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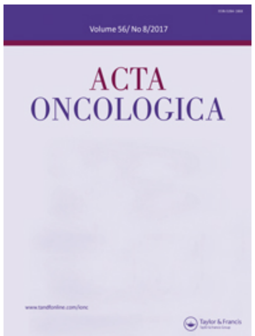

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[15] Heppt MV, Eigentler TK, Kahler KC, et al. Immune checkpoint blockade with concurrent electrochemotherapy in advanced melanoma: a retrospective multicenter analysis. Cancer Immunol Immunother. 2016;65:951–959.
[16] Mozzillo N, Simeone E, Benedetto L, et al. Assessing a novel immuno-oncology-based combination therapy: ipilimumab plus electrochemotherapy. Oncoimmunology. 2015;4:e1008842.
[17] Mir LM, Gehl J, Sersa G, et al. Standard operating procedures of the electrochemotherapy: instructions for the use of bleomycin or cisplatin administered either systemically or locally and electric pulses delivered by the Cliniporator (TM) by means of invasive or non-invasive electrodes. EJC Suppl. 2006;4:14–25.
[18] Kalialis LV, Drzewiecki KT, Klyver H. Spontaneous regression of metastases from melanoma: review of the literature. Melanoma Res. 2009;19:275–282.
[19] Kuriyama S, Mitoro A, Tsujinoue H, et al. Electrochemotherapy can eradicate established colorectal carcinoma and leaves a systemic protective memory in mice. Int J Oncol. 2000;16:979–985.
[20] Miyazaki S, Gunji Y, Matsubara H, et al. Possible involvement of antitumor immunity in the eradication of colon 26 induced by low-voltage electrochemotherapy with bleomycin. Surg Today. 2003;33:39–44.
[21] Di Gennaro P, Gerlini G, Urso C, et al. CD4 + FOXP3+ T regulatory cells decrease and CD3 + CD8+ T cells recruitment in TILs from melanoma metastases after electrochemotherapy. Clin Exp Metastasis. 2016;33:787–798.
[22] Daud AI, DeConti RC, Andrews S, et al. Phase I trial of interleukin-12 plasmid electroporation in patients with metastatic melanoma. J Clin Oncol. 2008;26:5896–5903.
[23] Teulings HE, Limpens J, Jansen SN, et al. Vitiligo-like depigmentation in patients with stage III–IV melanoma receiving immunotherapy and its association with survival: a systematic review and meta-analysis. J Clin Oncol. 2015;33:773–781.
[24] Frandsen SK, Gibot L, Madi M, et al. Calcium electroporation: evidence for differential effects in normal and malignant cell lines, evaluated in a 3D spheroid model. PLoS One. 2015;10:e0144028.
[25] Frandsen SK, Gissel H, Hojman P, et al. Direct therapeutic applications of calcium electroporation to effectively induce tumor necrosis. Cancer Res. 2012;72:1336–1341.
[26] National Institute for Health and Care Excellence (NICE). Electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma. [Internet]. United Kingdom: National Institute for Health and Excellence; 2013 [cited 2017 Jan 10]. Available from: https://www.nice.org.uk/guidance/ipg446

LETTER TO THE EDITOR

Impact of assumptions – the example of the Welch-analysis of mammography screening effectiveness

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Introduction

Based on analysis of SEER data from 1975 to 2012, Welch et al. [1] concluded that in screening, women were more likely to have breast cancer detected 'that was overdiagnosed than to have earlier detection of a tumor that was destined to become large', and that 'the reduction in breast cancer mortality after the implementation of screening was predominantly the result of improved systemic therapy.'

Welch assumptions

The Welch et al. analysis builds on a number of assumptions that might not be unproblematic.

First, it was assumed 'that the underlying probability that clinically meaningful breast cancer would develop was stable' over time given no screening. This assumption was based on the observed, very low and stable incidence of metastatic breast cancer. As the breast cancer incidence data analyzed by Welch et al. started in 1975 and screening in the USA disseminated shortly thereafter, limited data were available from a prescreening period. However, long-term breast cancer incidence data from Rochester, Minnesota [2], from Kaiser Permanente, Portland [3], and from the Connecticut Tumor Registry [4], showed prescreening, cohort-related increases in the breast cancer incidence. Based on long-term prescreening breast cancer incidence data from other countries (for instance Denmark, see section below), it seems likely that the US prescreening cohort trends would have continued also after the start of screening.

