An tSeirbhís Náisiúnta Scagthástála
National Screening Service

# Ethical Issues in Population Cancer Screening Programmes

## An Evidence Synthesis

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**The objective of any ethical analysis in the context of biomedical science is twofold: first, to provide a balanced consideration of the harms and benefits associated with a given intervention and, second, to examine the values and principles which determine how the harms and benefits in question are understood. The resulting analysis will then provide a more robust basis for decision-making. The following report provides an ethical analysis of screening programmes for breast, colorectal and cervical cancer in Ireland.**

## Population screening and public health values

Ethical issues which arise in public health are distinct from those which arise in clinical medicine (CADHT, 2019: 136). The overall aim of any public health intervention is "to pursue the highest possible level of physical and mental health in the population, consistent with the values of social justice" (Gostin and Wiley, 2016: 4). Because public health promotes a collective good, there will inevitably be tension between the state's responsibility to improve and protect the health of the public and the importance of respecting individual rights and interests: a tension, namely, between health and freedom (Gostin and Wiley, 2016: 7; CADHT, 133-4; Kramer and Croswell 2009: 126). Whereas clinical medicine is defined by a focus on the well-being of the individual patient, measures taken in the interests of maximising population health will not always be in the interests of all members of society (Gostin and Wiley 2016: 6; Elton, 2021: 510). In population screening, given that the target population for screening is healthy people, all participants are potentially at risk for physical and psychological harm, while the vast majority of participants will not benefit individually from the intervention (Broderson *et al* 2014: 407; Gates, 2014: 626; Kramer and Croswell, 2009: 126; Shieh *et al*, 2016: 30). As such, improving the aggregated health of the population will entail the materialisation of risks at the individual level. Given the ethical obligation not to make healthy people worse off (Shieh *et al* 2016: 2), however, the net gains at population level from implementing a screening programme should be shown to outweigh the harms posed to healthy individuals. Viewed through a public health lens, there is an ethical imperative to increase uptake in cancer screening programmes. Failure to prevent a preventable death from cancer raises concerns, not just about ethics, but also about equity and fairness (CADTH, 2019: 131) and even the most accurate test has 'no impact' on cancer incidence and mortality in a population if it is not widely applied (Kuipers *et al*, 2015: 14). However, while sufficient uptake is necessary to maintain effective and cost-efficient screening programmes, there is a growing concern that increased uptake should not be achieved at the cost of compromising the voluntariness of participants (Hofmann, 2017: 634; Raffle, 2000: 92), not only because of an increased awareness of the harms associated with screening, but also given the low reduction in absolute risk screening offers and the potential for false reassurance provided by false-negative results (CADTH, 2019: 150). Whereas focusing solely on the interests of individuals rather than on communities and the 'goods' which are of value to them may undermine the ethical complexity of public life (Widdows and Cordell, 2013: 14) and deflect attention from considerations of justice (O'Neill, 2002: 37), an alternative way of viewing community benefit may be to see it in terms of the sum of the benefits accruing to the individuals who make up the community (Irwig *et al*, 2006: 1149).

Much of the controversy arising from the discussion of screening is rooted in disagreements between stakeholders about which values to prioritise in public health decision-making. Broadly speaking, values are an expression of what a given individual perceives to be important or worthwhile (Grisso and Appelbaum, 2006: 294). Values play a role in defining both personal and professional identity and, as such, they influence how both individuals and communities of practice make decisions[1]. Values are integral to the planning of public health interventions, although they remain implicit in much of the literature (Parker, Rychetnik and Carter, 2015: 2). Policy decisions in relation to how best to implement population screening programmes must negotiate the tension between the value ascribed to screening as a means of reducing mortality and morbidity, the value of minimising harm to individuals and the value of empowering potential participants to make fully informed choices. The presentation of evidence in the discussion of screening is similarly influenced by a wide range of ethical and epistemological values, with proponents of screening and those adopting a more cautious approach differing in their approaches to selecting evidence and interpreting data (Parker, Rychetnik and Carter 2015: 6)[2]. How the evidence is evaluated in turn determines how the benefits and harms of screening are perceived and traded off against one another (Juth and Munthe, 2011: 13). Evidence of both benefits of harms is substantive, yet incomplete (Barratt and McKenna 2011: 248) and "inescapable knowledge gaps" persist (Heyman, 2010: 4). No consensus exists in relation to the line distinguishing an acceptable from an unacceptable balance of harms and benefits in population screening (CADTH, 2019: 150). As such, the evaluation of harms and benefits should focus on the perspective of the participant and health-related quality of life should be considered in conjunction with years of life saved (Barratt and McKenna, 2011: 248).

## Establishing a balance between benefits and harms of screening for cancer

The intention behind screening is to enable diagnosis at an earlier point in time in order to improve prognosis through earlier intervention (Marmot *et al*, 2012: 2205; Shieh *et al*, 2016:3; IARC, 2005, 163). The goal of population-level screening for cancer is to reduce the burden of mortality and morbidity associated with cancer by detecting precursor lesions or early-stage invasive cancer in asymptomatic people (Petry *et al*, 2014: 51; Shieh *et al*, 2016:3; Saquib *et al*, 2015: 265). Like any state-funded population screening programme, screening for cancer is ethically justifiable only if it meets two conditions: first, it must be shown to be beneficial, namely, to produce an outcome which is perceived as positive and which would not have been achieved in the absence of screening (Newsom 2011, 125; Gostin 2000: 397). Second, the benefits of the intervention must be shown to outweigh the harms associated with the intervention and any potential harms to individuals must be minimised in the design of screening programmes. Establishing a balance between harms and benefits is a complex undertaking (Broderson *et al* 2014: 408) because, while the benefits of screening — decreased cancer-related morbidity and mortality — are well known and widely promoted, the harms receive less attention and can take a variety of forms (Sawaya, 2009: 2503).

In recent years, increasing attention has been paid to the potential harms associated with screening, anchored in a larger discussion about overdiagnosis and overtreatment of disease (Biddle, 2020: 1). Screening programmes encourage people who are healthy in respect of a given disease to undergo a clinical intervention which they would not have undergone in the absence of the promotion of screening (CADTH, 2019: 136). All medical testing is accompanied by

1. Values are not synonymous with ethical principles, but ethical conflict is often underpinned by a clash between discordant values or value-systems.
2. Ethical values are associated with beliefs about the 'right thing to do', whereas epistemological values refer to preferred sources of knowledge, including the value of evidence-based reasoning and views about what constitutes 'good' scientific evidence (Parker, Rychetnik and Carter, 2015: 4, 6).

a risk of harm, including what have been termed the 'cascade effects' of screening (Deyo, 2002: 38). Early detection and intervention are beneficial when cancer incidence or death is prevented, but can be harmful when the cancer precursor or cancer would not have become symptomatic in the person's lifetime (Riddle *et al*, 2017:1). The harms associated with screening should be taken seriously because individuals themselves do not request access to the intervention but are invited by the health system to participate (Heleno *et al*, 2013: 1). While in principle there is no disagreement about the responsibility to minimize harms (CADTH, 2019: 139), different individuals will place different values on the benefits and harms associated with screening (Welch and Passow, 2014: 448; Keating and Pace, 2019: 2014) and individuals will vary in their acceptance of different benefit-harm thresholds (Sroczynski *et al*, 2019: 1139).

## Overdiagnosis

Overdiagnosis is the most serious potential harm associated with screening (Marmot *et al*, 2012: 2206; Srivastava *et al*, 2019: 349) and a price commonly paid for the capacity to detect cancer early (Kramer and Croswell, 2009: 131). Overdiagnosis occurs when an individual is diagnosed with a disease which would not have harmed them (Carter *et al*, 2016: 705) or would not have become clinically significant in that person's lifetime (Srivastava *et al*, 2019: 349). As such, it can be described as an "extreme form of length-time bias" (Croswell *et al*, 2010:8). Overdiagnosis occurs when a condition is correctly labelled with a specific diagnosis, but the label itself or an intervention related to it is associated with an "unfavourable balance between harms and benefits" (Carter *et al*, 2016: 709-10). Overdiagnosis may result from a number of factors: expanded definitions of disease, greater frequency of testing, increasingly sensitive tests, incidental test findings of uncertain significance, the growing emphasis on risk reduction as an indicator of the effectiveness of testing and commercial interests (Carter *et al* 2016: 705-6).

Overdiagnosis in cancer screening is the detection of cancers which meet the pathological definition of cancer but will never progress to cause symptoms and would never have been diagnosed clinically in the absence of screening (Wegwarth and Gigerenzer, 2013: 2086; IARC 2016: 459). Cancers grow at different rates and the rates at which they grow determine whether or not they can be detected by screening (Gates, 2014: 626). Indolent tumours are tumours which grow very slowly or stop growing altogether, and all screening tests have an inherent tendency to detect these slower growing cancers, because cancers which grow more rapidly are more likely to present between screens (Esserman *et al*, 2014: e235). Overdiagnosis is not observable at the level of the individual, but is inferred statistically when the implementation of a screening programme is followed by an increase in the incidence of early-stage disease without a corresponding reduction in the incidence of advanced disease (Carter *et al*, 2016: 708). Scientific observation is not capable of predicting which individual will suffer future harm as a result of receiving a true positive result from a given test (Hofmann *et al* 2016: 364) and therefore it is impossible to know what would have happened if a given individual who undergoes screening had not been screened. The extent to which overdiagnosis is prevalent in screened populations is contested (Kopans, 2018: vii). Currently, there is very little consensus in relation to what methods should be used to estimate overdiagnosis on a population level or in relation to which outcomes, variables and data should be included in these estimates (Canelo-Aybar 2021: 401; Hofmann *et al*, 2021: 364; IARC, 2016:460; Clift, 2020: 306; Autier and Boniol, 2018: 50)[3]. Although there is variation among existing studies of overdiagnosis in terms of their validity and susceptibility to bias, carefully-designed ecological and cohort studies may provide reliable estimates of overdiagnosis (Carter, Colletti and Harris, 2015: 7). Quantification and monitoring of overdiagnosis is needed if the benefits of screening are to be maximized and harms to participants minimized (Carter, Colletti and Harris, 2015: 7).

3. The methodology for estimating overdiagnosis in observational studies varies; the two most common approaches are the cumulative incidence approach and statistically adjusting for lead time bias (IARC 2016: 460).

The most obvious harm associated with overdiagnosis is unnecessary treatment (Marmot *et al*, 2021: 2206; Wegwarth and Gigerenzer 2013: 2086). People with 'overdiagnosed' cancers will be treated without gaining any benefit from the treatment, but will incur the risk of complications and any adverse effects associated with the treatment (van Dam and Bretthauer, 2014: 318; Barratt and Jacklyn, 2016: 134). However, overdiagnosis itself has a number of serious consequences in addition to treatment for harmless lesions. It "turns healthy people into patients" who will need to attend consultations and follow-up examinations, with associated anxiety and reduced quality of life (Kolthoff *et al*, 2016: 279; Marmot *et al* 2013: 2216 ). It also has the not insignificant downstream effect of utilising expensive resources ineffectively (Hofmann, 2017: 635). Insofar as overdiagnosis is ethically unjustifiable in situations in which it is avoidable, health systems need to pay attention to both the benefits and the potential harms of screening and regularly reevaluate themselves so that they prioritise beneficial over harmful healthcare (Carter *et al*, 2016: 710; 713-4).

In terms of the probability of different outcomes, and particularly the ratio of benefit to harm for participants, the consequences of participating in screening vary across cancer types and available screening modalities, and this variation underpins the difference in recommendations about whether screening should be offered and at what point it should be implemented (Hersch *et al*, 2017: 1). Heleno and colleagues list seven harms associated with cancer screening: overdiagnosis, false positive findings, somatic complications arising from screening or from follow-up procedures, the additional number of participants subjected to invasive procedures, an increase in all-cause mortality (encompassing harms relating to invasive follow-up procedures and overtreatment) and withdrawal from screening because of 'adverse events' (Heleno *et al*, 2013: 2). Among existing programmes to detect and prevent cancer, screening for colorectal cancer is the least controversial, whereas the balance between benefits and harms in breast cancer screening is perceived as finer (Hersch *et al*, 2017:1).

# Colorectal cancer screening: benefits and harms

## Benefits

Colorectal cancer is the second and third most commonly diagnosed form of cancer in women and men respectively, and the second most common cause of cancer death in the world (Rawla *et al*, 2019: 89; Sawicki *et al* 2021: 2). Screening for colorectal cancer aims to reduce the incidence of colorectal cancer by detecting and removing adenomas or polyps before they progress to colorectal cancer and to reduce mortality by detecting colorectal cancer at an early stage (van Dam and Bretthauer, 2014: 316). Adenomas are recognized as precursors in the majority of cases of colorectal cancer (Strum, 2016: 1065) but the progression of colorectal adenoma into cancer is a multistep process which takes at least 5-10 years. Colorectal cancer is more suitable than any other cancer for population screening because its long preclinical phase provides a large window of opportunity for detection (Kuipers *et al*, 2015: 12-13). Colorectal cancer generally progresses for years prior to the appearance of symptoms and early-stage diagnosis is rare in symptomatic patients (Larsen *et al*, 2018: 99). There is a strong association between survival and the stage of disease at the time of diagnosis (Larsen *et al*, 2018: 99) and endoscopic removal of adenomas as well as treatment of early-stage cancer are extremely effective in reducing mortality from colorectal cancer (Kuipers *et al*, 2015: 13). In their review of the evidence, the US Preventive Services Task Force concluded with high certainty that there is substantial net benefit associated with screening for colorectal cancer in adults between 50 and 75 years (USPSTF, 2017: 254b) while IARC found sufficient evidence that FIT-based screening every two years reduces mortality from colorectal cancer (Lauby-Secretan *et al*, 2018: 1736).

