On the basis of several randomized clinical trials,[1-3] the World Health Organization concluded in 2002 that screening mammography for women between the ages of 50 and 69 years reduced the rate of death from breast cancer by 25%.[4] Nevertheless, the use of screening mammography is still debated, chiefly because of concern regarding methodologic limitations in some of the randomized trials.[5] In addition, the benefit of mammography when implemented in a population-based service program remains poorly quantified. Therefore, continued evaluation of breast-cancer screening programs is warranted.[6]

The main challenge in quantifying the reduction in mortality from nonrandomized screening programs is to provide valid comparison groups. Although historical, prescreening control groups are often used, such a comparison has important limitations because it does not take into account confounding by chronological trends in breast-cancer mortality, reflecting such factors as advances in breast-cancer awareness and treatment. According to a statistical model based on data regarding breast-cancer mortality in the United States from 1975 through 2000, only half the observed reduction in mortality was causally related to the mammographic intervention itself, whereas the other half was attributable to improved management.[7] To establish a valid comparison group, we took advantage of several unique features of the nationwide Breast Cancer Screening Program in Norway, which was implemented by means of gradual geographic expansion over a 9-year period.

Methods

Screening Program

Norway, with a total population of 4.8 million, has a public health care system. Patients generally receive treatment in their county of residence, and there is no private primary care for breast cancer.[8] The nationwide Cancer Registry of Norway is close to 100% complete.[9,10] Patients are identified in the registry by their individually unique national registration number, which includes the date of birth. The registry runs the Breast Cancer Screening Program, which began as a pilot project in 4 of the 19 Norwegian counties in 1996. Two years later, the government decided to expand the program, and over a period of 9 years, the remaining 15 counties were enrolled in a staggered fashion[11] (Fig. 1). The rollout of the program followed no specific geographic pattern. Since 2005, all women in the country between the ages of 50 and 69 years have been invited to participate in screening mammography every 2 years.

Before enrollment in the program, each county was required to establish multidisciplinary breast-cancer management teams and breast units.[12] As a result, breast-cancer management became centralized for all residents within each county, and dedicated teams of radiologists, radiologic technologists, pathologists, surgeons, oncologists, and nurses managed the care of all patients, regardless of age.

The screening program is organized with 26 stationary and 4 mobile screening units.[13] The Central Population Registry of Norway identifies eligible women on the basis of their national registration number. Invitations are mailed to each eligible woman, suggesting a time for an appointment.[14] Overall, 77% of all women who are invited participate in the program.[15] In accordance with European guidelines, mammograms are obtained in two views, which are independently read by two radiologists.[12]

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An Investigation of the Apparent Breast Cancer Epidemic in France: Screening and incidence trends in birth cohorts

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Background

Between 1980 and 2005, age-standardized cancer incidence in France increased by 38%, primarily due to increased reported prostate cancer incidence in men and breast and lung cancer among women [1]. The case-fatality rate of breast cancer estimated from incidence and mortality decreased from 39% in 1980 to 23% in 2005. The increase in breast cancer incidence may be related to increasing exposure to causal factors, such as use of hormone replacement therapy (HRT), alcohol, obesity and change in family size, but may also be an artefact of increased screening.

Reports from the International Agency for Research on Cancer (IARC) and from the French National Institute for Health Research (INSERM) considered the distinction between real and artificial increases in cancer frequency in France by emphasizing mortality data over incidence data [2,3]. When comparing the trends between cancer sites, the IARC report hypothesised that the net impact of early detection methods is to increase reported cancer incidence independently of environmental or lifestyle risk factors. Figure 1 shows breast cancer incidence and breast cancer mortality for the period 1980 to 2005, revealing a substantial discrepancy. If the true incidence in breast cancer was not increasing over time, both screening and improvements in treatment should have substantially reduced breast-cancer mortality.

The goal of breast-cancer screening (testing for the disease in asymptomatic patients) is to reduce mortality by diagnosing and treating tumours earlier in the disease process. Initially, screening programs will increase rates of cancer diagnosis because prevalent tumours are detected earlier. After the introduction of screening, when the reservoir of undiagnosed cases is depleted, a decline of incidence is

expected before a new steady state is achieved [4]. However, recent papers suggest that publicly available mammography screening programs are associated with 10% to 50 % overdiagnosis [5,6], where overdiagnosis is defined as the detection, through screening, of disease that would never have been diagnosed in the absence of screening and thus unlikely to have imposed health consequences throughout life [7]. Increase in screening activity also occurs without organized screening program. For example, after careful modelling, overdiagnosis was over 40% for the younger cohorts that had been exposed to mammograms in Catalonia [8].

A Norwegian study suggested that mammography screening leads to a larger increase in detected invasive breast cancer than can be explained by earlier diagnosis or increased exposure to risk factors. The authors suggested that mammography screening detects many tumours that otherwise would spontaneously regress [9].

Most breast cancers are diagnosed by biopsy following identification by self palpation, clinical examination by a physician, or by mammography. Overdiagnosis is inevitable when testing for asymptomatic disease in almost all screening programs. Clinicians use histology for diagnosing a true progressive disease that would metastasise and cause death without treatment if no other health problem interfered with its progression. The validity of testing for true progressive cancer by histology depends on the sensitivity and the specificity of slides from the biopsy. The number of diagnosed cancer cases in an examined population is the sum of women with progressive cancer correctly diagnosed and of women diagnosed with a cancer that would not progress to clinical detection in their lifetime. The number of true progressive cancers detected in a population reflects the frequency of examinations

among women with progressive cancer, the sensitivity of diagnosis procedures before the biopsy, and the sensitivity of examination by histology.

Global sensitivity is the proportion of progressive cancers correctly identified in a population. All nonprogressive tumours diagnosed as cancer by histology are overdiagnoses. They reflect the frequency of examinations among women without a progressive cancer, the specificity of diagnostic procedures before the biopsy, and the proportion of women without a progressive cancer correctly identified when examined by histology. All the cancer-free women not tested contribute to increase *global specificity*: the proportion of women without a true progressive cancer correctly considered as cancer free in the population. Screening increases global sensitivity. But by doing this, it also results in decreasing global specificity, which in turn produces more overdiagnosis.

Overdiagnosis includes all nonprogressive tumours diagnosed as cancer using histology and those progressive cancers that would never cause symptoms or death during a patient's lifetime. Such cases are *functional* overdiagnoses related to a patient's outcome rather than to the physiological or structural causes of overdiagnosis. Functional overdiagnosis depends not only on the cancer but also on competing causes of death and life expectancy. It occurs more frequently when screening is performed among women with a short remaining life expectancy and when global sensitivity is high.

Our study investigates how the increase in mammography screening is associated with increase in the apparent breast-cancer incidence in France. Such information is relevant to the debate about the benefits and side effects of breast-cancer screening [10-15].