

SYNTHESIS

EVALUATION OF BREAST CANCER SCREENING IN BELGIUM



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■ FOREWORD

In Belgium, over 10 000 people are diagnosed with breast cancer every year. Although the disease can also affect men, the vast majority of patients are women. Breast cancer is the most common cancer among women and the leading cause of premature death. Around 2000 women die from the disease in Belgium every year. Despite significant progress in the prognosis for breast cancer – over 90 percent of patients are still alive five years after diagnosis – the toll of breast cancer on our society remains high.

As with most cancers, the prognosis for someone diagnosed at an early stage is much better than for someone diagnosed at an advanced stage. Screening would therefore seem to be the logical solution: the earlier we detect the cancer, the better. The extent to which a screening programme actually results in better health for participants depends on several factors, such as the reliability of the test used for screening, the biological characteristics of the tumour and the individual undergoing the screening. For example, a test may not be sensitive enough to detect cancers at an early stage, or may be not sufficiently specific, leading to many irrelevant findings also being detected. The cancer may grow so rapidly that no screening test can detect it in time, or so slowly that there is still plenty of time when the cancer becomes symptomatic. The person undergoing screening may, due to a limited life expectancy, no longer benefit from early detection, or may, due to a genetic predisposition, be at very high risk of cancer, in which case more intensive screening or a different, preventive approach is more appropriate.

The effect of screening therefore seems intuitively logical but must be demonstrated in reliable studies, precisely because of the multitude of factors that can influence the ultimate outcome. These studies provide insight into the benefits and harms, such as an improved prognosis, but also overdiagnosis, false-positive test results, missed cancers, etc. On this basis, the cost-effectiveness of screening can then be calculated.

In this report, we have summarised the available scientific evidence for breast cancer screening and calculated its cost-effectiveness, partly based on Belgian data. Alternative scenarios, such as extending the age at which women are invited for screening or using other screening methods, were also evaluated. The result is a nuanced and highly rigorous analysis, which can help policymakers make decisions regarding screening programmes and assist healthcare providers in properly weighing the pros against the cons. This report can also contribute to providing clear and balanced information to women, enabling them to make an informed choice about whether or not to participate in breast cancer screening.

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■ SUMMARY

1 INTRODUCTION

1.1 Breast cancer screening in Belgium

1.1.1 Organised breast cancer screening

Breast cancer is the most common cancer among women in Belgium and other high-income countries, and one of the leading causes of cancer-related deaths. To detect breast cancer at the earliest possible stage and reduce breast cancer mortality, various countries have initiated **breast cancer screening programmes using mammography**.

In Belgium, breast cancer screening was first introduced in Flanders (2001), followed by the Brussels-Capital Region and Wallonia (2002). From the calendar year in which a woman turns 50 until she reaches the age of 69, she is invited every two years for a free mammography. To ensure quality, the mammography images are assessed by two independent radiologists. In 2023, **more than 600 000 women** received an invitation. **Almost 41%** of them accepted the invitation and participated in screening as part of the organised screening programmes.^a Participation rates in the organised screening programmes vary significantly between the federated entities, with the largest uptake in Flanders (54%), followed by Brussels (9%) and Wallonia (4%).^b

Although the **federated entities** are responsible for the organisation of screening programmes, the costs of the mammography, its assessment and any additional procedures and treatments following suspicious screening results are reimbursed by the federal National Institute for Health and Disability Insurance (NIHDI).

1.1.2 Opportunistic breast cancer screening

In addition to the organised screening programmes, there are also women who undergo screening **outside the organised programmes**, either on their own initiative or based on the advice of their physician. We refer to this practice as **opportunistic screening**.

Of note, unlike in the official screening programmes, opportunistic mammography does not include a systematic second reading, and there is a patient cost-sharing. Yet, while the fee schedule stipulates that an ultrasound cannot be invoiced on the same day as a screening mammography, this is not the case for opportunistic/diagnostic mammographies. In addition, the frequency of opportunistic screening is not fixed.

In administrative databases, mammographies carried out as part of the organised screening programmes are clearly identifiable by specific invoicing codes. Opportunistic screenings, on the other hand, cannot be distinguished from **diagnostic mammographies** which are performed in women with symptoms. As a consequence, it is very difficult to obtain an accurate estimate of the number of opportunistic screenings in Belgium.

^a Source: Cancer Registry Foundation

^b Source: Cancer Registry Foundation and Centre for Cancer Screening (CvKO). Year 2023.

1.2 Research questions and aim of the report

The *European Commission Initiative on Breast Cancer* (ECIBC) recently proposed extending organised breast cancer screening to women aged 45–49 (2021^c) and had previously made the same recommendation for women aged 70–74 (2016^c).

In this report, we therefore examine the benefits, harms and cost-effectiveness of the proposed extensions to the current breast cancer screening programmes in Belgium. As previous KCE reports on breast cancer screening are no longer up to date, we also evaluated the current programmes.

More specifically, we addressed the **following research questions**:

1. What is the clinical effectiveness and cost-effectiveness of breast cancer screening^d using mammography in adult women with no suspicion of breast cancer and no specific increased risk of breast cancer
 - **aged 50–69** (i.e. the current screening programmes in Belgium),
 - **aged 40–49**,
 - **aged 70 and older?**

In addition, we have also evaluated the screening frequency and the combination of mammography with ultrasound. This led to the following research questions:

2. What is the clinical effectiveness and cost-effectiveness of
 - **biennial versus annual**, and
 - **biennial versus triennial**
 breast cancer screening^d with mammography in adult women with no suspicion of breast cancer and no specific increased risk?
3. What is the clinical effectiveness and cost-effectiveness of breast cancer screening^d **using mammography combined with ultrasound** compared with **mammography alone** in adult women with no suspicion of breast cancer and no specific increased risk?

Ultimately, the study was undertaken to inform Belgian policy makers on whether or not to adapt the current breast cancer screening programme, based on the best available evidence.

1.3 How was the study conducted?

We carried out **systematic literature reviews** of the clinical effectiveness, safety and cost-effectiveness of breast cancer screening for the various age groups, screening intervals and the combination of mammography and ultrasound. We analysed a database containing **Belgian data** compiled specifically for this study by the Belgian Cancer Registry (BCR), which includes data on breast cancers (source: BCR), health insurance (source: the Intermutualistic Agency – IMA), life status (source: Crossroads Bank for Social Security) and breast cancer screening (source: the regional screening organisations, i.e. CvKO, BruPrev and CCRef). Based on these data and the identified literature, we carried out a de-novo **cost-effectiveness analysis** of the breast cancer screening programmes in Belgium in accordance with the [KCE guidelines for economic evaluations](#).