Guaiac-based faecal occult-blood testing (gFOBT) has been shown to be effective in detecting cancer and reducing mortality from colon cancer by 15-33% in the short term, although its use has not affected all-cause mortality in the long term (Strum 2016: 1071;

van Dam and Bretthauer, 2014:322). Faecal immunochemical testing (FIT) has higher sensitivity than gFOBT for detecting advanced adenomas and invasive cancers, with comparable specificity (Chiu *et al*, 2015: 3221; Kuipers *et al* 2015: 14; USPSTF, 254D). FITs are now more widely used than gFOBTs because of this higher sensitivity, while the removal of dietary restrictions before testing and a more-user friendly method of sample-taking have increased uptake (Chiu *et al*, 2015: 3221; Kuipers *et al*, 2015). In a nationwide cohort study of the long-term effectiveness of FIT screening with 10 years of follow-up in Taiwan, Chiu *et al* found a reduction of 34% in the incidence of advanced colorectal cancer and a 40% reduction in mortality from colorectal cancer (Chiu *et al*, 2021: 2326).

## Harms

While the FIT-based screening program for colorectal cancer detects colorectal cancer in earlier stages and thereby increases the likelihood of a better prognosis for patients, it is unclear whether higher adenoma detection rates are effective in preventing cancer or increase the overdetection and unnecessary removal of polyps (Helsingen and Kalager, 2022: 8). Currently, there is a lack of evidence in relation to the rate of overdiagnosis associated with the introduction of a FIT-based colorectal screening program and the risk is unknown (Larsen *et al*, 2015: 105; Helsingen and Kalager 2022:6). The harms of stool-based testing arise primarily from adverse events associated with follow-up colonoscopy after a positive test (USPSTF254D) and with the number of colonoscopies performed, as well as with the removal of polyps (Helsingen and Kalager, 2022: 10). A recent study found that 18.8% of 9576 colonoscopies performed after a positive FIT were associated with adverse events and that hospitalisation was required in 11.9% of cases (Denis *et al*, 2021: E224)[4]. While there was a decrease in the overall rate of adverse events in comparison with colonoscopies following positive gFOBTs, no significant difference was found between the two methods of screening in the rate of adverse events requiring hospitalization (Denis *et al*, 2021: E228). While the IARC panel view the benefits of screening for colorectal cancer as outweighing the risks (Lauby-Secretan *et al* 2018: 1738), Denis and colleagues conclude that the risks are 'roughly proportionate' to the benefit (Denis *et al*, 2021: E231), and call for more specific information about the nature and frequency of adverse events associated with colonoscopy to be provided to participants invited to screening for colorectal cancer (Denis *et al*, 2021: E230). As with other forms of screening, false negative results in stool-based screening give rise to false reassurance and may lead participants to disregard future symptoms of colorectal cancer, while false-positive results may create unwarranted anxiety and may result in participants undergoing unnecessary diagnostic testing (van Dam and Bretthauer, 2014: 320).

4. Hospitalisation was required in relation to 16.6% of cases of therapeutic colonoscopies and 3.3% of diagnostic colonoscopies. Although data quantifying adverse events related to colonoscopy in Ireland have not been collated or published, it is of note that the results of the study carried out by Denis and colleagues are at variance with experiential Irish data. The consent form signed by Irish patients undergoing colonoscopy states that the risk of perforation of the bowel during colonoscopy is 1 in 1000, with approximately 50% of patients requiring emergency surgery, while the risk of significant bleeding post-polypectomy is between 1 in 500 and 1 in 1000, with approximately 20% requiring surgery.

# Cervical cancer screening: benefits and harms

## Benefits

Cervical cancer is the fourth most common cause of cancer incidence and mortality in women worldwide, with the mean age at diagnosis lower than for other cancer types (Arbyn *et al*, 2020: e197-8). The aim of screening for cervical cancer is to identify pre-invasive lesions of the cervix, and by providing appropriate treatment, to prevent the development of lesions which might progress into fatal cancers (Vicus *et al*, 2014: 167). Cervical cancer has a slow genesis (Petry *et al*, 2014:48), taking ten to fifteen years to progress from persistent HPV infection to CIN to invasive cancer, and early stage cervical cancer is eminently treatable, with an excellent five-year survival rate. It is generally accepted on the basis of observational data that quality-assured screening for precursors of cervical cancer reduces disease-specific mortality by 70-80% and reduces the incidence rate of cervical cancer by an estimated 50-60% (CADTH, 2019: 131; Jansen *et al*, 2020: 208). The reduction in disease-specific mortality and morbidity associated with the introduction of cytology-based screening is consistent across populations (USPSTF, 2018: 679; Loopik *et al*, 2021: 200.e1) and screening is associated with a reduction in rates of cancer diagnosis at all ages (Landy *et al*, 2016: 1142). The observed reduction in mortality from cervical cancer is subject to variation, however, because the effectiveness of a screening programme in reducing mortality depends on a number of factors, including the epidemiology of HPV infection in the population, the performance and characteristics of the screening programme (starting and stopping ages and length of screening interval), access to treatment and quality of follow-up for women in whom lesions are detected (Jansen *et al*, 2020: 208)[5]. The effect of screening attendance on mortality is greater than the effect on cancer incidence because cervical screening 'downstages' cancers, in addition to preventing them (Landy *et al*, 2016: 1144).

HPV 16 and HPV 18 jointly cause 70–75% of all cervical cancers and 40–60% of precursors of cervical cancer (Arbyn *et al*, 2020: e191; USPSTF 2018: 675; Salcedo *et al* 2022: 637)[6]. HPV 16, HPV 18 and HPV 45, in conjunction with four additional oncogenic types of HPV (31, 33, 52, 58), account for approximately 90% of all cases of invasive cervical cancer (HIQA, 2017: 13). Recognition of the role played in the development of cervical cancer by persistent infection with these high-risk oncogenic strains of HPV has led to an increase in HPV-based testing for cervical cancer. Recent evidence from randomized controlled trials shows that molecular HPV-based screening as the primary test for cervical cancer is more sensitive than cytology and has a higher negative predictive value (Ogilvie *et al*, 2017: 441). As such, HPV testing detects more cervical precancers and prevents more cervical cancers than cytology-based screening (Thomsen *et al* 2021: 395), and in many jurisdictions HPV testing has replaced cytological screening as the primary test for cervical cancer[7]. The long preclinical phase between infection and the development of precancerous lesions which may potentially progress to cervical cancer provides an opportunity to screen for, identify and treat precancerous lesions, preventing progression to invasive disease (USPSTF, 2018: 683). If detected, precancerous lesions can be treated using an excisional or ablative procedure, thereby avoiding the need for more extensive treatments indicated once invasive cancer is diagnosed, such as removal of the cervix, hysterectomy, or chemotherapy and radiotherapy if surgery is not an option. (Jansen *et al* 2020: 208; Vicus *et al* 2014, 167). Treatment of precancerous lesions can preserve future fertility by ensuring that the uterus and the majority of the cervix are retained.

5. In a systematic review of ten European observational studies, Jansen and colleagues found a reduction in disease-specific mortality ranging from 41%-92% among women who attended screening for cervical cancer, compared to women who did not attend (Jansen et al, 2020: 207). Although all of these studies used cytology as a primary method of screening, it can be assumed that the mortality reduction associated with HPV-based screening will be at least as high (Jansen et al, 2020: 214).
6. If the virus is of an oncogenic type and is not cleared by an appropriate immune response, it can result in the incorporation of HPV gene sequences into the host genome and may lead to the development of precancerous lesions (USPSTF 2018: 683). It has not been possible to date to identify a measure to distinguish between women who are infected and will clear the virus and those in whom the infection will persist and who will develop cancer.
7. In Ireland, HPV screening has been implemented by the CervicalCheck programme since 2020.

## Harms

Although screening for precursors of cervical cancer has been more successful in lowering disease-specific mortality than other forms of cancer screening, the benefits of cervical screening, similarly to the benefits of all cancer screening programmes, need to be viewed in relation to the potential physical and psychological harms associated with the intervention. There is considerable histological variation in types of cervical cancer, with squamous cell carcinomas accounting for 76% of all invasive cervical cancers detected in Ireland and adenocarcinomas accounting for 15% (HIQA, 2017: 57)[8]. Prior to the advent of HPV screening, low-grade abnormalities were detected in 4-12% of all adequately performed cytology tests in countries with organized screening programmes, most of which were categorized as atypical squamous cells of uncertain significance (ASC-US) or equivalent (Sharp *et al*, 2014: 142)[9]. Because of an increase in the sensitivity of the test without a corresponding increase in specificity, HPV screening will detect more precursor lesions which will not progress to cancer than cytology-based testing (CADTH 2019: 138). It will also lead to an increase in the incidence of false positives and detect more cases of high-risk oncogenic HPV infection that will not progress to precursors of cancer (Ogilvie *et al* 2017:447; USPSTF, 2018: 679). False-positive test results pose physical and psychological risks to the individual from overdiagnosis and overtreatment (CADTH, 2019: 131), while a false negative result may lead to undertreatment, advanced disease and possibly death. The Canadian health technology assessment of HPV screening found that changing the nature of the primary screen for cervical cancer changes the participant's experience of a false positive result, because a true-positive result for high-risk oncogenic HPV infection is a false-positive result for a cervical lesion (CADTH, 2019: 133, 140)[10]. This could be described as a second kind of overdiagnosis which has important implications, both in terms of the interpretation of test results and in terms of what is communicated to potential candidates for screening during the informed consent process (CADTH, 2019: 140). While cervical cancer screening is an important risk-reducing strategy in preventing mortality from cervical cancer in women over the age of 30 (Vicus *et al* 170), HPV infection is most prevalent in women younger than 35 and most of these infections are transient (USPSTF 2018: 676-7). Given that screening may result in an increased proportion of false positive screens and unnecessary interventions in women of child-bearing age which may result in obstetric complications, there may be an unfavourable balance of harm and benefit associated with offering HPV-based screening to these younger cohorts (Thomsen *et al* 2021: 399; Vicus *et al* 2014: 169).

A corollary of the increased sensitivity of HPV screening is an increased colposcopy referral rate (USPSTF 2018: 676-7). The HPV SCREEN DENMARK study found that HPV-based screening detected 90% more CIN3+ cases than cytology-based screening, but that this increase in detection was accompanied by a threefold increase in colposcopy referrals, amounting to a colposcopy referral rate of 6.6% in the HPV group, compared to 2.1% in the cytology group, which translates into an additional 44 women referred for every 1000 women screened (Thompson *et al*, 2021: 398). Similarly, the Canadian HPV FOCAL study found a significant increase in colposcopy referral rates in the HPV arm of the trial compared to the cytology arm across all age groups, despite the use of reflex cytology to increase the specificity of HPV

8. Worldwide, HPV 16 and 18 are associated with 70% of cases of squamous cell carcinoma, while HPV 16, HPV 18 and HPV 45 contribute to approximately 85% of adenocarcinoma cases (HIQA, 2017: 19).
9. While both cytology and HPV-based screening are associated with a reduced risk of developing both types of cancer, the risk reduction is significantly greater for squamous cell carcinoma than for adenocarcinoma (HIQA, 2017: 43)
10. The SCREEN DENMARK study found that the positive predictive value of colposcopy referral was lower in the HPV arm than in the cytology arm (Thompson et al 2021: 399).

screening, with the colposcopy referral rate in the HPV arm more than double that in the cytology arm for women under 30 (Ogilvie 2017: 447; Thompsen *et al* 2021: 398). In a retrospective cohort study conducted within the Dutch screening programme, Loopik and colleagues found that the rate of overdiagnosis increased to 143% in HPV-based cervical screening, compared to cytology-based screening, resulting in a decrease of the positive predictive value of the test in respect of cancers >CIN2 (Loopik *et al* 2021: 222.e4). Although the Dutch study found a higher rate of invasive management, such as biopsy, associated with HPV-based screening, there was no corresponding rise in the rate of overtreatment (Loopik *et al* 2021: 222. e8). However, accumulating evidence suggests that women with low-grade abnormal cytology results who are referred for colposcopy are at risk of experiencing adverse psychological consequences, including anxiety, short-term distress associated with the procedure itself, long-term distress associated with the follow-up process and continued surveillance, and ongoing worries about cancer, fertility and sexual activity (O'Connor *et al*, 2016: 529-30; Sharp *et al*: 2014:4ff)[11].

