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FALSE-NEGATIVE RESULTS IN SCREENING PROGRAMS

Medical, Psychological, and Other Implications

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Abstract

Objectives: Assessment of the appropriateness of screening programs involves consideration of the harms as well as the benefits. These harms include the risk of false-negative results, the consequences of which have remained underinvestigated. This paper reports the results of a systematic literature review that aimed to assess the medical psychological, economic, and legal consequences of false-negative results in national screening programs.

Methods: The review included a comprehensive literature search and contact with experts to identify relevant literature. Most studies that were identified presented only anecdotal evidence. However, thirteen studies presented quantitative information on medical consequences of false negatives, eight studies presented information on psychological consequences, and two studies presented information on economic consequences.

Results: The strength of evidence from most of the primary studies was low. There is some evidence, however, that false-negative results may have a large legal impact. There is also a consensus in the literature that false negatives may have a negative impact on public confidence on screening; evidence is however limited.

Conclusions: False negatives are evident even in high-quality screening programs. They may have the potential to delay the detection of breast and cervical cancer, but there is little evidence to help in assessing their psychological consequences. They also may lead to legal action being taken by those affected and may reduce public confidence in screening. Their impact may be reduced by provision of full information to participants about the benefits and limitations of screening programs and by increasing public education on these issues.

Keywords: Mass screening, Human, Informed consent

Assessment of the appropriateness of screening programs involves consideration of the harms as well as the benefits. These harms include the risk of false-negative results, which

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are inherent in any screening program that does not have 100% sensitivity. However, their consequences have remained underinvestigated, partly because they are often not easy to identify, but also because any harms deriving from them are perhaps assumed to be small in comparison to the benefits of screening.

There is a risk that the harms of false negatives may be overlooked when new population screening programs are introduced. A recent editorial also warned of the clinical, organizational, and legal impacts that false negatives may have and suggested that they may have important implications for informed consent to screening (45). But what do we know about the harms and wider consequences of false negative results? Some evidence on these and other impacts is available from a recent systematic literature review (30).

MEDICAL CONSEQUENCES OF FALSE NEGATIVES

False negatives may become manifest in a relatively short time after screening, for example, through the birth of a baby with Down syndrome. However, in some cases (for example, in cancer screening) the main medical consequence of a missed diagnosis is likely to be a delay in detection, compared with what would have happened without screening. When the cancer then becomes symptomatic, it may be at a more advanced stage and require more invasive treatment, which may be less successful and more costly. However, the identification of false negatives is not straightforward. While those suspected of having the relevant condition go on to have further investigations, thus revealing any false positives, false negatives may only be identified in further cycles of a screening program. They may also be picked up in quality assurance exercises, may remain undetected and manifest themselves only when the condition becomes symptomatic, or may even remain hidden until death from some other cause.

False-negative rates vary widely between screening tests and range from 1% in some forms of neonatal screening to more than 30% in some studies of cervical screening. In cervical screening it has been suggested that there is an irreducible false-negative fraction of about 5% (41). Most of the evidence relating to the medical consequences of false negatives derives from studies of breast, cervical, and neonatal screening. In the latter case, untreated phenylketonuria (PKU) leads to severe mental handicap and behavioral and neuropsychological problems, while early PKU is treatable (31). Early detection is also important in the case of congenital hypothyroidism; the longer the delay in starting treatment with thyroxine, the worse the eventual outcome (31). In the case of neonatal health screening, a recent systematic review highlighted the consequences of a missed diagnosis of congenital hearing impairment (10), since early interventions are likely to be more effective. False-negative results in screening for hip dysplasia have also been reported (17). A systematic review of antenatal screening for Down syndrome (44) has also suggested that the consequences of a false-negative result include an affected pregnancy, with the associated shock, and the lifetime costs of care.

False Reassurance

False reassurance is commonly suggested as a likely consequence of a false-negative result, but evidence for this impact is hard to find. However, it has been shown that delays in seeking further investigations for breast cancer may result from the false reassurance given by negative results (5;43). In one retrospective study women with palpable breast cancers whose biopsies had been delayed by negative mammograms were more likely to have positive axillary nodes at surgery (6). However, a retrospective U.K. study has reported no difference in prognosis associated with false-negative diagnosis (24). It has also been suggested that in some screening programs, subjects with interval cancers (which may include false negatives) have a worse survival rate than those arising in an unscreened

population (13). In the Canadian National Breast Screening Study, screening errors delayed diagnosis by 1 to 11 months in 35% of interval cancers (4). This has not been reported in some analyses of U.K. data (8;11). Overall, the evidence relating to the medical consequences of false negatives in breast cancer screening is limited, deriving mainly from small studies using mainly retrospective review of mammograms. The evidence does not consistently suggest that false negatives result in a more advanced stage of cancer at detection, though this may reflect absence of evidence rather than evidence of absence.

With respect to cervical cancer screening, a recent review of Pap smear error rates reported false-negative rates of 15% to 22% in retrospective studies (15). However, such studies cannot be used to estimate sensitivity because the number of true-positive results is not known, and such studies may not reflect real-life screening practice (21). Moreover, not all of the "missed" positive smears would eventually have progressed to invasive cancer. So again, the evidence relating to the medical consequences of false-negative results in cervical screening is somewhat limited.