Furthermore, the report includes a discussion on the **ethical aspects** of breast cancer screening based on the literature, and we **consulted clinical experts and other stakeholders**, including representatives

^c Conditional recommendation, moderate level of evidence.

^d Strictly speaking, the ‘invitation to breast cancer screening with mammography’ was evaluated, as an *intention-to-treat* analysis was carried out in the RCTs. For the sake of readability, this is abbreviated in this document to ‘breast cancer screening with mammography’.

of patients and healthcare providers, screening organisations and government bodies. Finally, the scientific quality of the [scientific report](#) was assessed and approved by three independent scientific experts (see colophon).

1.4 Out of scope

We did not consider the **budgetary and organisational implications** of any changes to the screening programmes. Nor did we address factors **affecting participation in screening** or initiatives to increase such participation.

Although we briefly describe the various **imaging techniques** (see section 2.3.2 of the scientific report), we did not systematically compare their effectiveness against one another.

Several randomised controlled trials (RCTs)^e are currently being conducted to examine **personalised screening strategies** based on individual risk.^f The underlying rationale is intensifying screening of those at high risk, while reducing screening among low-risk individuals who are unlikely to benefit from screening, but who are nevertheless subject to the harms of screening. The topic was considered out of scope for this report, as the full results of these trials were not available yet at the time this report was concluded.^g

Finally, while **artificial intelligence (AI)** is increasingly being integrated into healthcare systems, including (breast) cancer screening, it was considered out of scope for the present report. Despite promising improvements in several outcomes, issues with overdiagnosis, false positives and demographic variations in accuracy have highlighted the need for further research in this domain.

1.5 Previous KCE reports on breast cancer screening

This report **updates and replaces** the earlier KCE reports 11 (breast cancer screening in general; 2005), 129 (breast cancer screening in women under the age of fifty; 2010), 176 (breast cancer screening in women over the age of seventy; 2012), and 216 (decision aids for breast cancer screening; 2014).

The present report differs from the previous in several ways, e.g. updated mortality data of two low risk of bias RCTs have been included, additional outcomes (e.g. overdiagnosis) have been assessed, GRADE assessments and Summary of Findings tables have been included, cost-effectiveness was assessed and the screening frequency as well as addition of ultrasound have been evaluated.

^e A randomised controlled trial is a study in which participants are randomly assigned to different groups. One group receives the treatment or intervention, whilst another group receives a control treatment or no treatment/intervention. This random allocation ensures that the groups are comparable, making it easier to attribute differences in outcomes to the treatment/intervention. This makes it a robust method for investigating whether a treatment/intervention is genuinely effective.

^f Examples of individual risk include family history, hormonal factors and dense breast tissue.

^g The WISDOM study is one of the ongoing randomised controlled trials (RCTs) comparing personalised breast cancer screening with annual screening in women aged 40 to 74 years. Since it does not include a comparison with no screening (for women under 50 or over 69 years of age) or with biennial screening (for women aged 50–69 years), it will be difficult to apply its findings to the Belgian context. The results of the European MyPeBS (My Personal Breast Screening) study are expected by the end of 2027.

2 BREAST CANCER IN FIGURES AND PRINCIPLES FOR THE EVALUATION OF BREAST CANCER SCREENING

2.1 Breast cancer in Belgium

2.1.1 Incidence

Breast cancer is the **most frequently diagnosed** cancer among women in Belgium, with 11 533 new cases of invasive breast cancer in 2023. The lifetime risk of developing breast cancer is 15.4% for women, while it was 'only' 0.2% in men.

Over the last few decades, the overall **incidence** of breast cancer among women in Belgium has remained **stable**. Yet, while the number of cases remained stable among women under 50, it decreased slightly among women aged 50 to 69 (the group invited to take part in the organised screening programmes) and increased in women aged 70 years and older.

2.1.2 Age at diagnosis

In 2023, **almost half** of all female breast cancers were diagnosed in the 50 to 69 age group, i.e. **the target group for breast cancer screening**. The majority of cases (about 85%) were detected at an early stage (I or II).

2.1.3 Breast cancer mortality

In Europe, breast cancer is the **most common cancer cause of death** among women, accounting for nearly 17% of all cancer deaths in women. In 2021, 2048 women (and 21 men) died from the disease in Belgium.

Breast cancer mortality has **decreased significantly** in many countries over recent decades, particularly in the first ten years following the introduction of screening programmes. However, this decline was not entirely new: in several countries, mortality rates were already falling before screening was initiated. Furthermore, countries that started screening later did not observe a marked acceleration in the downward trend following its introduction. This suggests that, alongside screening, other factors – such as improved treatment and care – also play an important role.

2.1.4 Survival rates

This trend is reflected in the **survival** rates for women with invasive breast cancer. These have **improved substantially** over the past twenty years. For women diagnosed between 2014 and 2023, the net survival rate^h was **92% after 5 years** and **86% after 10 years**.

Stage at diagnosis is inversely related to net survival: the earlier the stage, the better the prognosis.

Further information on survival is available in section 2.1 of the scientific report.

2.2 Principles of cancer screening

The primary aim of cancer screening programmes is **to reduce cancer-specific mortality**. This goal is achieved through the detection of cancers at an early stage of their progression, before they become symptomatic. The direct consequence of effective cancer screening is the decrease in the incidence of advanced stage cancers which will lead to reductions in cancer-specific mortality. The implicit assumption is that early detection, i.e. before the development of clinical symptoms, will lead to a more

^h Net survival is an estimate of the probability of survival for patients with a particular condition (such as cancer), taking into account only mortality from the condition in question, as if it were the sole cause of death.

favourable prognosis because treatment initiated at that stage will be more effective and result in less morbidity than provided at a later stage of the disease.

Organised (cancer) screening programmes must adhere to the **principle of beneficence and doing no harm**. Screening must maximise benefits and minimise harms, which is especially critical since (cancer) screening targets individuals without symptoms or higher risk for breast cancer.