Unnecessary colposcopies may lead to overtreatment of regressive cervical intraepithelial neoplasia (Thompsen *et al* 2021, 395). Although approximately 40% of CIN 2 lesions and 30% of CIN3 lesions regress spontaneously, 22% of CIN 2 progress to CIN 3 and 5% of these progress to cancer, while approximately 15% of CIN 3 progress to cancer (Salcedo *et al*, 2022: 644). Treatment for pre-invasive or early invasive cervical cancer is associated with an increased risk of overall, severe and extreme prematurity in women who become pregnant after undergoing the procedure (Kyrgiou *et al*, 2017: 24), with complications such as premature rupture of membranes, preterm birth and low birthweight in turn associated with an increased risk of stillbirth or neonatal death (HIQA, 2017: 57). This risk is greater among women who undergo excisional treatments compared to ablative procedures, with the risk increasing in proportion to the depth of the excision and persisting into the woman's subsequent pregnancies (Castanon *et al*, 2015: 1194-1196). While women with CIN have a higher baseline risk of prematurity compared to the general population, women attending colposcopy clinics should be counselled about the potential morbidity associated with treatment for CIN (Kyrgiou *et al*, 2017: 24) and this information should be incorporated into the design and evaluation of cervical screening programmes which aim to maximise benefits and minimise harms in the screened population (Vicus *et al* 2014: 169). The development of better triage algorithms may reduce the number of women called for repeat screening and reduce the rate of colposcopy referrals at the repeat screen (Thomsen *et al*: 399). Finally, equity concerns have also been raised in relation to the implementation of HPV screening, given that some underscreened populations may have reservations about HPV screening as a test associated with a sexually-transmitted infection, which may lower uptake (CADTH, 2019:150).

11. Modification of existing information materials in relation to cervical screening and colposcopy may help to reduce short-term distress (O'Conner et al 2015: 533), while counselling women who are considering having children and more efficient discharge from surveillance may help to alleviate long-term distress among women referred for colposcopy (ibid.).

# Breast cancer screening: benefits and harms

## Benefits

Of the three screening programmes discussed in this report, mammography screening for breast cancer is the most controversial. Disagreements between those who believe that the benefit of a decrease in mortality from breast cancer outweighs the harms and those who believe, conversely, that individual harms outweigh population-level benefits are increasingly polarised (Marmot *et al*, 2013: 2206; (Zielonka *et al*, 2020: 192). The issue cannot be settled by appealing to the evidence, because evidence is subject to interpretation and this interpretation in turn influences the generation of further evidence (Marmot, 2013: 2553)[12]. Disagreements arise from conflicting views about the validity and applicability of data from available randomised controlled trials of breast screening and from questions about the usefulness and interpretation of observational data on breast cancer incidence and mortality (Marmot *et al* 2206).

Breast cancer is the most commonly diagnosed cancer in women and the most common cause of death from cancer globally, with approximately half of all breast cancer cases diagnosed in women between 50 and 74 (IARC, 2016: 451). While the appropriate way to determine the benefit of mammography screening is to look at breast cancer mortality in screened and unscreened cohorts, rather than focusing on survival time from diagnosis (Marmot *et al*, 2013: 2207), it is ethically unfeasible to conduct randomised trials with long-term follow-up in which participants in the control arm cannot avail of the benefits of screening. Both existing randomised controlled trials and observational studies have shown that regular mammography screening reduces mortality from breast cancer (Zielonka *et al*, 2020: 192). In 2012, the UK Independent Panel review of older RCTs and more recent observational studies found a 20% reduction in mortality in women invited to attend screening (Marmot *et al*, 2012: 2207), while Duffy *et al* found a mortality reduction of 28% in women aged 50-69 who attended screening every three years for 20 years (Duffy *et al*, 2010: 28). Analysing data from 20 cohort studies and 20 case control studies, the International Agency for Research on Cancer (IARC) estimated that women between 50 and 69 years of age who attended mammography screening had a 40% reduction in the risk of death from breast cancer (Lauby-Secretan *et al* 2015: 2356), although the evidence for a risk reduction in women between 40 and 44 or 45 and 49 who were invited to attend or did attend screening was less pronounced (Lauby-Secretan *et al* 2015: 2356)[13]. Dunn and colleagues found that the risk of death from breast cancer was reduced by 39% in women who participated in mammography screening, compared to women who did not participate (Dunn *et al*, 2020:4). A systematic review of the evidence commissioned by the USPSTF found that screening 10,000 women aged 60 to 69 over a 10-year period will result in 21 fewer breast cancer deaths, screening 10,000 women aged 50 to 59 years will result in 8 fewer breast cancer deaths over the same period, and screening 10,000 women aged 40 to 49 years will result in 3 fewer breast cancer deaths (Siu *et al*, 2016: 282). On the basis of this review, the USPSTF has concluded with moderate certainty that the net benefit of screening mammography in women aged 50 to 74 years is moderate.

## Harms

The relationship between the benefits and harms of mammography screening has been a matter of heated debate for years and there is considerable polarisation in the literature (Zielonka *et al*, 2020: 192). Disagreements between experts have persisted even after the publication of the UK Independent Panel report, particularly in relation to the degree of benefit associated with breast screening and the risk of overdiagnosis (Parker,

12. This point is relevant in relation to all three screening programmes.
13. An ecological study conducted by Duffy and colleagues found a 25% reduction in mortality from breast cancer 10 years after randomisation among women aged 40-49 in the intervention group compared to the control group, amounting to just under one life saved for every 1000 women screened, but no overall reduction in mortality after more than 10 years of follow-up (Duffy et al 2020:1170).

Rychetnik and Carter, 2015: 1; Ghanouni *et al*, 2016b: 603). Taksler *et al* estimate that, over a 10-year period, approximately 50% to 61% of women undergoing annual mammography will experience a false-positive result (Taksler *et al* 2018: 2390). In addition to the risk of receiving false negative results and false-positive results and undergoing unnecessary biopsies, all women undergoing regular screening mammography are at risk for the diagnosis and treatment of non-invasive and invasive breast cancer that would otherwise not have manifested clinically or become a threat to their health during their lifetime (Siu *et al*, 2016: 280).

Overdiagnosis is the most important harm of mammography screening (Keating and Pace, 2019: 2014). Currently, the accepted view is that overdiagnosis is prevalent in breast cancer screening, but how frequently it occurs remains unclear (Barratt and Jacklyn, 2016: 142). Health professionals are currently unable to distinguish between or predict which breast cancers will be nonprogressive and which ones will progress, due to a lack of accurate prognostic markers (Barratt and Jacklyn 2016: 153; Shieh *et al*, 2016: 1). Within the range of detectable tumour sizes, slow-growing tumours have existed for longer than fast growing tumours and are more likely to be detected by mammography screening (Gotzsche and Jorgensen, 2013:12). These screen-detected cancers are often treated because not enough is known about the growth patterns of breast cancer and the mechanisms involved in metastatic spread to distinguish them from cancers that would progress if not treated (IARC 2016: 459; (Autier and Boniol 2018: 54; Marmot *et al*, 2013: 2206; Barrett and Jacklyn 2016: 154). Overdiagnosis would not be such a significant problem if it were possible for screening to distinguish between cancers which would not otherwise have presented clinically and cancers which, if left untreated, would lead to death, because the psychological distress and unnecessary treatment associated with it could be avoided (Marmot *et al*, 2021: 2206).

There is an ongoing debate about the optimal method for measuring overdiagnosis in mammography screening (Lauby-Secretan *et al*, 2015: 2356; Marmot *et al* 2012: 2207). In their Cochrane review, Gotzsche and Jorgensen estimated that 30% of mammography-detected cancers were overdiagnosed in optimally-randomised trials (Gotzsche and Jorgensen, 2013:12), while the UK Independent Panel cautiously estimated the rate of overdiagnosis in three large-scale RCTs to be approximately 19%. The IARC working group estimated the rate of overdiagnosis in European studies of breast screening which adjusted for lead-time and incidence trends to be 6.5%, congruent with a rate of 4-11% in RCTs with lengthy follow-up times (Lauby-Secretan *et al*, 2015: 2356). Canelo-Aybar and colleagues estimated a pooled overdiagnosis rate of 10.1% from a population perspective and 17.3% from an individual perspective in women aged between 50 and 69 years[14], concluding that, for every 100,000 women between the ages of 50 and 69 invited to screening, 138 deaths would be avoided, with four cases of breast cancer overdiagnosed for every one death averted (Canelo-Aybar *et al* 2021: 395). Adjusting for bias in studies reporting lower rates of overdiagnosis, Barratt and Jacklyn estimate that 15-30% of breast cancers diagnosed in women who regularly participate in screening programmes are overdiagnosed (Barratt and Jacklyn, 2016: 134).

Ductal carcinoma in situ (DCIS) is not synonymous with overdiagnosis in breast screening, but it contributes to cases of overdiagnosis (Marmot *et al*, 2012: 2222). Mammography screening has been very successful in detecting DCIS, which was rarely diagnosed before the advent of population screening, but now comprises 25% of screen-detected breast cancers (Van Seijen *et al*, 2019: 285). Despite being pre- or non-invasive, DCIS is often regarded as precursor lesion for invasive breast cancer (Barratt, 2015:1). Approximately 20% of cases will progress to invasive ductal

14. In women aged 40-49 this estimate increased to 12.4% and 22.7 % respectively.

carcinoma (Kim *et al*, 2018: 579). The evidence is unclear in relation to both the natural history of DCIS and how aggressively to treat it (Marmot *et al*, 2012: 2022; Carter *et al*, 2015: 280; Esserman *et al*, 2014: e238). DCIS is more challenging to manage than invasive breast cancer because of prognostic uncertainty and because treatment options are potentially associated with detrimental outcomes for patients (Kim *et al* 2018: 580). Conventional treatments include mastectomy or breast-conserving surgery with radiotherapy (Van Seijen *et al*, 2019: 285). Because most women with DCIS will never develop invasive disease and will have a favourable prognosis (Kim *et al*, 2018: 579), these therapeutic approaches result in overtreatment of some women. There are short- and longer-term risks associated with treatment for breast cancer. Radiotherapy for early-stage breast cancer increases the risk of developing lung and oesophageal cancers and is associated in the longer term with an increased risk of heart disease, especially in women with left-sided cancers, while adjuvant hormone therapy can have a significant impact on quality of life (Barratt 2015: 2-3). Following treatment, women may experience anxiety and depression, often at levels on a par with those associated with invasive breast cancer (Kim *et al*, 2018: 588). In their systematic review for the European Commission, Canelo-Aybar and colleagues observed an increase in mastectomies in RCTS evaluating the effectiveness of mammography screening (Canelo-Aybar *et al*, 2021: 401). Given the fact that both diagnosis and treatment of DCIS have a profound psychosocial impact on women's lives, accurate and adequate perception of risk by both clinicians and patients is critical for determining which treatment modalities are appropriate (Van Seijen *et al* 2019: 286). Algorithms may be developed to identify women who may benefit from active surveillance rather than treatment after carcinoma in situ is found upon evaluation of a biopsy specimen (Alvarado *et al* 2012: e44?), while Esserman *et al* suggest creating observational registries for "lesions with low malignant potential". The aim of surveillance would be to predict the progression of precancerous lesions to invasive cancer and establish when an intervention is needed to treat slow-growing, low-risk lesions and information about their diagnosis and the dynamics of their disease would have to be clearly communicated to patients in order to enable them to make fully informed decisions about opting for strategies such as active surveillance (Esserman *et al*, 2014: e239). Currently, there is a lack of consensus in the medical community in relation to how to communicate information to patients about DCIS and the associated risk of progression to invasive cancer (Van Seijen *et al* 2019: 286). This poses particular challenges, given the fact that most women with mammography-detected DCIS who participated in a recent study had little knowledge of DCIS and "inaccurate perceptions of associated risks and prognosis" (Kim *et al*, 2018: 588)

The risk of death from radiation-induced breast cancer is 1-10 per 100,000 women, depending on age and on the frequency and duration of screening, although this is lower by a factor of 100 than the estimated risk of death from cancer in the absence of mammographic screening (Lauby-Secretan 2015: 2357). After considering the balance of benefits and harms associated with mammographic screening, the IARC working group concluded that the benefit from inviting women aged 50-69 to screening outweighs the harms of screening (Lauby-Secretan 2015: 2357).