Second, screening implies a change in time of diagnosis and therefore a change in the incidence pattern. At the start of screening, a prevalence peak is observed, during screening an artificial aging, and when the women have exited screening a compensatory dip will be seen in the incidence [5]. If it takes 2 years to carry out the prevalence screen, around a 100% increase in incidence will be observed during the period [6]. Screening started gradually in the USA, with 17% (aged 50+) in 1978 having had a mammogram to 74% in 1992 (aged 40+) [7]. This means that in the USA, the prevalence peak is spread out over a long time interval, and that very long time will pass before the compensatory dip becomes visible at the population level. It is therefore questionable when Welch et al. attribute the observed increase in breast cancer incidence to overdiagnosis. The use of

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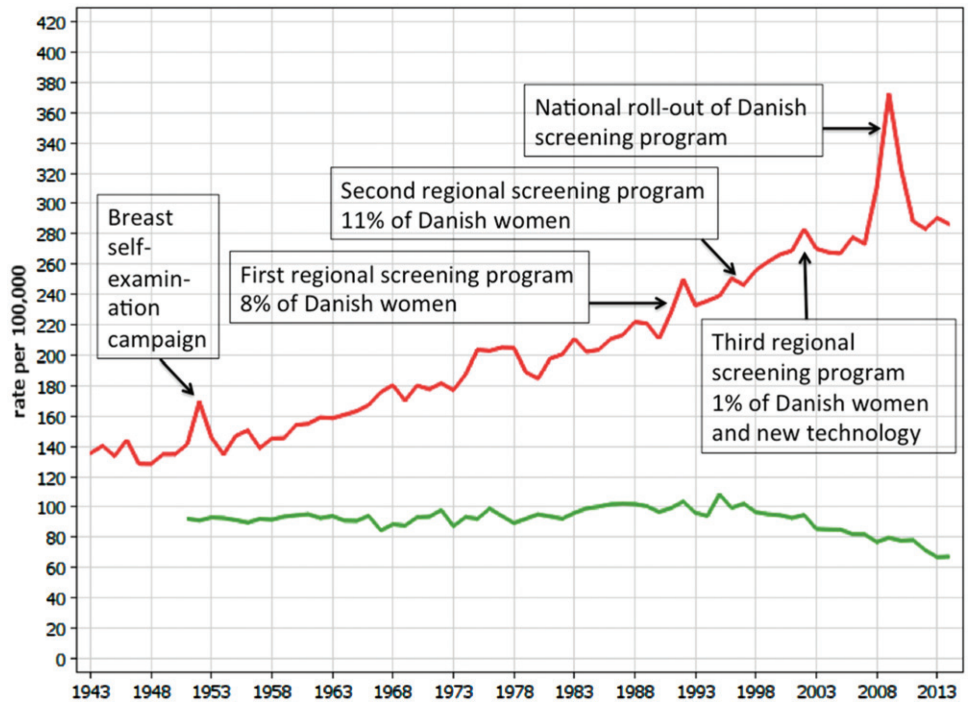

Figure 1. Age-standardized (2000 Nordic population) breast cancer incidence (red) and mortality (green) for women 40+ years in Denmark 1943–2014.

calendar-specific, age-standardized breast cancer incidence rates for all women aged 40+ is simple a too crude tool to identify the dynamic of the incidence rates during screening.

Third, Welch et al. estimated the impact of screening on breast cancer mortality by combining stage-specific incidence and case fatality rates, and concluded that 'improved treatment was responsible for at least two-third … of the reduction in breast cancer mortality'. However, this calculation is still based on the questionable assumption 'that the underlying probability that clinically meaningful breast cancer would develop was stable' over time given no screening.

Breast cancer incidence in Denmark

In Denmark, nationwide registration based on international coding schemes started for incident cancer cases in 1943, and for causes of death in 1951. The age-standardized (2000 Nordic population) breast cancer incidence for women age 40 years and above increased steadily over time, while the breast cancer mortality was stable up until the mid-1990, thereafter it decreased [8] (Figure 1).

In 1951–1952, a breast self-examination campaign took place in Denmark [9]. In modeling of lymph node status data from 1978 to 1994, the overall increase in breast cancer incidence derived from node-negative and moderately node-positive tumors, indicating increased breast cancer awareness [10]. Population-based screening was implemented step-wise in Denmark, though always targeting only women aged 50–69 years, and screening outside the organized programs was rare [11]. The first regional program started in Copenhagen in 1991 and targeted about 8% of women [12], the next regional programs started around 1994, targeting about 11% of women [13], and a very small regional program started in 2001. In 2001–2002, also high-frequency ultrasound devices and stereotactic breast biopsies were implemented which increased the screen-detection rate [14]. National roll-out of screening took place in 2008–2010 [15].

The breast self-examination campaign and the start of the screening programs left marks on the time trend in breast cancer incidence in Denmark. But in the long-time perspective, these marks appeared as irregularities on an underlying increasing trend. In the years before screening, the increase in incidence seems to have come primarily from node-negative and moderately node-positive tumors. As improved awareness – like screening – will move the time of diagnosis forward, it can have some temporary impact on the time trend in the incidence. Some may interpret an increase in node-negative tumors as an indicator of overdiagnosis of indolent tumors. But women will not harbor an inexhaustible pool of indolent tumors. Overdiagnosis is therefore unlikely to explain the doubling of the breast cancer incidence over the past 60 years in Denmark.

Conclusions

Welch et al. presented an interesting and novel approach to assess the effect of breast cancer screening. However, the opportunistic and gradual implementation of screening in the USA makes it very difficult to separate out a possible screening effect from the underlying time trends and improvement in treatment.