The World Health Organisation has developed a list of criteria that a screening programme should meet in order to provide added value. The most important of these are:

- The availability of an **effective and reliable screening method** (see section 2.3 below);
- A screening method that is **safe and acceptable** to the individual participant;
- The availability of an **intervention** (e.g. a treatment) that can improve the patient's outcome;
- The **overall benefits of screening must outweigh the potential harms** to participants or the population;
- An **economic evaluation** of the screening program, using a health system or societal perspective, should be conducted to assess the full costs and effects of implementing, operating and sustaining the screening program.

2.3 Reliability of a screening method

The **validity** of a screening method is assessed through the calculation of its:

- **Sensitivity**, the proportion of those who have the adverse outcome (disease) who are correctly identified, i.e. the 'true positives';
- **Specificity**, the proportion of those who do not have the adverse outcome who are correctly identified, i.e. the 'true negatives'.

Ideally, a screening method would have both a **high sensitivity and a high specificity**. A low specificity, for instance, implies that the screening programme would identify many people without the outcome as having the outcome ('false positives'). This may result in unnecessary investigations (which may lead to complications), psychological harm and strain on the health system.

According to the most recent figures (2022), the screening programme in Flanders has the highest **specificity** (98%), followed by Brussels (90%) and Wallonia (89%).ⁱ **Sensitivity**, on the other hand, is slightly higher in Brussels (73%) and Wallonia (71%) than in Flanders (68%).^j

2.4 The early detection paradigm and the heterogeneous progression of cancer

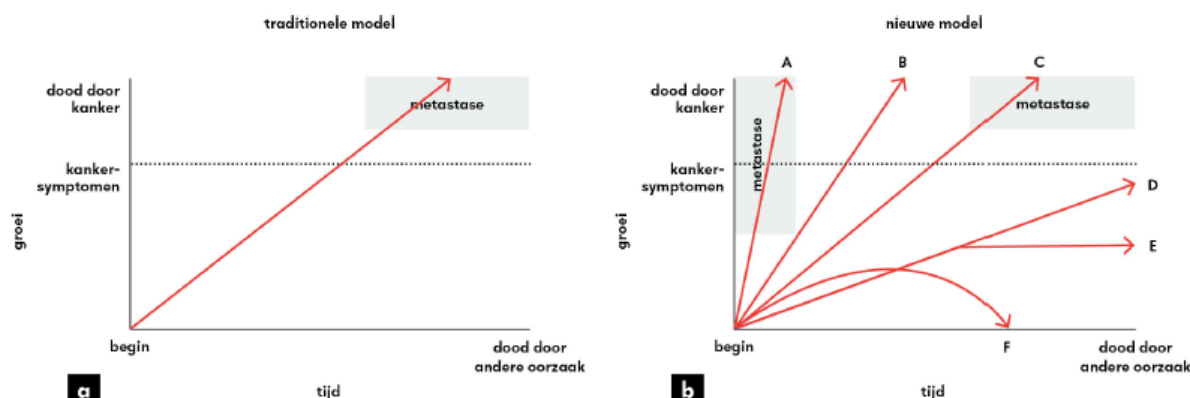
The rationale behind cancer screening is the '**early detection paradigm**'. The general idea is that by detecting cancer at an early stage, it is possible to prevent it from being diagnosed at a later stage, when treatments are more complex and the prognosis is less favourable. As a consequence, the number of deaths can ultimately be reduced.

This reasoning is based on the **linear growth model**. It assumes that all cancers follow the same trajectory: from a primary tumour to locoregional spread and then to distant metastases, ultimately leading to death (see Figure 1, a).

ⁱ Figures for 2022 are almost complete. The specificity figures for 2021 are identical to those for 2022.

^j Figures for 2022 are almost complete. In 2021, a greater difference in sensitivity was observed between the regions (Brussels: 79.4%, Wallonia: 78%, Flanders: 70%).

Figure 1 – Traditional and new models of cancer progression



Translation: begin = start; dood door andere oorzaak = death due to other cause; dood door kanker = death due to cancer; groei = growth; kankersymptomen = cancer symptoms; metastase = metastasis; nieuwe model = new model; tijd = time; traditionele model = traditional model.

Source: Mali WPTM, van der Graaf Y. Cancer screening: blessing or curse? *Ned Tijdschr Geneesk.* 19 March 2026;170:D8758

However, over time we learned that cancer evolves in a much more heterogeneous manner (Figure 1, b). Research over the past decades shows that the growth rate and behaviour of tumours can vary greatly. Some cancers metastasise at an early stage (arrow A), others are mainly locally aggressive without spreading (arrow B), and yet others grow so slowly that they never cause symptoms and patients die from other causes (arrow D). Still other tumours stop growing (arrow E) or disappear again (arrow F).

2.5 How can the effectiveness of a (cancer) screening programme be assessed?

Evaluating the effectiveness of a screening programme is complex. It requires the selection of appropriate **outcome measures** that are aligned with the programme's objectives. Key outcomes include:

- **Incidence:** logically, at the start of a screening programme a **rise in the incidence of (early-stage) cancer** is expected, which is followed by a decrease in advanced-stage cancer over time. This increase may also (partly) reflect overdiagnosis (see below), as some of these additional tumours would never have caused symptoms or led to death.
- **Advanced-stage diagnoses:** incidence trends of advanced-stage cancer have been proposed as an appropriate measure to evaluate the effect of a cancer screening programme, because this outcome is independent of treatment. After all, effective screening ensures that fewer tumours are diagnosed at a late stage, as they should have already been detected earlier.
- **All-cause mortality and cancer-specific mortality:**
 - **Cancer-specific mortality** is often selected as the primary outcome as the aim of screening is the prevention of premature death caused by cancer. However, this requires a correct determination of the cause of death, which in reality is not always accurate. Furthermore, this outcome does not take deaths resulting from the screening programme (e.g. radiation-induced breast cancers, deaths due to complications after surgery) into consideration, nor does it take potential adverse consequences from a cancer diagnosis (e.g. increased cardiovascular mortality and risk of suicide) into account.
 - **All-cause mortality** is a more robust measure, as it does not require a judgement on the cause of death and captures unexpected lethal side effects of screening and medical care. For this study, we opted to present results for **both outcome measures**.