Patients, clinicians and policy makers need information about the frequency of overdiagnosis in order to weigh the benefits against the harms of screening for breast cancer (Carter, Coletti and Harris, 2015, 1). In a US-wide study of 407 women, Yu and colleagues found that women rated the benefits of mammography screening as much more important than the harms, with only 26% of participants having any prior knowledge about overdiagnosis (Yu *et al*, 2017: 1382). Similarly, Waller *et al* found that participants had difficulty understanding the concept of overdiagnosis in breast screening, with 49% of women unaware that some cancers are slow-growing and unlikely to cause problems, and a similar proportion wanting to be tested for a cancer for which nothing could be done (Waller *et al*, 2015: 563). Emerging evidence suggests that, overall, public understanding of

the term 'overdiagnosis' is poor, with only 2.9% of 390 participants in a recent study providing a definition which was even broadly consistent with the correct meaning (Ghanouni *et al*, 2016a: 3). This indicates that brief written information materials might not be sufficient to enable participants to achieve a full appreciation of the balance of benefits and harms associated with breast screening and may not be sufficient to facilitate informed choice, particularly in relation to overdiagnosis (Waller *et al*, 2014: 1834). Evidence also suggests that the risk of receiving false-positive or false-negative results in cervical screening is poorly understood by participants (Korfage *et al*, 2011:217) and that the meaning of an 'abnormal' result is often misinterpreted, resulting in anxiety and fear (Jepson *et al*, 2007: 894). More generally, the possibility that individuals considering screening are predisposed to consider benefits as more important than harms poses a challenge for informed decision-making, and reinforces the need for targeted interventions to educate both the general public and individual participants about harms (Yu *et al*, 2017: 1382).

## Informed consent and shared decision-making

Informed consent is a legal and ethical prerequisite of participation in population screening for cancer. A robust informed consent process requires that potential candidates for screening are provided with comprehensible, unbiased, evidence-based information about the benefits and harms associated with screening and that they understand this information (Damhus *et al*, 2018: 243). While the complexity of decision-making in relation to cancer screening has been acknowledged for many years (Parker *et al*, 2017: 2), the availability of more sensitive tests - often at the expense of specificity - and stronger evidence of the harms associated with screening increase the need for a robust process of shared decision-making in relation to screening (Fletcher, 2011: 128). Emphasis on achieving high participation rates may predispose organisations and policy-makers to encourage screening attendance rather than engaging potential participants in discussion about "what sits best with their individual values" (Parker *et al*, 2017: 3; CADTH, 2019: 131) and challenges associated with obtaining informed consent to screening participation have given rise to a wider discussion about whether the goal of information provision in the informed consent process is to promote uptake or to promote informed choice (CADTH, 2019: 143; Raffle 2001: 93). Because screening programmes exist to minimize the burden of disease in populations, screening promotion materials are often designed to maximize participation and these do not always provide complete information about the limitations of screening or about potential negative outcomes (Williams *et al* 2014: 297; Parker *et al*, 2017: 3; Hofmann *et al*, 2014: 253-256; Irwig *et al*, 2006: 1148)[15].

As such, built into the implementation of population screening is an ethical tension between the need to achieve high participation rates in order to justify and optimise the efficiency of the programme, and protecting the autonomy interests of potential participants (Jepson *et al*, 2005: 192), who may be deterred from participating by information about harms (Kolthoff *et al*, 2016: 274). Lower uptake may lead to a reduction in population-level benefits and could reduce the cost-effectiveness of the programme if the viability of services is compromised by low participation rates (Jepson *et al*, 2005: 192; Raffle, 2001: 92). Low uptake may also exacerbate existing health inequities, given that those most likely to be deterred from participating in screening may be the most socially disadvantaged or the hardest to reach (Raffle, 2001: 92). Nonetheless, in recent years, the "longstanding paternalistic view" that communication relating to screening should

15. In a survey of 1134 adults over the age of 50 who had participated in decisions about breast, colorectal or cancer screening, Hoffman and colleagues found that the overall quality of decision-making was poor, with the harms associated with screening addressed in only 7-14 % of discussions, while the benefits of participation were addressed in 51-67% of discussions (Hofmann et al, 2014: 253-256).

prioritise high levels of uptake has been replaced by the view that uptake should only be maximised insofar as this is possible within the parameters of informed choice (Ghanouni *et al*, 2016b: 602; Chorley *et al*, 2018: 64; Helsingen and Kalager, 2022: 9).

Given that more information, and information that is more easily understandable, is associated with greater wariness in relation to treatments or tests (Edwards, Elwyn and Mulley 2002: 828), there are two major challenges associated with developing an informed consent process which is fit for purpose in respect of population screening. The first challenge is to ensure that potential participants have an adequate and accurate understanding of the benefits and harms associated with participation. Candidates who do not understand the balance of benefits and harms associated with screening are not only unable to participate in shared decision-making, but may also be unable to provide valid, fully informed consent (Damhus *et al*, 2018: 241, 245). The second challenge is to ensure that people who decide to participate in screening are doing so voluntarily, without any external constraints on their autonomy. If a participant receives information which is biased or unbalanced, or is nudged into favouring participation, his or her voluntariness is compromised and valid informed consent has not been obtained. In summary, the quality of the information provided to participants and the way in which it is framed determines the validity of the consent provided by participants.

## Information about benefits and risks: understanding

Clear communication to prospective participants about the harms and benefits of screening is vitally important and "goes to the heart of how a modern health system should function" (Marmot *et al*, 2012: 2207). In order to enable informed decision-making, all of the relevant benefits, harms and limitations associated with a screening programme must be conveyed to prospective participants (Williams *et al*, 2014: 296). It is not sufficient simply to inform participants that there are benefits and harms associated with screening; participants must be given information about the relative magnitude of the harms and benefits in question (Welch and Passow, 2014: 448) and should ideally be able to demonstrate that they have "absorbed and internalised [this information] in a meaningful way" (Ghanouni *et al*, 2016b: 603; Jepson *et al*, 2005: 195). However, conveying information about harms and benefits in relation to a given screening programme is a complex undertaking, first, because the information itself is complex (Williams *et al*, 2014: 296) and, second, because there is a lack of consensus in relation to some of the evidence in support of screening and most participants are not equipped to grapple with uncertainty or to interpret conflicting expert opinion (Parker *et al*, 2017:2). There are many sources of variability in the evidence base, including "statistical uncertainty, heterogeneity of the populations studied (…) and the methods and assumptions investigators use to assess the effects of screening" (Welch and Passow, 2014: 448; Autier and Boniol, 2017: 35)[16]. Interpreting the evidence is challenging because methods of data collection may not be comparable across randomised controlled trials, different cohorts are studied and diverse approaches to modelling are employed in different studies (Carter *et al*, 277ff). Case-control studies may exaggerate the benefits of screening, modelling may be based on unverified assumptions and observational studies are susceptible to specific kinds of bias such as lead-time bias, length bias and

16. For example, the Swedish Two-County trial found an estimated reduction in breast cancer mortality of 36%, whereas the two Canadian National Breast Screening studies found no reduction in mortality (Welch and Passow, 2014: 449).

healthy volunteer bias (Carter *et al*, 2015: 175 Barratt, 2015: 3; Autier and Boniol, 2018:35). On the basis of a deepening understanding of the biases and 'heuristic' or intuitive assumptions which underpinned the implementation of many screening programmes, Croswell *et al* call for rigorous empirical testing of the evidence supporting claims about the efficacy of these programmes (Croswell *et al*, 2010: 14).

Screening for breast cancer is particularly controversial in this regard. While there has been a decline in mortality from breast cancer in higher-income countries, the role played by mammographic screening in this reduction is a matter of debate, particularly in respect of the challenge of distinguishing the effect of screening from the effects of more widespread use of adjuvant therapies and other improvements in cancer care (Duffy *et al* 2020:1171; Marmot *et al* 2021: 2208)[17]. Changes in treatments for breast cancer over time make the results of studies of the efficacy of mammography screening difficult to interpret (Zielonke *et al* 2020: 202). While randomised controlled trials with extended follow-up provide reliable evidence of the relative benefit of screening, some of the randomised trials examining the efficacy of screening are now decades old (Marmot *et al*, 2012: 2212). In a position paper published in 2018, Autier and Boniol argue that accumulating epidemiological data suggest that, in jurisdictions which have implemented widespread mammography screening, there has only been a modest decline in the incidence of advanced cancers and claim that the reduction in breast cancer mortality rates is similar in areas where screening was introduced early with a high uptake and in areas where screening was implemented later with lower penetration (Autier and Boniol, 2018:34).

In addition to challenges posed by lack of consensus in relation to the evidence available, further challenges arise in relation to ensuring that clinicians and participants understand the existing evidence. The term *collective statistical illiteracy* refers to the fact that many people are unable to understand the meaning of numbers (Gigerenzer 2010, 469; Gigerenzer (2003) cited in Damhus *et al*, 2018, 243). Statistical concepts can be challenging even for highly educated clinicians to understand (Ghanouni *et al*, 2016b: 602; Keen and Keen, 2009:10; Wegwarth *et al*, 2012: 348) and individuals invited to attend screening may be expected to understand the concept that 'screening saves lives' without having a corresponding understanding of the underlying statistics and their implications (Ghanouni *et al*, 2016b: 603). Simply providing patients with statistical data does little to enhance the quality of their decision-making about screening (Moyer, 2012: 392). Not only may statistical illiteracy prevent prospective participants from evaluating the true benefit of participation in screening (Keen and Keen 2009:10), it may also prevent clinicians from effectively communicating information about risk, with the result that decision-making is not truly 'informed' (Moyer, 2012: 392; Gaissmeier and Gigerenzer, 2003: 413; see Woloshin *et al*, 2012: 1678). It is important for policy makers to address the challenges posed by statistical illiteracy and to promote informed decision-making, rather than focusing on ways to encourage high participation rates in the interest of public health (Keen and Keen 2009:10).

The nature and quality of the information presented to participants also depends on the quality of existing published studies and the way in which their results are reported. In an analysis of published data relating to 57 screening trials for breast, colorectal, liver lung, ovarian, oral, prostate and testicular cancers, Heleno and colleagues found that the harms of screening were poorly reported (Heleno *et al*, 2013: 5), with only 7% of trials quantifying overdiagnosis and 4% quantifying false positive findings, while 89% of the trials reviewed reported the effect of cancer screening on cancer-specific mortality. On the basis of these findings, Heleno and colleagues concluded that this imbalance creates challenges for both clinicians and participants evaluating the relationship between harm and benefit in cancer screening and undermines the quality of the informed decision-making process (Heleno *et al*, 2013: 3-4).

17. While the IARC working group concluded that adjuvant therapies in use since the late 80s have 'probably affected' the effects of screening (IARC 2016: 459), the Marmot report advocated viewing the benefits of screening and the effects of improved treatments separately (Marmot et al 2012: 2213).

## Information about benefits and risks: voluntariness

Screening may appear to be an 'innocuous' intervention because the procedures involved are relatively non-invasive, yet the downstream effects of participation can be substantial (Croswell *et al* 2010: 9). Over a decade ago, Schwartz and Meslin argued that less attention is paid to the consent process for interventions deemed 'low risk' than to the process of obtaining consent for invasive procedures (Schwartz and Meslin, 2008: 867). There is accumulating evidence that prospective participants do not receive sufficient information about the risks or harms associated with screening to enable truly informed decision-making. Schwartz and Meslin found that information provided to prospective participants about recommended screening tests varied in quality, particularly in relation to the description of the risk of false positives, false negatives and overtreatment, and that, consequently, participants often overestimated the benefit and underestimated the risks of screening (Schwartz and Meslin, 2008: 867). Several recent studies have corroborated these findings (van den Bruel *et al*, 2015: 6). In a series of interviews exploring participants' understanding of the information presented to them in a pamphlet on colorectal cancer screening published by the Danish Health Authority, Damhus and colleagues found that the information was presented in a way which downplayed risks and nudged individuals towards participation (Damhus *et al*, 2018: 251). Interviewees misunderstood or misinterpreted important parts of the pamphlet, including information about relative risk reduction and the risk of overdiagnosis, resulting in an "apparent overestimation of the benefits and underestimation of the harms of screening" (Damhus *et al*, 2018: 251). Many of the study participants perceived the limitations, risks and harms of screening described in the pamphlet as benefits and not as potential harms (Damhus *et al*, 2018: 249). Analysing invitations to participate in publicly-funded cervical screening programmes in eleven countries, Kolthoff and colleagues found that the material sent to prospective participants was "information poor and biased in favour of participation" (Kolthoff *et al*, 2018: 278). The benefits of screening were mentioned and quantified in the information materials more often than the harms, and the most important harms, overdiagnosis and overtreatment, were generally downplayed or left unmentioned (see also CADTH, 2019: 144). Only 50% of invitations mentioned the risk of overdiagnosis and overtreatment, while 50% mentioned the risk of receiving a false-negative result and only 33% mentioned the risk of false-positive results (Kolthoff *et al*, 2018: 278). In an earlier study, Wegwarth and Gigerenzer found that only 9.5% of 317 participants invited to screening had been informed by their doctor about overdiagnosis and overtreatment (Wegwarth and Gigerenzer, 2013:2086).