PSYCHOLOGICAL CONSEQUENCES

It has been widely suggested that people receiving a negative result from screening could interpret this as a "certificate of health" and alter their behavior accordingly (42). This may be a result of the widely different medical and lay perspectives of screening: the medical aim is to seek out, diagnose, and treat, while the lay aim is to be reassured (26). Other psychological consequences of false negatives may include the feeling that one has been wrongly treated, leading to loss of faith in the medical profession. However, there is relatively little information on the psychological consequences of false-negative results, and only antenatal screening appears to have attracted any research on the issue. One suggestion is that a child with Down syndrome born after no screening may be better accepted than a child affected after a false-negative result (19;39). This is supported by a recent U.K. study that found that mothers of children in the false-negative group were more likely to blame others for this outcome, and this was associated with poorer acceptance of the child (20).

Overall, though it is commonly suggested that false reassurance is a major problem in breast screening, there is little evidence to support this (23). This is also suggested by a recent systematic review of factors predicting delayed presentation of symptomatic breast cancer (33).

In summary, while it has often been suggested that false negatives result in false reassurance, there is relatively little empirical evidence to support this. Theoretical and anecdotal accounts do suggest that this outcome is likely, but further investigation of this issue would be valuable.

ECONOMIC AND FINANCIAL CONSEQUENCES

In the case of cancer screening services, the financial consequences include the costs of treating a more advanced cancer. Other costs are incurred when flaws in a screening program are detected. These include the costs of rescreening tens of thousands of tests, recalling a proportion of those rescreened, establishing helplines, and dealing with any litigation that may arise. Hard evidence on these issues is again limited, though one review provides an explicit statement of the potential costs of false-negative results, contrasting them with the consequences of the other possible results (40) (Table 1). Valuing the consequences of false negatives may often be difficult, for example, in prenatal screening.

In summary, the evidence on the economic implications of false-negative results is largely theoretical and focuses mainly on ways in which these consequences may be valued and included in analyses of screening.

Table 1. Consequences of a False-negative Result

| Consequence | Benefits |
|--|---|
| False reassurance (the “unworried ill”) The possibility of legitimizing an unhealthy lifestyle A delay in treatment, which may be more unpleasant, more expensive, and have a worse prognosis than treatment at an earlier stage of the illness An increased cost per desired outcome | Spared anxiety if treatment of no benefit |

Source: Shickle and Chadwick (40).

LEGAL IMPLICATIONS

The legal consequences of false negatives have been demonstrated in the United Kingdom and elsewhere, and screening for breast and cervical cancer has been cited as a common cause for litigation (45). Although there may be fewer cases arising out of antenatal screening, the costs can be considerable (30). More generally, high-profile cases may result in pressure to increase the sensitivity of screening at any cost, and one possible consequence of this is “defensive” reporting of minor abnormalities (22). Most of the literature in this area relates to the U.S. experience, where the risk of a lawsuit relating to false negative reporting is high, (25;37) and delay in the diagnosis of breast cancer is one of the most common reasons for malpractice claims against doctors (7). Litigation resulting from false-negative Pap smears has even been cited as a threat to the use and availability of the test (15;16).

SUMMARY OF EXISTING RESEARCH

Overall, there is insufficient research evidence to help in quantifying the likely consequences of a false-negative result. It is widely reported, however, that the main impact of false-negative results is false reassurance, leading to delay in diagnosis and treatment (1;3;14;27;34;35).

False negatives are evident in all screening programs, even when the quality of the service provided is high. They may have the potential to delay the detection of breast and cervical cancer, but there is little evidence available at present to help in assessing the psychological and other consequences in most screening programs. They may, however, lead to legal action being taken by those affected. There is also a possibility that they may result in reduced public confidence in screening; this is discussed below.

PUBLIC CONFIDENCE IN SCREENING

There is a strong consensus in the literature that false-negative results have a powerful impact on public confidence in screening. It has been suggested that the outcomes of screening are broader than most other types of health care, and are not limited to health gain, but may extend to investment in knowledge and reassurance (12). For the public, any benefits of screening may therefore be compromised by recurring scares involving false-negative results. However, while maintaining public confidence is important, it has some risks attached: for example, high public confidence in the efficacy of screening and perhaps falsely high expectations may have created a situation in which all deaths from cervical cancer following screening are perceived as screening “failures” (32). This may be due to the public being underinformed by providers about the limitations of screening, and a more realistic presentation of the limitations and the benefits of all types of screening is likely to be more useful (38). This could include provision of information on what can be reasonably

be expected from screening programs and, in particular, advice that false negative results are likely to remain, even after all possible cost-effective organizational and technological steps have been taken to try to eliminate them. It is particularly important that all participants in screening programs be provided with full information about the meaning of negative results to help them to make informed decisions about whether to participate.

It should also be recognized that, although there are potential benefits of improved public knowledge about the limitations of screening, there may also be costs, e.g., such information may reduce public confidence in screening. Belief in the efficacy of screening is also associated with adherence, so emphasizing the limitations may also result in reduced coverage (18;28;36), and what has been referred to as “mass informed consent” may even limit the effectiveness of screening (29). Care would need to be taken that any message about the limits of screening does not reduce uptake of effective screening tests among those most likely to benefit, or that it becomes simply a further barrier to access. It has also been argued that, above all, patients’ autonomy should be respected, which includes their right to decide not to undergo screening, even when refusal may result in harm to themselves (2).

CONCLUSION

The introduction of screening tests into the U.K. National Health Service has been characterized as piecemeal, uncoordinated, and without adequate quality assurance (9). Ensuring that this does not happen in the future is likely to be one way of reducing the impact of false negatives. It has also been emphasized that “a properly informed public is a vital but often forgotten ingredient in any analysis of screening” (9). Screening technologies, like other healthcare technologies, are liable to be rapidly disseminated without full consideration of their harms as well as benefits. Striving to increase public understanding of such technologies and encouraging more realistic public expectations of screening may well be the most important steps that could be taken to help reduce the adverse impacts of false negatives in screening.

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