- **Quality of life and psychological burden:** Screening can improve quality of life by avoiding burdensome treatment for advanced stage cancer, which is often associated with many side effects that may affect patients in the long term. Yet, cancer screening may also lead to anxiety and stress when waiting for the test result or more importantly, the distress related to false-positive (or intermediate) results. Moreover, not all individuals with screen-detected cancer benefit in terms of quality of life, as screening may also lead to overdiagnosis. These patients are unnecessarily labelled as cancer patients and undergo unnecessary treatment, with potential adverse consequences (e.g. discomfort related to the test, or more severe morbidity such as bowel perforation after colonoscopy), which may have an important negative impact on quality of life. These harmful effects on the quality of life should hence not be overlooked.

2.6 Factors that may influence (the assessment of) effectiveness and other key concepts

Research into the **effectiveness of a (cancer) screening programme** may be subject to various sources of bias. The most important ones for (breast) cancer screening are:

- **Selection bias**, meaning there are systematic differences between the study and control groups. In the case of (breast) cancer screening, this specifically concerns '*healthy user bias*': in general, people who actively participate in preventive health measures, such as cancer screening and vaccinations, tend to have better overall health, a healthier lifestyle and a higher level of education than those who do not. Solely for that reason, they are at a lower risk of premature death. Differences in outcomes between participants and non-participants therefore cannot be attributed solely to the screening, but also to these background differences. For this reason, observational studies are often subject to selection bias (see section 2.7.2 below).
- **Length time bias** results from screening programmes being more likely to detect tumours with slow progression, which are, on average, less aggressive than those diagnosed based on clinical signs or symptoms. The latter are usually faster-growing and more aggressive tumours. Because slow-growing tumours have a better prognosis – though not necessarily due to early detection – this can lead to an overestimation of the effectiveness of screening. Fast-growing tumours can also develop between two screening rounds. These are referred to as **interval cancers**.
- **Lead-time bias:** 'Lead-time' is the time interval between the screen-detection of a cancer and the occurrence of symptoms. Lead time has no influence on cancer outcome. In the context of evaluating survival benefits for tumours detected through screening versus those identified clinically, it is essential to account for lead time. A screen-detected tumour is diagnosed earlier than it would be through clinical detection, potentially resulting in an apparent extension of survival. However, (a portion of) this apparent survival benefit may be attributed to earlier detection rather than an actual improvement in prognosis. Consequently, when reporting survival based on time since diagnosis, tumours detected through screening may appear to exhibit superior survival outcomes.

A **major drawback** of cancer screening is **overdiagnosis**. Overdiagnosis in screening is the detection of a disease or abnormal condition that would not have caused the person any harm during lifetime if left undiscovered.

In the context of cancer, overdiagnosis refers to:

- Detection of a tumour that would have regressed spontaneously (Figure 1b, arrow F);
- Detection of a slow or non-growing tumour which would not have posed a problem for the patient during his or her lifetime (Figure 1b, arrow E);
- Detection of a tumour at a time when the patient is more likely to die from other diseases or old age (Figure 1b, arrow D).

As a result, the diagnosis of one of these conditions through screening **does not lead to any tangible improvement in the patient's health, wellbeing, or life expectancy**. On the contrary, overdiagnosis and overtreatment have **harmful consequences**. They lead to unnecessary anxiety, stigmatisation and (financial) consequences, as well as overtreatment with potential complications and additional costs for patients and the healthcare system.

Overdiagnosis can only be determined at **population level**. If the roll-out of a screening programme leads to more cancers being detected at an early stage, without a corresponding reduction in the number of advanced cancers, this reflects the presence of overdiagnosis. Overdiagnosis cannot be measured at the level of the screened individual. It is therefore impossible to determine who has benefited from the screening and who has suffered harm as a result of overdiagnosis.

For cancer patients, the concept of overdiagnosis is therefore difficult to grasp: those who are treated for a cancer detected through screening often perceive the screening as life-saving. However, in some patients, the cancer in question would never have caused harm or clinical symptoms had it not been detected through screening.

Overdiagnosis should not be confused with **false-positive results**: in the latter case, the suspicion of cancer obtained through screening is later dismissed through follow-up tests. False-positive results are also an undesirable consequence of screening, as the anxiety caused by a possible (cancer) diagnosis, together with the subsequent procedures, can have harmful consequences. Unlike overdiagnosis, false-positive results can be identified at an individual level.

2.7 What is the best study design to evaluate the effect of screening programmes?

2.7.1 *Randomised controlled trials (RCTs)*

Because randomisation eliminates many of the biases mentioned above, the **randomised controlled trial (RCT)** is regarded as the best type of study for investigating the effectiveness of screening programmes.

However, the available RCTs on breast cancer screening are (very) old: they were conducted between 1963 and 1997. In addition, since their publication, there has been extensive debate on their methodological quality. Only two studies were considered to have a low risk of selection bias. As a result, the **certainty of the evidence** (regarding both the benefits and the harms of breast cancer screening) is generally **low to very low**.

Furthermore, questions have been raised on the extent to which these old studies are still representative of current screening practice (e.g. digital mammography has replaced film mammography), as well as of the incidence of breast cancer and current treatment, which has improved considerably since then. Systemic therapies in particular (e.g. chemotherapy, targeted therapy, immunotherapy) have led to a clear reduction in mortality across all stages of cancer. The greatest benefit has been observed in younger women, a group that is currently excluded from the screening programme.

2.7.2 *Are recent observational studies a better alternative?*

Although observational studies better reflect the current reality of screening and treatment, they have the major drawback of **selection bias**. Self-selection carries a high risk that the **presumed benefits of screening** will be **overestimated** (see above).

Unlike in RCTs, 'participants' in observational studies are not randomly assigned to the study or control group. In the case of breast cancer screening, women who voluntarily took part in mammography screening are compared with women who did not want to participate.

As a result, there may already be significant differences between participants and non-participants prior to screening. For example, women who take part in screening are often healthier, more health-conscious or have a higher socio-economic status, whilst non-participants are more likely to have health problems or have worse access to healthcare.



This selection bias can lead to the benefits of screening being overestimated, as differences in outcomes are caused not only by screening but also by underlying differences between the groups.

Although observational studies better reflect current screening and treatments, they are therefore not suitable for reliably determining the true effect of breast cancer screening.

We have therefore chosen to include the results of observational studies in the scientific report for illustrative purposes only. As a consequence, they were not taken into account in the conclusions when assessing the effect of screening.