How risk is presented has implications for the autonomy of people deciding whether or not to participate in screening programmes. Any quantitative data can be described in many ways and such framing can have a significant effect on how participants understand the information (Schwartz and Meslin 2008: 867)[18]. Providing information in terms of relative risk is 'more persuasive' than presenting information about absolute risk (Edwards, Elwyn and Mulley 2002: 827; Damhus *et al* 2018: 243), because relative risk reduction tends to overestimate the effect (Dreier *et al*, 2014: 1). Reduction in absolute risk is generally represented by 'small' numbers, whereas the corresponding reduction in relative risk tends "to look big", particularly when the cancer in question is not very common (Gaissmaier and Gigerenzer, 2008: 412; WHO, 2022: 25). Framing risk in a manner which encourages both clinicians and non-clinicians to overemphasise benefits and minimise harms ultimately undermines the

18. Logically equivalent choices can be framed in different ways, for example by using survival data or mortality data, and this framing can influence the decisions made by participants. 'Loss framing' (the potential losses from not having a test) has more of an impact on the uptake of screening than 'gain framing' (Edwards, Elwyn and Mulley 2002: 827)

autonomy of prospective participants (Carter *et al*, 2015: 282; Schwartz and Meslin, 2008: 868; Korfage *et al*, 2011: 214) and may violate the requirements of informed consent (Damhus *et al*, 2018: 245). Influencing choice though the deliberate framing or presentation of options is a strategy associated with libertarian paternalism - the idea that the state can promote the well-being of its citizens without compromising their liberty - but this cannot be justified in the context of screening, given the potential harms associated with screening at an individual level (Ploug, Holm and Brodersen 2009: 2012; Damhus *et al*: 254). Providing just the relative risk reduction is not an ethically acceptable level of disclosure (Schwartz and Meslin, 2008: 868) and interventions with modest or uncertain benefits merit a detailed consideration of harms (Kolthoff *et al*, 2016: 274). If the aim of communicating information about screening is to help prospective participants to understand the likelihood of benefitting individually from participation in screening, information about relative risk should be replaced by information about frequency, absolute risk and the numbers needed to screen in order to avoid one death (Williams *et al* 2014: 296). When discussing the harms and benefits of a given screening programme, measures of outcome and effect size which can be most easily understood by prospective participants should be used (Dickinson *et al*, 2018: 507). Given that many adults have difficulty understanding numerical concepts in general and particular difficulty with probability statements, the most adequate way of presenting both benefits and risks is by using natural frequencies, namely, the expected probabilities of various outcomes in a population of 1000 individuals undergoing screening, compared to an equivalent unscreened population (Schwartz and Meslin, 2008: 867)[19]. It has been suggested that standards for information provision should be higher for preventive interventions offered to people who are healthy (Williams *et al*, 2014: 295; CADTH 2019: 143).

## Communication and shared decision-making

Given the heterogeneity in the way people interpret and value benefits and harms, shared decision making is now considered an essential element of high-quality health care (Barratt and McKenna, 2011: 252). Shared decision-making is widely viewed as an important patient-centred approach to 'preference-sensitive' decisions, namely, those in which benefits and harms are closely balanced and the best decision for a given individual will depend on his or her values and preferences for particular outcomes (Lillie *et al*, 2014: 47). In contrast to an approach which promotes a particular intervention, shared decision-making involves a consideration of the available evidence in light of the patient's values and preferences (Lillie *et al*, 2014: v). While there is accumulating evidence for the benefits of a shared decision-making approach in relation to screening, healthcare providers often feel underequipped when confronted with complex conversations and do not know how to implement shared decision-making in the clinical encounter (Croes *et al*, 2020: 1674). Primary care providers may themselves lack sufficient knowledge to discuss screening in detail with prospective participants, and people are more likely to recall information in a way which leads them to underplay risk (Petticrew *et al*, 2000:27). Shared decision-making takes time; evaluating the importance of comorbidities and competing risk factors can be difficult to accomplish during a single appointment and describing the harms of screening is challenging (Spring *et al*, 2017: 405)[20], particularly in a context in which participants themselves are rarely consulted in relation to their perception of the harms and benefits associated with screening (Hofmann, 2017: 364). Different messages need to be communicated to different age groups; younger women, for example, may be less likely to be diagnosed with breast cancer, yet the potential years of life lost due to breast cancer are greater (Spring *et al*, 2017: 405).

19. Gaissmeier and Gigerenzer argue that it is possible to achieve understanding amongst prospective participants by communicating risks in absolute - not relative - terms, by using a frequentist formulation which "makes the reference class clear instead of communicating 'single event probabilities'", and by communicating natural frequencies rather than conditional probabilities (Gaissmeier and Gigerenzer, 2003: 413).
20. Spring et al argue that the term "harm" can be highly charged, and that more specific language may be helpful to describe the potential risks associated with screening (2017: 405).

Conversely, providing too much information risks compromising the quality of decision-making and undermining choice (Volk *et al*, 2018: 247; Austoker and Ong, 1994: 243). Optimising information provision to improve the quality of informed decision-making in screening is a matter of vital importance.

In breast screening in particular, a robust approach to informed decision-making is especially important in those age groups where the balance of benefit and harm is less clear (Canelo-Aybar *et al*, 2021: 402). Interpreting complex evidence around breast screening is challenging and real effort is needed to convey information about risk and benefit as comprehensibly as possible (Elmore, 2016: 23) so that women can be "informed partners in the decision to screen or not" (Marmot, 2013: 2554). Keating and Pace recommend stating explicitly to prospective participants that the majority of women diagnosed with breast cancer do well and that breast screening is responsible for a small absolute decrease in the number of women likely to die of breast cancer, and asking them how they feel about additional testing and the possibility of overtreatment, as well as how the might feel about the 'unlikely' possibility of receiving a diagnosis of a potentially deadly cancer, having not been screened regularly (Keating and Pace, 2019: 1815). Engaging prospective participants more effectively in dialogue about risks and benefits may make shared decision-making more "feasible and efficient" (Keating and Pace 2018: 1815). Although not every participant will want to make an individually-based choice (Korfage *et al* 2011:217; Irwig *et al*, 2006: 1149), evidence suggests that participants want information about the cancer for which they are being screened, about the benefits, harms and limitations associated with screening and about the consequences of the process itself (Jepson *et al*, 2007: 894). Supporting participants to understand and appreciate this information through a process of shared decision-making should be seen as a strategy for enhancing the informed consent process. Decision aids and other tools may improve the quality of the information provided to participants, increase their understanding and enable them to clarify their preferences in relation to screening (Irwig *et al*, 2006: 1149). These tools need to be designed in such a way that they are easily understandable and can be used by all members of the community and a more tailored approach may need to be developed to ensure that underserved groups or groups who are at greater risk have equitable opportunities to access screening programmes (Williams *et al*, 2014: 296; Irwig *et al*, 1149. Damhus *et al*, 255). Given the fact that among members of the public, levels of acceptance of overdetection vary widely, specific information about the risk of overdiagnosis and its implications should be provided to all individuals considering participation in cancer screening (Van den Bruel *et al*, 2015: 5). Consumer groups should be involved in the process of developing information materials for participants. Public communications which encourage people to consider screening and to discuss it in detail with their GP should be devised, and incentives for GPs who engage in shared decision-making may be of value (Williams, 2014: 297).

## Public awareness and education

In general, there is a high degree of public enthusiasm for cancer screening (Chorley *et al*, 2018: 64; Damhus *et al*, 2018: 253; Douma *et al* 2018: 6). A recent survey of 1895 UK residents corroborated the findings of earlier studies, with nearly 90% of respondents agreeing that screening for healthy individuals is 'almost always' a good idea, 75% believing that treatment for cancers detected at an earlier point in time can save lives 'most' or 'all' the time, and 64% believing that an earlier diagnosis results in less treatment (Waller *et al*, 2015: 563). For decades, public health messaging in relation to cancer screening has reflected the positive views held by public health organisations, professional organisations, clinicians, patient advocacy groups and academics and has relied on persuasive communication strategies to maximise uptake (Hersch *et al*, 2017: 2; Woloshin *et al*, 2012: 1677;

Elmore, 2016: 7). This well-established positive public perception of screening may, however, influence individuals' understanding and recall of information which "does not confirm those beliefs", such as information about the risks and limitations of screening (Douma *et al*, 2018: 6). Positive attitudes towards screening may also make participation a type of 'reflex' action which does not allow for a 'rational' appraisal of information about risk and benefit, with implications for the informed consent process (Waller *et al*, 2015: 565).

Despite the importance and promise of cancer screening, there is evidence that public understanding of the nature and implications of screening is less than optimal, with both the lay public and many medical professionals lacking adequate understanding of its limitations (Woloshin *et al*., 2012: 1678)[21]. There is an important difference between medical and lay perspectives on screening (Petticrew *et al*, 2001: 166), just as population and individual perspectives are irreducible to one another (Hofmann 2017: 364). Whereas the aim of screening from a medical perspective is to identify disease precursors and early-stage cancers in order to enable earlier treatment, members of the public participate in screening programmes primarily to seek reassurance (Petticrew *et al*, 2001: 166). Many members of the public believe that cancer is much more common than it is and assume that early detection is synonymous with cure (Moyer 2012: 392). This optimism, however, may be misplaced, particularly in the case of interval cancers. Targeted public education in relation to the limitations of screening is needed in order to address the discrepancy between societal expectations of existing screening programmes and the 'actual sensitivities' of these programmes (Grimes *et al*, 2021:9; Parker *et al*, 2017:3). Misperceptions about screening include the belief that screening prevents cancer rather than detecting it earlier (see Chorley *et al*, 2018: 68-69) and the belief that interval cancers must have been "missed", leading to poorer prognostic outcomes (Wilson, 2000: 1352). Interval cancers are cancers which are diagnosed during the interval between a negative screening and the next scheduled screening appointment (Durand *et al* 2021: 296; Weigel *et al*, 2017: 2745). While a small proportion of interval cancers are cancers which could have been detected by screening but were missed, the vast majority are 'true' interval cancers which either developed since the previous screen or were undetectable by the test (Petticrew *et al*, 2000:3). True interval cancers are not false negatives, but whereas undetectable false-negatives are unavoidable, missed cancers are avoidable false-negatives, the result of human error (Petticrew *et al*, 2000:3).

There is an imperative to increase awareness among members of the public that there are uncertainties inherent in population screening programmes because 'perfect' detection is a mathematical impossibility (Grimes *et al*, 2021: 10). For example, the overall sensitivity of digital mammography in population screening is approximately 79%, although the sensitivity of the test decreases in relation to increases in breast density (Weigel *et al* 2017: 2746). There are no screening tests so accurate that they rule out the possibility of false-negative results, and, even if there were, interval cancers would still arise (CADTH, 2019: 147). Members of the public should understand that both false-positive and false-negative results are an inevitable and expected outcome of any screening programme which does not have 100% sensitivity, even when the service meets high performance standards (Petticrew *et al*, 2000: iii; Expert Reference Group, 2020a: 50; 94). Individuals invited to participate in organised screening programmes should be given clear, explicit, properly-contextualised information about false positives and false negatives and their implications during the process of obtaining informed consent.

21. Studies have shown that inadequate understanding of the limitations of screening and misplaced optimism about the value of screening tools are also common among clinicians, many of whom lack understanding of concepts such as sensitivity, specificity, and positive predictive value, or the number of individuals needed to screen and/or treat to save one life.

Participants in screening programmes must be provided with full information about the meaning of negative results, including the potential for false-negative results (Petticrew *et al*, 2000: iv). Patients and clinicians who understand the limitations of screening and the inevitability of false-negative results are better prepared to respond promptly to clinical symptoms which emerge between screens (CADTH, 2019: 145). People invited for screening must be informed about the limitations of screening in a way which instils realistic expectations about the intervention and ensures that their consent to participation is fully informed (Wilson, 2000: 1353). Without an understanding of the risk of false-negatives, people who receive a negative result may ignore important symptoms, resulting in a delayed diagnosis, and may perceive the diagnostic delay as a failure of the screening programme rather than as an inherent limitation of screening as a technology (WHO, 2020:15). If a cancer is not detected until it becomes symptomatic, it may be more advanced at the point of diagnosis and may require more invasive treatment which may be less successful, and as a result the patient may seek legal redress for distress caused (Petticrew *et al*, 2000: 2). In the absence of a 'bedrock' of public understanding of the context in which screening is carried out, the risk increases that individuals' experiences of false negatives will be interpreted as 'scandals' (Raffle, 2001: 97). Failure to provide information to participants about potential harms may lead to disappointment, anger, reduced trust in healthcare in general, and, potentially, to litigation (Kolthoff *et al*, 2016, 279; Raffle, 2001: 97). Conversely, the impact of receiving false-negative results can be lessened if participants have a better understanding of the nature of the screening test and the meaning of the results, and they may have less incentive to seek legal redress even for what they perceive as 'clinical errors' (Petticrew *et al*, 2000: 25).