In this respect, data from countries with population-based, organized screening programs are more useful. This is especially the case, if the screening program has been implemented region-wise, because it is then possible to identify a comparison group not yet invited to screening. However, screening changes the age-specific incidence in cohorts of women offered screening. This includes a prevalence peak at first screen; an artificial aging at subsequent screens; and a compensatory dip after end of screening [5,6]. Therefore, studies of overdiagnosis require also that women can be followed for a sufficiently long period after end of screening for the compensatory dip to materialize. Such studies have been undertaken in for instance Florence Italy [16]; in Finland [17]; and in Denmark [18].

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

References

[1] Welch HG, Prorok PC, O'malley AJ, et al. Breast-cancer tumor size, overdiagnosis, and mammography screening effectiveness. N Engl J Med. 2016;375:1438–1447.
[2] Ballard-Barbash R, Griffin MR, Wold LE, et al. Breast cancer in residents of Rochester, Minnesota: incidence and survival, 1935 to 1982. Mayo Clin Proc. 1987;62:192–198.
[3] Glass AG, Hoover RN. Rising incidence of breast cancer: relationship to stage and receptor status. J Natl Cancer Inst. 1990;82:693–696.
[4] Holford TR, Roush GC, McKay LA. Trends in female breast cancer in Connecticut and the United States. J Clin Epidemiol. 1991;44:29–39.
[5] Boer R, Warmerdam P, de Koning H, et al. Extra incidence caused by mammographic screening. Lancet. 1994;343:979.
[6] Duffy SW, Lynge E, Jonsson H, et al. Complexities in the estimation of overdiagnosis in breast cancer screening. Br J Cancer. 2008;99:1176–1178.
[7] Zheng T, Holford TR, Chen Y, et al. Time trend of female breast carcinoma in situ by race and histology in Connecticut, U.S.A. Eur J Cancer. 1997;33:96–100.
[8] NORDCAN [Internet]; [cited 2017 Jan 17]. Available from: http://www-dep.iarc.fr/NORDCAN/English/frame.asp
[9] Clemmesen J, Stancke B. The effects of an anti-cancer campaign. Ugeskr Laeg. 1964;126:1564–1565.
[10] Rostgaard K, Væth M, Rootzén H, et al. Why did the breast cancer lymph node status distribution improve in Denmark in the pre-mammography screening period of 1978–1994? Acta Oncol. 2010;49:313–321.
[11] Jensen A, Olsen AH, von Euler-Chelpin M, et al. Do nonattenders in mammography screening programmes seek mammography elsewhere? Int J Cancer. 2005;113:464–470.
[12] Olsen AH, Njor SH, Vejborg I, et al. Breast cancer mortality in Copenhagen after introduction of mammography screening: cohort study. BMJ. 2005;330:220.
[13] Njor SH, Schwartz W, Blichert-Toft M, et al. Decline in breast cancer mortality: how much is attributable to screening? J Med Screen. 2015;22:20–27.
[14] Utzon-Frank N, Vejborg I, von Euler-Chelpin M, et al. Balancing sensitivity and specificity: sixteen year's of experience from the mammography screening programme in Copenhagen, Denmark. Cancer Epidemiol. 2011;35:393–398.
[15] Dansk Kvalitetsdatabase for Brystkræftscreening. Danish Quality database for breast cancer screening. Annual report 2010, first national screening round, Denmark; 2011 [Internet]; [cited 2017 Jan 17]. Available from: http://www.kcks-vest.dk/siteassets/de-kliniske-databaser/mammografiscreening/arsrapport-dkms-2010.pdf
[16] Puliti D, Zappa M, Miccinesi G, et al. An estimate of overdiagnosis 15 years after the start of mammographic screening in Florence. Eur J Cancer. 2009;45:3166–3171.
[17] Heinävaara S, Sarkeala T, Anttila A. Overdiagnosis due to breast cancer screening: updated estimates of the Helsinki service study in Finland. Br J Cancer. 2014;111:1463–1468.
[18] Njor SH, Olsen AH, Blichert-Toft M, et al. Overdiagnosis in screening mammography in Denmark: population based cohort study. BMJ. 2013;346:f1064.

LETTER TO THE EDITOR

A case of isolated small cell carcinoma of the brain

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Case description

Presentation

A 43-year-old Caucasian female presented to the emergency department with a four week history of decreased fluency of speech and headache. She had no significant previous medical history or regular medications, although was a current cigarette smoker with 20 pack-year history. On examination, she had expressive dysphasia, global right-sided hypoesthesia, hypertonicity and weakness of the right upper limb.

Investigation

Her initial MR brain revealed prominent rim-enhancing neoplasms to the left parietal (41 mm AP × 35mm T) and posteromedial temporal lobes (25 mm AP × 11 mm T) with associated mass effect (as shown in Figure 1). A provisional diagnosis of brain metastases from an unknown primary was made. Staging investigations (including CT, MR and FDG PET-CT modalities) showed no evidence of extra-cranial disease. Serum haematology, biochemistry and tumour markers

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