3 IS BREAST CANCER SCREENING USING MAMMOGRAPHY EFFECTIVE?

3.1 Breast cancer mortality and all-cause mortality

The systematic literature review shows that mammography screening programmes lead to a **statistically significant reduction in breast cancer mortality for all age groups combined**.

The effect is most pronounced in women **aged 50 to 69 years old**, where the **greatest reduction** (an average of 169 fewer deaths per 100 000 women invited for screening) is observed. There is also a modest but statistically significant reduction among women **under 50** (an average of 49 fewer deaths per 100 000 women invited for screening). No statistically significant effect on breast cancer mortality has been demonstrated among **women aged 70 and older**.

However, the results for breast cancer mortality should not be viewed in isolation from **all-cause mortality**. Mammography screening has **no** statistically significant **effect on all-cause mortality**, either for all age groups combined or for specific age groups.

3.2 The stage of breast cancer at diagnosis

According to the RCTs, mammography screening leads to a **statistically significant reduction in the number of advanced breast cancers for all age groups combined** (stage II or higher and stage III or higher).

For this outcome measure, the **effect** is also **most pronounced** in women **between 50 and 69 years old**: screening leads to a significant reduction in both stage II or higher and stage III or higher. In women **under 50**, there is a slight reduction in cancers diagnosed in stage II or higher, but no clear effect on the most advanced stages (stage III or higher). For **women aged 70 and older**, no relevant RCT data were identified.

3.3 Overdiagnosis

As mentioned in the previous chapter, overdiagnosis is a major harm of (breast) cancer screening.

According to the literature, among women between **50 and 69 years old** who are invited for screening, overdiagnosis accounts for approximately **21%** of diagnosed (invasive and non-invasive) cancers (7–9 years follow-up). Among women **under 50**, the rate of overdiagnosis is approximately **23%** (7–9 years follow-up). For women **of 70 years and older**, no relevant RCT data on overdiagnosis were retrieved.

With a longer follow-up period, some tumours are still detected without screening, thereby reducing the difference in the number of tumours diagnosed in both groups. At the same time, a longer follow-up period may also introduce a new source of bias, more specifically **contamination**, which leads to an underestimation of overdiagnosis. This occurs when women from the control group undergo screening after the study has ended. This narrows the gap between the groups, creating the illusion of less overdiagnosis than actually occurs.

3.4 Conclusion

After an average follow-up of 13 years, breast cancer screening using mammography appears to reduce **breast cancer mortality** and the number of **tumours diagnosed at an advanced stage**. However, it has no statistically significant effect on **all-cause mortality** and is associated with **significant overdiagnosis**.



4 EFFECTIVENESS OF OTHER SCREENING INTERVALS AND OF THE COMBINATION WITH ULTRASOUND

4.1 Other screening frequencies

In Belgium, the organised screening programmes invite women from age 50 to 69 for a biennial mammography. The procedure is free of charge for participants. In this study, we also examined whether an **annual** or **triennial** screening would be more (cost-)effective compared to the current biennial screening.

However, we found **no relevant RCTs** to determine the optimal frequency for mammography screening. **Annual screening** is certainly **less cost-effective than biennial screening**, as the additional benefits (induced by fewer interval cancers) are, in relative terms, definitively smaller than the additional costs. Conversely, triennial screening could, in theory, lead to a proportionally greater reduction in costs than in benefits, thereby improving cost-effectiveness. However, there is currently no evidence on the extent to which triennial screening leads to an increased number of interval cancers.

Further details are available in section 6.4.6 of the scientific report.

4.2 Combination with ultrasound

Is the addition of ultrasound more effective than mammography alone, which is currently standard practice in organised screening? Or, to put it differently, does an additional ultrasound result in fewer advanced cancers, lower (cancer-related) mortality and less overdiagnosis? If so, does the value of an additional ultrasound justify the additional expense?

There is currently **no convincing evidence from RCTs** that adding ultrasound to mammography leads to better clinical outcomes in women without an increased risk of breast cancer. The only large, well-conducted study (performed in a population of Japanese women under the age of 50) shows that the combination of mammography and ultrasound **has no statistically significant effect on all-cause mortality or breast cancer mortality** compared with mammography alone.

However, the addition of ultrasound does lead to a **significant increase in false-positive results**.

There is therefore **insufficient rigorous evidence for routinely adding ultrasound** to mammography in women who are not at increased risk of breast cancer. As there are no clinical arguments in favour of this more expensive combination, it cannot be considered cost-effective either.

Further information is available in section 3.2.4 of the scientific report.

5 ARE THE CURRENT REGIONAL BREAST CANCER SCREENING PROGRAMMES COST-EFFECTIVE?

5.1 When is breast cancer screening cost-effective?

Breast cancer screening **would be cost-effective if screening a particular group of women yielded sufficient health benefits** (e.g. lower overall and breast cancer mortality — and fewer advanced tumours at diagnosis) **in relation to the costs and harms of the programme**, such as expenses associated with the screening itself, diagnostic evaluations following false-positive results, and with medical care and follow-up.

The result of this analysis is **an ICER^k**, which indicates **the additional cost** of screening compared with no screening, **in order to gain one additional year of life in perfect health** (*Quality-Adjusted Life Year* – QALY).

5.2 Our approach

The reliability of an economic evaluation depends heavily on the quality of the underlying clinical evidence. Given that the scientific evidence from the RCTs is outdated and the majority is characterised by a high risk of bias (see section 2.7), we refer to the analysis as a **‘hypothetical’ economic evaluation**.

The decision to carry out an economic evaluation nonetheless was prompted by the **limitations of existing economic studies**, of which most are difficult to apply to the Belgian context. For example, they do not take the full cost of the screening programme into account, assume unrealistically high participation rates and offer little transparency regarding overdiagnosis. Furthermore, the assumptions regarding quality of life are not always realistic. We therefore carried out a **de-novo analysis** that is better suited to the Belgian situation and takes these factors into account, based on the best available evidence. The hypothetical economic evaluation **combines a decision tree and a Markov model**, and is performed from the **healthcare payer’s perspective**. ICERs were expressed as incremental costs/life year gained and incremental cost/QALY gained. A **lifetime time horizon** was adopted, with the impact of shorter time horizons presented in scenario analyses.