Trust among service users is fundamental to the success of screening programmes and 'high-profile' controversies within screening programmes can erode trust (O'Donovan *et al*, 2022: 3). Although 'high-profile lapses' can provide an opportunity to educate the public about the nature and limitations of screening, media coverage of these incidents can generate fear and anger, with devastating consequences for clinicians responsible for delivering these programmes (Petticrew *et al*, 2000: 22-3). Interviews conducted with 48 women accessed through the Irish cervical screening register in the wake of the CervicalCheck controversy revealed "a striking loss of faith, trust and confidence" in screening arising from perceived deficiencies in communication and "mishandling" of information, despite the fact the cervical screening programme was found on review to be performing at international standards (O'Donovan *et al*, 2022: 3). The same study found that participants often misunderstood the purpose of screening, particularly the difference between screening and diagnostic tests, reflecting a broader lack of understanding among members of the public and the media. O'Donovan and colleagues draw attention to the need for initiatives to improve public understanding of screening and enable informed decision-making around participation, but their findings also suggest that greater availability of information about screening in the public domain may in fact strengthen public confidence in the value of screening and result in an improved service in the long term (O'Donovan *et al*, 2022: 3).

In addition to reducing public trust in the screening programme, legal claims arising from false negative results can be very costly for the programme in question (WHO, 2020: 16). And while reducing risk of exposure to litigation is not itself an ethical issue, it has ethical ramifications insofar as high legal costs will undermine the cost-effectiveness of screening, lead to professional demoralisation and lack of retention, divert resources from other areas of

healthcare and, ultimately, threaten the continued survival of the exposed programme. A rigorous quality assurance process which ensures that the performance of screening programmes exceeds minimum standards is vital and sufficient resources should be devoted to screening to ensure the maintenance of standards and keep cases of false negatives to a minimum (Wilson, 2000: 1353). Given that screening which is not effective diverts resources from other areas of public health (Riviera and Brawley, 2019:6), it needs to be shown, not only that screening programmes are ethically sound in their own right, but that the resources they command "would not be better spent elsewhere in the health and healthcare sector" (Juth and Munthe, 2011: 149). Economic evaluations, including cost-effectiveness analyses, are tools which enable decision-makers to identify to the most efficient way of deploying healthcare resources, using outcomes such as the incremental cost-effectiveness ratio (ICER) which represents incremental costs per unit of incremental health gained and thus allows interventions to be ranked by relative cost-effectiveness (Ratushnyak *et al*, 2019: 792). While policy makers and public health administrators require robust information about the cost-effectiveness of publicly-funded interventions in order to maximise the impact of governmental spending on healthcare (Pinkerton, 2002: 71), however, resource allocation decisions guided by cost-effectiveness analyses sit uneasily with ethical principles such as equity and distributive justice (Rutstein *et al*, 2017: 4; Pinkerton *et al*, 2002: 80). Cost-effectiveness analyses are ethically and technically complex (Pinkerton *et al*, 2002: 78ff) and "spending money wisely does not necessarily mean spending less money" (Owens 1998: 717). Determining whether cancer screening as an intervention is "reasonably efficient, of questionable efficiency, or inefficient" (Owens, 1998: 717) is further complicated by the need to incorporate anticipated legal costs into the analysis in jurisdictions such as Ireland in which litigation is increasingly common.

Policy makers and members of the public have different perspectives on what information is needed to make an informed decision about screening, and historically policy makers have determined what information should be provided to people invited to screening (Jepson *et al*, 2007: 891). Consultation between policy makers and an informed public is an essential prerequisite for the development of ethically-sound screening policy (Irwig *et al* 2006: 1148). Citizens' juries have been shown to be a robust way of eliciting an informed community perspective on issues which members of the public consider important. Appointing a representative sample of the population to deliberate about the benefits and harms of screening would be of value in informing policy decisions (Hersch *et al*, 2017: 3; Irwig *et al*, 2006: 1148). In 2015-6, Abelson and colleagues organized four citizens' deliberation events in Ontario to explore the perspectives of members of the public on mammography screening. Participants in all four panels voiced strong support for informed decision-making in screening decisions and emphasised the importance of choice, information, trust, transparency and financial accountability (Abelson *et al*, 2018: 1367). The citizens who participated wanted mammography screening reframed as a choice, rather than as something women were obligated to undergo, and advocated for comprehensive information to be provided to women about the risks and benefits of screening, while allowing for variation in individual preferences for information (Abelson *et al*, 2018: 1369). On the basis of the juries' deliberations, Ableson and colleagues concluded that informing women about the risks of screening will not necessarily have a significant impact on screening uptake but will ensure that those who decide to be screened are doing so "with an understanding of the risks and a willingness to face those risks" (Ableson *et al*, 2018: 1369). Their results also drew attention to the vital role played by primary care providers in population-level breast-screening programmes.

# Conclusion

Organised screening programmes for breast, cervical and colorectal cancer have been shown to reduce mortality from cancer at a population level. Participation in these programmes will benefit some members of the population and will expose others to unnecessary harms. A resounding theme in the literature published during the past 15 years is the need for attention to the quality of decision-making in relation to participation in screening. Not only is there a need to enhance public understanding of what screening is, its benefits and limitations, but, on an individual level, prospective participants should have the opportunity to engage in a process of shared decision-making which enables them to appreciate the risks and benefits of screening and balance these on the basis of a consideration of their own preferences and values. There is a pronounced need to explore ways of "encouraging active engagement" with screening decisions (Waller *et al*, 2015: 565). While not every individual will wish to engage in individualised decision-making, evidence-based information about both the benefits and the risks of screening should be presented to prospective participants in an unbiased manner and they should be offered the opportunity to discuss this information with a clinician. Recommendations offered by informed healthcare professionals have a critical role in the decisions people make and these recommendations can be incorporated into the process of shared decision-making (Spring *et al*, 2017: 407).

While the harm associated with false negative test results has garnered significant public and media attention, particularly in Ireland, false negatives are only one known limitation of screening modalities implemented at population level. The need to raise awareness of the risk of receiving a false negative result exists on the same continuum of communication as ensuring that participants are aware of the possibility of false-positive results, overdiagnosis and overtreatment associated with a given screening modality. Although an individual who is overtreated will never know that he or she has been overtreated, there is an imperative to ensure that individuals considering participation in screening recognise this as a potential harm and understand what it means. Policy makers should give careful consideration to how information about the benefits, risks and limitations of screening is communicated and to the design of information materials and decision aids. Primary care providers should receive training and support to ensure that individuals who consent to screening do so voluntarily and on the basis of an adequate understanding of what is involved. A fine balance needs to be struck between communicating information about the risks and limitations in a manner which enables informed decision-making and ensuring that this does not serve as a barrier to access for underserved populations or those who stand most to benefit from screening (Petticrew *et al*, 2000: 26). Just as there are harms associated with a 'one-size-fits-all' approach to cancer screening (Esserman *et al*, 2014: e240), it may also be argued that there are harms accruing to a 'one-size-fits-all' approach to communication and decision-making in relation to cancer screening.

The role of informed choice in public health interventions has been controversial for well over a century (CADTH, 2019: 144). While the call for a different approach to decision-making in relation to screening may appear to challenge the values which have prevailed historically in public health decision-making and policy, however, the tide has clearly turned away from a narrow utilitarian perspective on screening which prioritises the concept of beneficence over the principle of non-maleficence (CADTH, 2019: 136). The emphasis on the value of lives saved which has been at the centre of discussions about cancer screening "downplays the variation in values attached by participants to different risks", undermines autonomy and potentially compromises the validity of the informed consent process (Plutynski, 2012:3). Public policy recommendations which do not give adequate consideration to the significance of a particular individual's risk profile and his or her weighting of preferences are no longer seen as ethically sound (Plutynski, 2012: 4). A better-educated public capable of making more informed decisions should be one of the goals of healthcare policy-making generally and cancer screening policy in particular. Improved communication is central to achieving this goal. A transparent balancing of the values underlying the rationale for the implementation of screening programmes with the values of those who stand to gain and lose from screening is a vital part of justifying these programmes (Juth and Munthe, 2011: 13).

# References


Abelson J, Tripp L and Sussman J (2018). "'I just want to be able to make a choice': results from citizen deliberations about mammography screening in Ontario, Canada". *Health Policy* 122, 1364-1371

Alvarado M, Ozanne E and Esserman L (2022). "Overdiagnosis and Overtreatment of Breast Cancer". American Society of Clinical Oncology Educational Book (Volume 32). Available at: https://ascopubs.org/doi/pdf/10.14694/EdBook_AM.2012.32.301

Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, Bray F (2020). "Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis". *Lancet Global Health* 8: e191–e203.

Austoker J and Ong G (1994). "Written information needs of women who are recalled for further investigation of breast screening: results of a multicentre study". *Journal of Medical Screening* 1: 238-244.

Autier P and Boniol M (2018). "Mammography screening: a major issue in medicine". *European Journal of Cancer* 90, 34-62.

Autier P, Boniol M, Koechlin A, Pizot C and Boniol M (2017). "Effectiveness of, and overdiagnosis from, mammography screening in the Netherlands: population-based study". *BMJ* 3359: j5224.

Barratt, Bruce and McKenna (2011). "Communicating Benefits and Risks of Screening for Prostate, Colon, and Breast Cancer". *Family Medicine* 43:4, 248-53.

Barratt, Alexandra L and Jacklyn, Gemma L (2016). "Challenges in understanding and quantifying overdiagnosis and treatment". *Breast Cancer Screening.* Elsevier Publishing, 134-159.

Barratt, Alexandra L (2015). "Overdiagnosis in mammography screening: a 45-year journey from shadowy idea to acknowledged reality". BMJ 350: h867.

Biddle, Justin B (2020). "Epistemic risks in cancer screening: implications for ethics and policy". *Studies in History and Philosophy of Biology and Biomedical Science* 79, 1-9.

Braddock CH (2013). "Supporting Shared Decision-Making When Clinical Evidence is Low". *Medical Care Research and Review* 70:1, 129S-140S

Braillon and Bewley (2015). "Shared Decision-Making for Cancer Screening: Visual Tools and a 4-Step Method)". *JAMA Internal Medicine* 175:11, 1862.

Broderson J and Jorgensen KJ (2014). "Screening Mammography: Do the Benefits Always Outweigh the Harms? "Clinical Advances in Haematology & Oncology Volume 12, Issue 6 June 2014, 407-413.

Brodersen J and Siersma VD (2013). "Long-term Psychosocial Consequences of False-Positive Screening Mammography". *Annals of Family Medicine* 11: 106-115.

Canelo-Aybar C, Ferreirs DS, Ballesteros M, Posso M, Montero N, Solá I, Saz-Parkinson Z, Lerda D, Rossi PG, Duffy SW, Follmann M, Gräwingholt A and Alonso-Coello P (2021). "Benefits and harms of breast cancer mammography screening for women at average risk of breast cancer: a systematic review of the European Initiative on Breast Cancer". *Journal of Medical Screening* 28:4, 389-404.

Castanon A, Landy R, Brocklehurst P, Evans H, Peebles D, Singh N, Walker P, Patnick J, Sasieni P (2015). “Is the increased risk of preterm birth following excision for cervical intraepithelial neoplasia restricted to the first birth post treatment?” *BJOG* 122:9, 1191-1199.

Carter JL, Coletti RJ and Harris RP (2015). “Quantifying and monitoring overdiagnosis in cancer screening: a systematic review of methods”. BMJ BMJ 350:g7773

Carter SM, Williams J, Parker L, Pickles K, Jacklyn G, Rychetnik L, Barratt A (2015). “Screening for Cervical, Prostate and Breast Cancer: Interpreting the Evidence”. *American Journal of Preventive Medicine* 49:2, 274-285.

Carter SM, Degeling, C, Doust J and Barratt A (2016). “A definition and ethical evaluation of overdiagnosis”. *Journal of Medical Ethics* 42:11, 705-714.

*HPV Testing for Cervical Cancer Screening: a Health Technology Assessment.* Ottawa: CATDH; 2019. (CADTH Optimal Use Report vol. 7. No 1b).

Chiu H-M, Je GH-H, Wang Y-W, Fann J C-Y, Hsu C-Y, Jeng Y-C, Yen A M-F, Chiu S Y-H, Chen S L-S, Hsu W-F, Lee Y-C, Wu M-S, Wu C-Y, Jou Y-Y, Chen TH-H (2021) “Long-term effectiveness of faecal immunochemical test screening for proximal and distal colorectal cancers”. *Gut* 70:2321–2329.

Chiu H-M, Li-Sheng Chen S, Yen A M-F, Chiu S Y-H, Fann J C-Y, Lee Y-C, Pan S-L, Wu M-S, Liao C-S, Chen H-H, Koong S-L and Chiou S-T (2015). “Effectiveness of Fecal Immunochemical Testing in Reducing Colorectal Cancer Mortality from the One Million Taiwanese Screening Program” *Cancer* 121: 3222-9.

Chorley AJ, Hirst Y, Vrinten C, von Wagner C, Wardle J and Waller J (2018). “Public understanding of the purpose of screening: a population-based survey”. *Journal of Medical Screening* 25:2, 64-69.

Clift A (2020). “Population-level breast screening: how to salvage the concept?” *Journal of the Royal Society of Medicine* 113: 8, 306–309.

