. Brousseau, et al., Screening decreases prostate cancer mortality: 11-year follow-up of the 1988 Quebec prospective randomized controlled trial, Prostate 59 (2004) 311–318.
[171] A. Kjellman, O. Akre, U. Norming, M. Tornblom, O. Gustafsson, 15-year followup of a population based prostate cancer screening study, J. Urol. 181 (2009) 1615–1621 discussion 21.
[172] G. Sandblom, E. Varenhorst, J. Rosell, O. Lofman, P. Carlsson, Randomised prostate cancer screening trial: 20 year follow-up, BMJ 342 (2011) d1539.
[173] G.L. Andriole, E.D. Crawford, R.L. Grubb 3rd, S.S. Buys, D. Chia, T.R. Church, et al., Prostate cancer screening in the randomized prostate, lung, colorectal, and ovarian cancer screening trial: mortality results after 13 years of follow-up, J. Natl. Cancer Inst. 104 (2012) 125–132.
[174] F.H. Schroder, J. Hugosson, M.J. Roobol, T.L. Tammela, S. Ciatto, V. Nelen, et al., Prostate-cancer mortality at 11 years of follow-up, N. Engl. J. Med. 366 (2012) 981–990.
[175] D. Ilic, M.M. Neuberger, M. Djulbegovic, P. Dahm, Screening for prostate cancer, Cochrane Database Syst. Rev. 1 (2013) CD004720.