We based our analysis primarily on the most recent **Belgian data** available from the Belgian Cancer Registry (BCR), the InterMutualistic Agency (IMA) and the Crossroads Bank for Social Security, which enabled us to take a snapshot of the current situation in Belgium, including the number of women invited to and participating in organised breast cancer screening, positive and negative screening results, true and false positives, interval cancers, staging of cancers detected by screening and interval cancers by age category, age- and stage-specific (long-term) survival, and stage-specific diagnosis and treatment costs for various cost categories. This allowed us to create a highly accurate, context-driven profile of the current situation with organised screening among women aged 50–69 in Belgium. These data were supplemented with data on the expected stage shift and overdiagnosis derived from the previously discussed RCTs and quality of life data derived from a separate literature review.

In our evaluation, the current situation in which women aged 50–69 years are invited for breast cancer screening was compared with the counterfactual (i.e. ‘what if these women had not participated in this programme’). To reflect this situation without screening, the inverse of the stage shift identified in the RCTs was applied to the current stage distribution while correcting for overdiagnosis (for more details, we refer to chapter 6 of the scientific report).

Given the considerable uncertainty in the clinical evidence, we opted for a hypothetical evaluation based on **optimistic assumptions**. If the result were to yield relatively high ICERs, the cost-effectiveness of the intervention could be questioned. In such a situation, less optimistic assumptions only worsen the

^k Incremental Cost-Effectiveness Ratio



cost-effectiveness. While the optimistic assumptions are prone to justified criticism, the outcome regarding the cost-effectiveness would nevertheless be clear. We did not develop a worst case scenario, as screening could never be cost-effective in such a scenario.

Examples of these optimistic assumptions, which lead to **overestimating** the **cost-effectiveness** of screening, include: we did not take into account any potential negative impact on quality of life due to overdiagnosis and overtreatment, as this information is also not available in the scientific literature; We also assumed that quality of life does not decline with age or the progression of the disease, and that participation in screening has no adverse effect on quality of life; Likewise, we did not include the adverse effect of lead-time bias, as is the case in all other economic evaluations. We also used Belgian survival data with a follow-up period of up to 20 years. In these figures, the difference between survival rates for early-stage and advanced-stage breast cancer is even greater than in more recent survival figures with a shorter follow-up period. This also leads to an optimistic estimate of the cost-effectiveness of screening.

5.3 Results

The variables with the greatest impact on cost-effectiveness were **overdiagnosis** and the probability of being diagnosed **with advanced-stage breast cancer** (*stage shift*). Overdiagnosis incurs additional costs without any health benefit and therefore reduces cost-effectiveness.

Based on all RCTs combined, the relative risk of being diagnosed **with advanced-stage breast cancer** is 0.66. In other words, women invited for breast cancer screening have a 34% lower risk of being diagnosed with advanced breast cancer (i.e. stages II, III and IV) compared with the control group (those not invited). This outcome is also referred to as “stage shift”. When only RCTs with a low risk of selection bias are considered, the relative risk of being diagnosed with advanced-stage breast cancer is 0.83.

Depending on the chosen magnitude of the stage shift, the ICER varies considerably: from approximately **€13 700 per QALY gained** (optimistic scenario, relative risk of advanced breast cancer at diagnosis of 0.66) to **€51 900 per QALY gained** (more conservative scenario, relative risk of advanced breast cancer at diagnosis of 0.83). The real-world data seem not to support the most optimistic scenario applying a risk ratio for being diagnosed with advanced disease of 0.66. As a result, the plausibility of this scenario, and thus the cost-effectiveness of the current screening programmes, can be questioned.

Furthermore, deviations from several optimistic assumptions (such as the use of relatively old survival curves with longer follow-up or the absence of a QoL loss associated with overdiagnosis) further increase the value of the ICER.

It is expected **that extending screening to younger or older women** would be **less cost-effective** than the current screening programmes: in **younger women** (younger than 50 years old), the incidence of breast cancer is approximately four times lower than in the 50–69 age group. This means that the screening will be less cost-effective compared to the current target group. The effort required to detect cancer will be much greater, while the harm caused by false positives and overdiagnosis will remain. The greater gain in life years due to higher life expectancy among younger women carries less weight in terms of preventing mortality because of the significant impact of discounting over the longer term. Furthermore, a higher probability of faster growing cancers would also negatively impact the balance between screen-detected and interval cancers.

In **older women** (70–74 age group), the incidence of breast cancer is slightly higher than among those in the 50–69 age group. However, the benefit of averting a breast cancer death will be much lower in this age group than in the 50–69 age group, as mortality from other causes is much higher. Furthermore, screening this age group will lead to more overdiagnosis, more precisely to the detection of a tumour at a time when the patient is more likely to die from other diseases or old age. This has a further negative impact on the cost-effectiveness of breast cancer screening.

To provide potential participants, healthcare professionals and policymakers with clear and balanced information, a **graphical representation of the health economic evaluation, showing the benefits**

and harms of screening, can be found in Figure 2.¹ More specifically, the benefits and harms were quantified in absolute numbers for 10 000 women participating in a screening round (being the first round for some participants and the second, third, etc. round for others). The figure shows the avoided mortality by screening 13 years after participation, for a relative risk of advanced breast cancer of 0.66 (resulting in 3 fewer deaths) or 0.83 (resulting in 1 fewer death).

Further information is available in Chapter 6 of the scientific report.

¹ The figure only shows the point estimates (without confidence intervals) to ensure its readability. The confidence intervals are reported below the figure.



Figure 2 – Benefits and harms of the current organised breast cancer screening programmes among 10 000 women**



Notes: *The 255 false positives include 4 interval cancers following a positive screening result **Due to rounding, the total does not equal 10 000. The remaining woman is shown in light grey. The 95% confidence intervals around the point estimates are: 9654 (9646–9663), 255 (249–262), 27 (24–29), 19 (16–23), 44 (39–48), 1 (0–3), 3 (2–4).