Coulter A and Collins A (2011). “Making shared decision-making a reality”. London: The King’s Fund. (kingsfund.org.uk)

Croes KD, Jones NR, DuBenske LL, Schrager SB, Mahoney JE, Little TA and Burnside ES (2020). “Core Elements of Shared Decision-Making for Women Considering Breast Cancer Screening: Results of a Modified Delphi Survey”. *Journal of General Internal Medicine* 35:6, 1668-77.

Croswell JM, Ransohoff DF and Kramer BS (2010). “Principles of Cancer Screening: Lessons from History and Study Design Ideas”. *Seminars in Oncology* 37:3, 202-215.

Damhus, CS, Petersen GB, Ploug T and Brodersen J (2018). “Informed or misinformed choice? Framing effects in a national information pamphlet on colorectal cancer”. *Health, Risk and Society* 20: 5-6, 241-258.

Denis B, Gendre I, Weber S and Perrin P (2021). “Adverse events of colonoscopy in a colorectal cancer screening program with faecal immunochemical testing: a population-based observational study”. *Endoscopy International Open* 9: E224–E232.

Deyo, Richard A (2002). “Cascade effects of medical technology”. *Ann Rev. Public Health* 23: 23-44

Dickinson JA, Pimlott N, Grad R, Singh H, Szafran O, Wilson BJ, Groulx S, Thériault G and Bell NR (2018). “Screening: when things go wrong”. *Canadian Family Physician* 64, 502-508.

Douma (2018). BMC Public Health 18:1212Dreier M, Borutta B, Seidel G, Munch I, Kramer S, Toppich J, Dierks M-L and Walter U (2014). “Communicating the benefits and harms of colorectal cancer screening needed for an informed choice: a systematic evaluation of leaflets and booklets”. *PLOS One* 9:9, 1-11.

Duffy SW, Vulkan D, Cuckle H, Parmar D, Sheikh S, Smith RA, Evans A, Blyuss O, Johns L, Ellis IA, Myles J, Sasieni PD, Moss SM (2020). “Effects of mammographic screening from age 40 years on breast cancer mortality (UK Age trial): final results of a randomised, controlled trial. *Lancet Oncology* 21: 1165-72.

Dunn N, Youl P, Moore J, Harden H, Walpole E, Evans E, Taylor E, Philpot S and Furnival C (2020). "Breast cancer mortality in screened versus unscreened women: long-term results from a population-based study in Queensland, Australia". *Journal of Medical Screening* 28:2: 193-199

Durand MA, Friedewald SM, Plecha, DM, Copit, DS, Barke LD, Rose SL, Hayes MK, Greer LN, Dabbous FM, Conant EF (2021). "False-Negative Rates of Breast Cancer Screening with and without Digital Breast Tomosynthesis". *Radiology* 298, 296–305.

Edwards A, Elwyn G and Mulley A (2002). "Explaining risks: turning numerical data into meaningful pictures". *BMJ* 324, 827-30.

Elmore, Joann G. (2016). "Breast cancer screening: balancing evidence with culture, politics, money and media". In (eds.) Houssami, N and Miglioretti, D, *Breast Cancer Screening: An Examination of Scientific Evidence.* Elsevier, 1-27.

Elton, Lotte (2021). "Non-maleficence and the ethics of consent to cancer screening". *Journal of Medical Ethics* 47, 510-513.

Esserman LJ, Thompson IM, Reid B, Nelson P, Ransohoff DF, Welch HG, Hwang S, Berry DA, Kinzler KW, Black WC, Bissell M, Parnes H, Srivastava S (2014). "Addressing overdiagnosis and overtreatment in cancer: a prescription for change". *Lancet Oncology* 15: e234–42

Expert Reference Group, 2020a:

Fletcher RH (2011). "Screening Under Scrutiny". *American Journal of Epidemiology* 174:2, 127-8.

Gaissmaier W and Gigerenzer G (2008). "Statistical illiteracy undermines informed shared decision-making". *Z Evid. Fortbild. Qual. Gesundh. Wesen* (ZEFQ) 102, 411-413.

Gates TJ (2014). "Screening for cancer: concepts and controversies". *American Family Physician* 90:9, 625-631.

Ghanouni A, Meisel SF, Renzi C, Wardle J, Waller J (2016a). "Survey of public definitions of the term 'overdiagnosis' in the UK." *BMJ Open* 6: e010723, 1-6.

Ghanouni A, Renzi C, Meisel SF, Waller J (2016b). "Common methods of measuring 'informed choice' in screening participation: challenges and future directions". *Preventive Medicine Reports* 4, 601-607.

Gostin LO and Wiley LF (2016). *Public health law: power, duty, restraint.* Oakland: University of California Press.

Gøtzsche PC, Jørgensen KJ. "Screening for breast cancer with mammography". Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD001877

Gøtzsche PC (2015). "Mammography screening is harmful and should be abandoned". Journal of the Royal Society of Medicine; 2015, Vol. 108(9) 341–345.

Grimes DR, Corry EMA, Malagon T, O'Riain C, Franco EL and Brennan DJ (2021). "Modelling Cervical Cancer Screening Strategies with Varying Levels of Human Papillomavirus Vaccination". *JAMA Network Open* 4:6: e2115321.

Grisso T and Appelbaum PS (2006). "Appreciating Anorexia: Decisional Capacity and the Role of Values". *Philosophy, Psychiatry and Psychology* 13:4, 293-297.

Harris RP, Sheridan SL, Lewis CL, Barclay C, Vu MB, Kistler CE, Golin CE, DeFrank JT, Brewer N (2014). *JAMA Internal Medicine* 174:2, 281-285.

Heleno B, Thomsen MF, Rodrigues DS, Jorgensen KJ and Brodersen J (2013). "Quantification of harms in cancer screening trials: literature review". *BMJ* 347: f5334.

Helsingen LM and Kalager M (2022). "Colorectal Cancer Screening — Approach, Evidence, and Future Directions". NEJM Evidence 1:1, 1-13.

Hersch J, Jansen J, Barratt A, Irwig L, Houssami N, Howard K, Dhillon H and McCaffery K (2013). "Women's views on overdiagnosis in breast cancer screening: a qualitative study". BMJ 346: f158.

Hersch JK, Nickel BL, Ghanouni A, Jansen J, McCafery KJ. "Improving communication about cancer screening: moving towards informed decision making". *Public Health Res Pract.* 27:3, e2731728.

Heyman, Bob (2010). “Screening for health risks: a social science perspective”. Health, Risk & Society, 12:1, 1-6.

Health Information and Quality Authority (HIQA) (2017). *Health technology assessment of human papillomavirus testing as the primary screening method for prevention of cervical cancer.*

Hoffman RM, Elmore JG, Fairfield KM, Gerstein BS, Levin CA and Pignone MP (2014). “Lack of Shared Decision- Making in Cancer Screening Discussions: Results from a National Survey”. *American Journal of Preventive Medicine* 47:3, 251-259.

Hofmann B, Reid L, Carter C and Rogers W (2021). “Overdiagnosis: one concept, three perspectives and a model”. *European Journal of Epidemiology* 36: 361- 366

Hofmann, Bjorn (2017). “Ethical issues with colorectal cancer screening—a systematic review”. Journal of Evaluation in Clinical Practice 23, 631–641.

Hofmann B and Stanak M (2018). “Nudging in screening: literature review and ethical guidance”. *Patient Education and Counselling* 101, 1561-1569.

International Agency for Research on Cancer (2005). *IARC Handbooks of Cancer Prevention Volume 10: Cervix Cancer Screening.*

International Agency for Research on Cancer (2016). *IARC Handbooks of Cancer Prevention Volume 15: Breast Cancer Screening*

Irvin VL, Zhang Z, Simon MS, Chlebowski RT, Luoh S-W, Shadyab AH, Krok-Schoen JL, Tabung FK, Qi L, Stefanick ML, Schedin P, Jindal S (2020). “Comparison of Mortality Among Participants of Women’s Health Initiative Trials With Screening-Detected Breast Cancers vs Interval Breast Cancers”. JAMA Network Open. 2020;3(6):e207227

Irwig L, McCaffery K, Salkeld G and Bossuyt P (2006). “Informed Consent for Screening: implications for evaluation”. BMJ 332: 1148-1150.

Jansen EEL, Zielonke N, Gini A, Anttila A, Segnan N, ´n Voko´ Z, Ivanus U, McKee M, de Koning HJ and de Kok IMCM (2020). “Effect of organised cervical cancer screening on cervical cancer mortality in Europe: a systematic review”. *European Journal of Cancer* 127, 207-223.

Jepson RG, Hewison J, Thompson AGH and Weller D (2005). “How do we measure informed choice? The case of cancer screening.” *J Med Ethics* 31:192-196

Jepson RG, Hewison J, Thompson A and Weller D (2007. “Patient perspectives on information and choice in cancer screening: A qualitative study in the UK”. *Social Science & Medicine* 65, 890–899.

Juth N and Munthe C (2011). *The Ethics of Screening in Healthcare and Medicine: Serving Society or Serving the Patient?* International Library of Ethics, Law and the New Medicine 51. Springer Netherlands.

Keating, Nancy L and Pace, Lydia E (2018). “Breast Cancer Screening in 2018: Time for Shared Decision-Making”. *JAMA* 319: 17, 1814-5.

Keen JD and Keen JE (2009). “What is the point: will screening mammography save my life?” *BMC Medical Informatics and Decision Making* 9: 18, 1-14.

Kim C, Liang L, Wright FC, Look Hong NJ, Groot C, Helyer L, Meiers P, Quan ML, Urquhart R, Warburton R, Gagliard AR (2018). “Interventions are needed to support patient–provider decision making for DCIS: a scoping review”. *Breast Cancer Research and Treatment* 168:579–592.

Kolthoff SK, Hestbech MS, Jørgensen KJ and Brodersen J (2016) “Do invitations for cervical screening provide sufficient information to enable informed choice? A cross-sectional study of invitations for publicly funded cervical screening”. *Journal of the Royal Society of Medicine* 109: 7, 274–281

Korfage IJ, van Ballegooijen M, Wauben B , Habbema DF, Essink-Bot M-L (2011). “Informed choice on Pap smear still limited by lack of knowledge on the meaning of false-positive or false-negative test results”. *Patient Education and Counseling* 85, 214–218.

Kopans, Daniel B (2018). “Breast cancer screening: Where have we been and where are we going? A personal perspective based on history, data and experience”. *Clinical Imaging* 48, vii-ix.

Kramer, Barnett S and Croswell, Jennifer M (2009). “Cancer Screening: the Clash of Science and Intuition”. *Annual Reviews of Medicine* 60: 125-37.

Kuipers EJ, Grady WM, Lieberman D, Seufferlein T, Sung JJ, Boelens PG, van de Velde CJH and Watanabe T (2015). “Colorectal cancer”. *Nature Reviews Disease Primers* 1, 1-51.

Kyrgiou M, Athanasiou A, Kalliala IEJ, Paraskevaidi M, Mitra A, Martin-Hirsch PPL, Arbyn M, Bennett P, Paraskevaidis E. Obstetric outcomes after conservative treatment for cervical intraepithelial lesions and early invasive disease. *Cochrane Database of Systematic Reviews* 2017, Issue 11. Art. No.: CD012847

Landy R, Pesola F, Castanon A and Sasieni P (2016). “Impact of cervical screening on cervical cancer mortality: estimation ousing stage-specific results from a nested case-control study”. *British Journal of Cancer* 115, 1140-1146.

Larsen MB, Njor S, Ingeholm P and Ander B (2018). “Effectiveness of Colorectal Cancer Screening in Detecting Earlier-Stage Disease—A Nationwide Cohort Study in Denmark”. *Gastroenterology* 155, 99-106.

Lauby Secretan B, Scoccianti C, Loomis D, Benbrahim Tallaa L, Bouvard V, Bianchini F and Straif K for the International Agency for Research on Cancer Handbook Working Group (2015). “Breast-Cancer Screening - Viewpoint of the IARC Working Group”. *The New England Journal of Medicine* 372: 24, 2353-2358.

Lauby-Secretan B, Vilahur N, Bianchini F, Guha N and Straif K (2018). “The IARC Perspective on Colorectal Cancer Screening”. *New England Journal of Medicine* 378:18, 1734-1740.

Lillie SE, Partin MR, Rice K, Fabbrini AE, Greer NL, Patel S, MacDonald R, Rutks I, Wilt TJ (2014). *The Effects of Shared Decision-Making on Cancer Screening.* VA ESP Project #09-009.

Loopik DL, Koenjer LM, Siebers AG, Melchers WJG, Bekkers RLM (2021). “Benefit and burden in the Dutch cytology-based vs high-risk human papillomavirus-based cervical cancer screening program”. *American Journal of Obstetrics and Gynaecology* 224: 200.e1-9.

Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, Wilcox M (2013). “The benefits and harms of breast cancer screening: an independent review”. *British Journal of Cancer* 108, 2205-2240.

Marmot, MG (2013). “Sorting Through the Arguments on Breast Screening”. *JAMA* 309:24, 2533-4.

Moyer, Virginia A (2012). “What We Don’t Know Can Hurt Our Patients: Physician Innumeracy and Overuse of Screening Tests.” *Annals of Internal Medicine* 156:392-393.