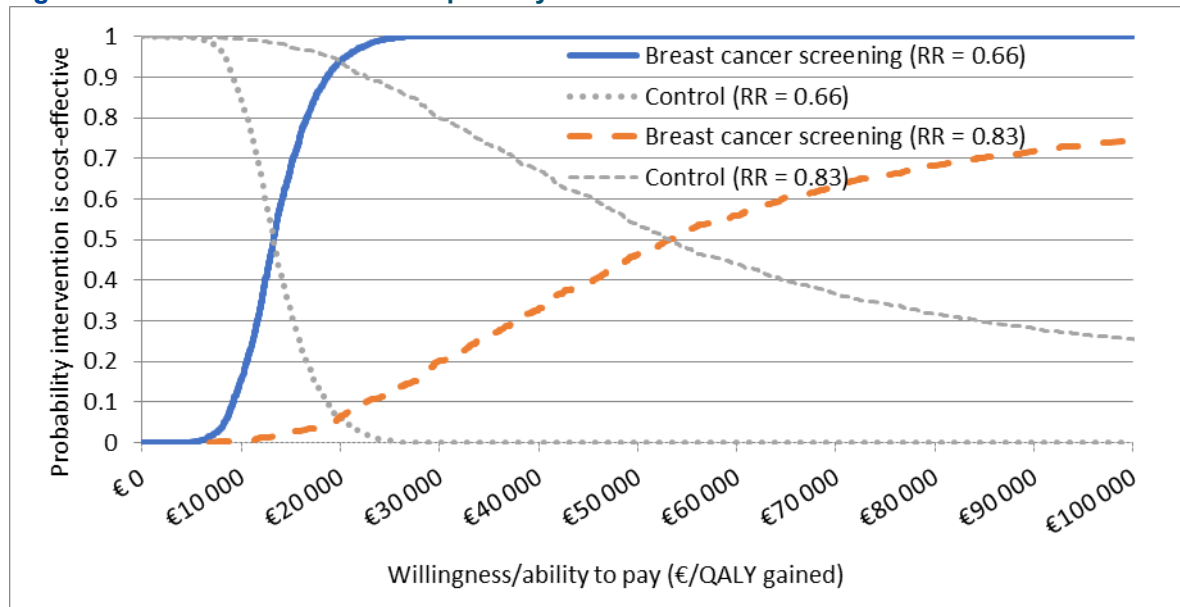
5.4 Cost-effectiveness and policy

In contrast to several other countries and global bodies, Belgium **does not apply an explicit ICER threshold** (see [KCE guidelines for economic evaluations](#)). Budgetary constraints impact what is considered cost-effective in our country. The threshold is therefore influenced by the ability to pay within available budgets, rather than by the willingness to pay.

To support policymakers, we present the results using a **cost-effectiveness acceptability curve** (see Figure 3), which expresses the probability that an intervention or comparator will be considered cost-effective as a function of the willingness to pay (WTP) per QALY gained.

In the less optimistic, but likely more realistic scenario (with a relative risk of being diagnosed with advanced breast cancer of 0.83), there is a probability of 0.5% that breast cancer screening is cost-effective if the policymaker is willing to pay €10 000 per QALY. If the willingness to pay increases to €20 000 or €30 000, this probability increases to 6% and 20% respectively. In the optimistic scenario (with a relative risk of being diagnosed with advanced breast cancer of 0.66), the probability that breast cancer screening is cost-effective is 16% for a willingness to pay threshold of €10 000, 94% for €20 000 and 100% for €30 000.

Figure 3 – Cost-effectiveness acceptability curve





6 CONCLUSION

The current organised breast cancer screening programmes are likely to offer benefits: a **modest reduction in breast cancer mortality**, but not in **all-cause mortality**. They lead to a **reduction in the number of advanced cancers**, particularly among women between 50 and 69 years old.

Conversely, screening carries a significant risk of overdiagnosis. A substantial number of identified cancers are indolent and would never cause symptoms, ultimately subjecting patients to unwarranted interventions, financial burdens, and diminished well-being. In addition, **the evidence underpinning the benefits and harms is limited and uncertain**, as the seven available RCTs are outdated and characterised by methodological shortcomings. More recent observational studies are not a valid alternative, as they overestimate the benefits of the screening programme due to selection bias.

The **cost-effectiveness** of breast cancer screening is therefore also **uncertain**. In a Belgian hypothetical economic evaluation, we estimated the cost-effectiveness of screening for women aged 50–69, under optimistic assumptions, at approximately **€13 700 per QALY gained**, but this figure rises to approximately **€51 900 per QALY gained** based on stricter, more reliable and likely more realistic assumptions regarding the impact on the probability of being diagnosed at an advanced stage. Other less favourable assumptions (e.g. higher rates of overdiagnosis or better survival for advanced breast cancers) make screening even less cost-effective. Consequently, the cost-effectiveness of the current screening programmes can be questioned.

Extending screening to younger or older age groups appears to further reduce cost-effectiveness, due to a lower risk of breast cancer and a higher risk of overdiagnosis, respectively.

Belgium does **not** apply a **fixed ICER threshold to determine whether an intervention is cost-effective**. Instead, budgetary limits play a central role: it is mainly a question of what is possible within the available budget (ability to pay), not just what one is willing to pay. The final decision also depends on other factors, such as the severity of the disease, the need for treatment, and the quality of the evidence.

There is no convincing evidence that **shortening the screening interval or adding ultrasound to mammography** yields sufficient benefits, whilst this is certainly associated with higher costs. Therefore, there is currently insufficient justification to support these strategies based on (cost-)effectiveness.

■ RECOMMENDATIONS

Preamble

In Belgium, organised breast cancer screening is aimed at women aged between 50 and 69 who have not been diagnosed with breast cancer in the past 10 years, have not undergone a bilateral mastectomy and do not have a significantly increased risk of breast cancer.

The recommendations below apply specifically to this target group. Therefore, they do not apply to women with a personal or family history of breast cancer, genetic risks (e.g. BRCA1 or 2) or symptoms (e.g. a lump in the breast).

To the Ministers responsible for Public Health, their departments responsible for the policy and/or funding of breast cancer screening programmes, the organisations that organise, promote and/or carry out breast cancer screening, the physicians involved in this screening, the professional and scientific associations of general practitioners, gynaecologists and other relevant healthcare professionals, to health insurance funds and patient organisations:

1. **Participation in breast cancer screening is a personal choice.** Provide women with balanced and clear information about the evidence-based benefits and harms of breast cancer screening, as well as the uncertainties surrounding this information, to enable them to make an informed decision that aligns with their personal values and preferences.