Conjoint Board in Ireland of the Royal College of Physicians and the Royal College of Surgeons (2019). National GI Endoscopy Quality Improvement Programme Fifth National Data Report.

Newsom, Ainsley (2011). Population screening. In (ed) Dawson, Angus (2011). *Public Health Ethics*. Cambridge: Cambridge university Press, 118-142.

Niraula, Saroj (2016). “Screening mammography: sparing the emperor’s blushes”. *Cancer Medicine* 5: 10, 3018–3020.

Niraula S, Biswanger N, Hu P, Lambert P and Decker L (2020b). “Incidence, Characteristics, and Outcomes of Interval Breast Cancers Compared with Screening-Detected Breast Cancers. JAMA Network Open 3: 9, 1-7.

Ogilvie G, Krajden M, van Niekerk D, Smith LW, Cook D, Ceballos K, Lee M, Gentile L, Gondara L, Elwood-Martin R, Peacock S, Stuart G, Franco EL and Coldman AJ (2017). “HPV for cervical cancer screening (HPV FOCAL): Complete Round 1 results of a randomized trial comparing HPV-based primary screening to liquid-based cytology for cervical cancer”. *International Journal of Cancer* 140, 440–448.

O'Connor M, Waller J, Gallagher P, Martin CM, O'Leary JJ, D'Arcy T, Prendiville W, Flannelly G, Sharp L (2015). "Understanding women's Differing Experiences of Distress After Colposcopy: A Qualitative Interview Study". *Women's Health Issues* 25: 5, 528-534.

O'Donovan B, Mooney T, Rimmer B, Fitzpatrick P, Flannelly G, Doherty L, Russel N, Martin CM, O'Leary JJ, Sharp L and O'Connor M (2022)."Trust and cancer screening: Effects of a screening controversy on women's perceptions of cervical cancer screening". *Preventive Medicine Reports* 25, 1-4.

O'Neill, Onora (2002). "Public Health or Clinical Ethics: Thinking Beyond Borders". *Ethics & International Affairs* 16: 2, 35-45

Owens DK (1998). "Interpretation of Cost-Effectiveness Analyses". *Journal of General Internal Medicine 13*, 716-717.

Owens and Cribb (2013). "Beyond choice and individualism: understanding autonomy for public health ethics". Public Health Ethics 6:3, 262-271.

Parker L, Carter S, Williams J, Pickles K and Barratt A (2017). "Avoiding harm and supporting autonomy are under-prioritised in cancer screening policies and practices". *European Journal of Cancer* 85, 1-5.

Parker L, Rychetnik L and Carter S (2015). "Values in breast cancer screening: an empirical study with Australian experts". *BMJ Open* 5: e006333

Patnick J, Blanks R and Muir Gray JA (2008). "Maximising Benefit and Minimising Harm of Screening". BMJ 336:7642, 480-483.

Petticrew M, Sowden A, Lister-Sharp D and Wright, K (2000). "False-negative Results in Screening Programmes: Systematic Review of Impact and implications". *Health Technology Assessment* 4: 5, 1-70.

Petticrew M, Sowden A and Lister-Sharp D (2001). "False-negative Results in Screening Programmes: Medical, Psychological, and Other Implications". *International Journal of Technology Assessment in Health Care* 17:2, 164–170.

Petry KU, Wörmann V and Schneider A (2014). "Benefits and Risks of Cervical Cancer Screening". *Oncology Research and Treatment* 37 (supplement 3), 48–57.

Pinkerton SD, Johnson-Masotti AP, Derse A and Layde PM (2002). Ethical issues in cost-effectiveness analysis". E*valuation and Program Planning* 25, 71-83.

Ploug T, Holm S and Brodersen J (2012). "To nudge or not to nudge: cancer screening programmes and the limits of libertarian paternalism". *Journal of Epidemiology and Community Health* 66, 1193-1196.

Plutynski, A (2012). "Ethical Issues in Cancer Screening and Prevention". *Journal of Medicine and Philosophy* 0, 1-14.

Raffle AE (2001). "Information about screening: is it to achieve high uptake or to ensure informed choice?" *Health Expectations* 4, 92-98.

Ratushnyak S, Hoogendoorn, M and van Baal, PHM (2019). "Cost-Effectiveness of Cancer Screening: Health and Costs in Life Years Gained". American Journal of Preventive Medicine 57: 6, 792–799.

Rawla P, Sunkara T and Barsouk A (2019). "Epidemiology of colorectal cancer: incidence, mortality, survival and risk factors". *Gasteroenterology Review* 14:2, 89-103.

Ripping TM, ten Haaf K, Verbeek ALM, van Ravesteyn NT and Broeders MJM (2017). "Quantifying Overdiagnosis in Cancer Screening: A Systematic Review to E Oncol Res Treat 2014;37(suppl 3):48–57valuate the Methodology". *J Natl Cancer Inst* 109:10: djx060, 1-13.

Rutstein SE, Price JT, Rosenberg NE, Rennie SM, Biddle AK and Miller WC (2017). "Hidden Costs: the ethics of cost-effectiveness analyses for health interventions in resource-limited settings" *Global Public Health* 12: 10, 1269–1281.

Rychetnik L, Carter SM, Barratt A and Irwig L (2013). "Expanding the evidence on cancer screening: the value of scientific, social and ethical perspectives". *Medical Journal of Australia* 198: 10, 536-539.

Salcedo MP, Phoolcharoen N, Schmeler KM (2022). “Intraepithelial neoplasia of the lower genital tract (cervix, vagina, vulva): Etiology, Screening , Diagnosis, Management”. In (eds.) Gershenson DM, Lentz GM, Valea FA and Lobo RA. *Comprehensive Gynecology* (8th edition). Elsievier, 637-647.e2

Saquib Nazmus, Saquib Julian, Ioannidis John PA (2015). “Does screening for disease save lives in asymptomatic adults? Systematic review of meta-analyses and randomized trials”. *International Journal of Epidemiology* 44:1, 264–277.

Sawaya, George F (2009). “Cervical-Cancer Screening — New Guidelines and the Balance between Benefits and Harms”. NEJM 361: 26, 2503-2505.

Sawicki T, Ruszkowska M, Danielwicz A, Niedzwiedzka E, Arlukowicz T and Przybylowicz KE (2021). “A review of colorectal cancer in terms of epidemiology, Risk Factors, Development, Symptoms and Diagnosis”. *Cancers* 13, 2025.

Schrager S, Philips G and Burnside E (2017). “A simple approach to shared decision-making in cancer screening”. *Family Practice Management.* May/June 2017, 5-10.

Schwartz PH and Meslin EM (2008). “The Ethics of Information: Absolute Risk Reduction and Patient Understanding of Screening”. *Journal of General Internal Medicine* 23(6):867–70.

Sheridan SL, Harris RP, Woolf SH (2004). “Shared Decision-Making About Screening and Chemoprevention: A Suggested Approach from the U.S. Preventive Services Task Force”. *American Journal of Preventive Medicine* 26:1, 56-66.

Spring LM, Marshall MR and Warner ET (2017). “Mammography Decision-Making: Trends and Predictors of Provider Communication in the Health Information National Trends Survey 2011 to 2014”. *Cancer* 123: 401-9.

Sroczynski G, Esteban E, Widschwendter A, Oberaigner W, Borena W, von Laer D, Hack H, Endel H and Sieber U (2019). “Reducing overtreatment associated with overdiagnosis in cervical cancer screening: a model-based benefit-harm analysis for Austria”. International Journal of Cancer 147, 1131–1142.

Sharp L, Cotton S, Cruickshank M, Gray NM, Harrild K, Smart L, Walker LG and Little J (2014). “The unintended consequences of cervical screening: distress in women undergoing cytologic surveillance”. *Journal of Lower Genital Tract Disease* 18:2, 142-150.

Shieh Y, Eklund M, Sawaya GF, Black WC, Kramer BS, Esserman, Laura J (2016). “population-based screening for cancer: hope and hype”. *Nature Reviews Clinical Oncology* 13:9, 550-565.

Srivastiva S, Koay EJ, Borowsky AD, De Marzo AM, Ghosh S, Wagner PD and Kramer BS (2019). “Cancer overdiagnosis: a biological challenge and clinical dilemma”. *Nature Reviews Cancer* 19: 349-358.

Strum, Williamson B (2016). “Colorectal adenomas”. *New England Journal of Medicine* 374: 1065-1075.

Thomsen LT, Kjær SK, Munk C, Ørnskov D, Waldstrøm M (2021). “Benefits and potential harms of human papillomavirus (HPV)-based cervical cancer screening: A real-world comparison of HPV testing versus cytology”. *Acta Obstet Gynecol Scand.* 100, 394-402

Taksler GB, Keating NL and Rothberg MB (2018). “Implications of False-Positive Results for Future Cancer Screenings”. *Cancer* 124:2390-8.

USPSTF (2017). “Screening for colorectal cancer: recommendation statement”. *American Family Physician* 95:4, 254A-254F

USPSTF (2018). “Screening for Cervical Cancer: US Preventive Services Task Force Recommendation Statement”. *JAMA* 320:7, 674-686.

High-quality evidence of efficacy of screening on reduction of cervical cancer

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Van den Bruel A, Jones C, Yang Y, Oke J and Hewitson P (2015). “People’s willingness to accept overdetection in cancer screening: a population survey”. BMJ 350: h980, 1-9.

Van Dam L and Bretthauer M (2014). “Ethical issues in colorectal cancer screening”. *Best Practice and Research in Clinical Gasteroenterology* 28, 315-26.

Vicus D, Sutradhar R, Lu Y, Elit L, Kupets R and Paszar L (2014) “The association between cervical cancer screening and mortality from cervical cancer: a population based case-control study” Gynecologic Oncology 13: 167-71

Vicus D, Sutradhar R, Lu Y, Eilt L, Kupets R, Paszat L (2014). “Association between cervical cancer screening and mortality from cervical cancer: a population-based case study”. *Gynecologic Oncology* 133, 167-171.

Volk RJ, Leal VB, Jacobs Le, Wolf AMD, Brooks DD, WEnder RC and Smith RA (2018). “From Guideline to Practice: New Shared Decision-Making Tools for Colorectal Cancer Screening from the American Cancer Society”. *Cancer Journal for Clinicians* 68: 246-249.

Waller J, Whitaker KL, Winstanley K, Power E and Wardle J (2014). “A survey of women’s responses to information about overdiagnosis in breast cancer screening in Britain”. *British Journal of Cancer* 111: 1831-1835.

Wegwarth, Odette and Gigerenzer, Gerd (2013). “Less is More. Overdiagnosis and Overtreatment: Evaluation of What Physicians Tell Their Patients About Screening Harms”. *JAMA Internal Medicine* 173:22, 2086-7.

Wegwarth O, Schwartz LM, Woloshin S, Gaissmaier W and Gigerenzer G (2013). “Do Physicians Understand Cancer Screening Statistics? A National Survey of Primary Care Physicians in the United States”. *Ann Intern Med.* 156, 340-349.

Weigl S, Heindel W, Heidrich J, Hense H-W, Heidinger O (2017). “Digital mammography screening: sensitivity of the programme dependent on breast density”. *European Radiology* 27, 2744–2751

Welch and Black (2010). “Overdiagnosis in cancer”.

Welch HG and Passow HJ (2014). “Quantifying the Benefits and Harms of Screening Mammography”. *JAMA Internal Medicine* 174:3, 448-453

Widdows H and Cordell S (2011). “Why Communities and Their Goods Matter: Illustrated with the Example of Biobanks”. *Public Health Ethics* 4:1, 14-25

Williams JH, Carter SM and Rychetnik L (2014). “Information provision in cervical screening in Australia”. *Medical Journal of Australia* 201:5, 295-297.

Wilson R (2000). “Screening for breast and cervical cancer as a common cause for litigation”. BMJ 320, 1352-3.

Woloshin S, Schwartz LM, Black WC, Kramer BS (2012) “Cancer Screening Campaigns: Getting Past Uninformative Persuasion” NELM 367: 18, 1677-1679.

WHO (2020). *Screening programmes: a short guide. Increase effectiveness, maximize benefits and minimise harm.* Copenhagen: WHO Regional Office for Europe.

WHO (2022). *A short guide to cancer screening. Increase effectiveness, maximize benefits and minimise harm.* Copenhagen: WHO Regional Office for Europe.

Yu J, Nagler RH, Franklin Fowler E, Kerlikowske K and Gollust SE (2017). “Women’s Awareness and Perceived Importance of the Harms and Benefits of Mammography Screening: Results from a 2016 National Survey”. *JAMA Internal Medicine* 177:9, 1381-1382.

Zielonke N, Gini A, Jansen EEL, Anttila A, Segnan N, Ponti A, Veerus P, de Koning HJ, van Ravesteyn NT, Heijnsdijk EAM (2020). “Evidence for reducing cancer-specific mortality dues to screening for breast cancer in Europe: a systematic review. *European Journal of Cancer* 127, 191-206.

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