To the Ministers responsible for Public Health and their departments responsible for the policy and/or funding of breast cancer screening programmes:

With regard to the **current screening programmes for women aged between 50 and 69:**

2. Offer women aged between 50 and 69 who have made a personal choice to participate in breast cancer screening a mammography **as part of the organised breast cancer screening programmes**. This guarantees quality control and ensures that women do not have to pay a co-payment.
3. There is considerable uncertainty regarding the balance between the clinical benefits and harms of breast cancer screening, as well as regarding the cost-effectiveness of the current screening programmes. Cost-effectiveness is only plausible under a number of optimistic assumptions, the real-world validity of which is highly uncertain. Take this uncertainty into account when prioritising and allocating available resources.

With regard to a **possible extension** of the current breast cancer screening programmes:

4. For **women under the age of 50**, the balance between the clinical benefits and harms of breast cancer screening is even less certain than for the current target group. Furthermore, the incidence of breast cancer in this group is lower than in the current target group, making the programme less cost-effective. Therefore, **do not extend** the current screening programmes to women under the age of 50;
5. For **women aged 70 and older**, breast cancer screening does not reduce (breast cancer) mortality. Furthermore, there is insufficient reliable data on the harms (e.g. higher risk of overdiagnosis). Therefore, **do not extend** the current screening programmes to women aged 70 and older;



With regard to the **screening interval**:

6. Currently, there are no RCT data available on the benefits and harms of annual versus biennial or triennial versus biennial breast cancer screening. For the target group, a shorter screening interval (e.g. annual screening) would result in an unfavourable balance between the number of additional breast cancers detected and the additional costs that this expansion would generate. This would result in a less favourable cost-effectiveness compared with the current biennial screening. Therefore, **do not implement annual breast cancer screening**.

With regard to breast cancer screening using a **combination of mammography and ultrasound**:

7. Breast cancer screening using a combination of mammography and ultrasound does not lead to a reduction in (breast cancer) mortality, but does result in more false-positive results. Therefore, **do not extend** the current mammography screening programmes **with ultrasound**.

To the professional and scientific associations of GPs, gynaecologists and other relevant healthcare professionals, to health insurance funds and patient organisations:

8. Make **additional efforts to provide women with accurate and clear information** on the following:
 - a. When women make the personal choice to participate in breast cancer screening, they should do so within the organised breast cancer screening programmes. In this regard, it is important to inform them accurately about the benefits of breast cancer screening within the organised breast cancer screening programmes, particularly the quality control of the programmes (including the double reading of every mammography and the regular training of radiologists), which is not the case with opportunistic screening, and the fact that they do not have to pay a co-payment;
 - b. There is currently no convincing evidence that annual breast cancer screening leads to health benefits;
 - c. The routine combination of mammography and ultrasound in breast cancer screening does not lead to a reduction in breast cancer mortality or all-cause mortality, but does result in more false-positive results and is therefore not recommended.
9. In the **training of physicians**, sufficient and ongoing attention should be attributed to the effects of cancer screening, as well as the correct interpretation of the results and the various sources of bias that complicate this interpretation.

To the Federal Minister for Social Affairs and Public Health and the NIHDI:

10. The current invoicing codes ('nomenclature') do not allow differentiation between, on the one hand, mammographies and ultrasounds carried out for diagnostic purposes (e.g. women with symptoms such as a lump in the breast) and, on the other hand, mammographies and ultrasounds carried out as part of opportunistic screening. Consequently, it is not possible to assess a) the scale of opportunistic screening, and b) the quality (e.g. sensitivity and specificity). The fee schedule should therefore be revised to enable assessments to be carried out, and to allow opportunistic screening to be discontinued if the quality is found to be inadequate.

To the organisations that organise, promote and/or carry out breast cancer screening, and to the physicians involved in this screening:

11. **Provide** women with **balanced and clear** information about the evidence-based benefits and harms of breast cancer screening, as well as the uncertainties surrounding this information. This will enable them to make an informed decision in line with their personal values and preferences.
12. Therefore, include a **decision aid** in the invitation letter and make it available to GPs, gynaecologists, radiologists and the general public, even if this would negatively affect the participation rate of the screening programmes. It is important that women are clearly informed about a) the benefits and harms (e.g. overdiagnosis) of participating in the screening, with the magnitude of both expressed in absolute numbers, and b) the potential consequences of these benefits and harms (e.g. anxiety following a false-positive screening result). This information must be understandable to people with varying levels of (health) literacy.

To the Ministers responsible for Public Health and their departments responsible for the policy and/or funding of breast cancer screening programmes, the scientific associations of medical specialists involved in breast cancer screening, and scientific research institutes:

13. Develop an evidence-based **decision aid** to inform women in a balanced and clear manner about the benefits and harms of participating in breast cancer screening.
14. Re-evaluate the current breast cancer screening programmes as soon as the (long-term) results of the ongoing RCTs into **risk-based screening** become available. Based on these results, provide recommendations if this could lead to a better balance between benefits and harms and/or a more efficient use of resources.
15. Re-evaluate the current breast cancer screening programmes as soon as the (long-term) results of the ongoing RCTs into breast cancer screening for **women with dense breast tissue** (e.g. the DENSE2 study) become available. Based on these results, provide recommendations if this could lead to a better balance between benefits and harms and/or a more efficient use of resources.
16. There is a lack of data on the **quality of life of women with breast cancer** in Belgium. Therefore, we recommend that a study is set up to accurately assess this. This study should be conducted among women with breast cancer and use the EQ-5D questionnaire. It should include a sufficient number of patients within each (invasive and non-invasive) stage of breast cancer and, preferably, conduct measurements at different points in time using a longitudinal design.

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In producing this work, the authors used Microsoft Copilot 365 and DeepL to assist with structuring the text, occasionally drafting sentences based on their original ideas, and improving the readability and clarity of the text. Following their use, all content was carefully checked and revised by the authors, who bear full responsibility for the final version of the manuscript.

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- Various external experts (see above) were consulted on a (draft) version of the scientific report. They were selected on the basis of their expertise in the subject matter of this report; potential conflicts of interest were taken into account during the selection process. Their comments were discussed in meetings and/or via email. They are not co-authors of the scientific report and do not necessarily agree with its content.
- The KCE research team then invited three independent experts ('validators', cf. supra), who had not previously been involved in the research, to carry out a peer review of the final version of the scientific report. They were selected on the basis of their expertise in the subject matter of this report; potential conflicts of interest were taken into account during the selection process. They determined whether or not the report was scientifically valid. The validators are not co-authors of the scientific report and do not necessarily all agree on its content. Their names and affiliations are listed in the colophon.
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