Curr Oncol, Vol. 22, pp. e6-10; doi: http://dx.doi.org/10.3747/co.22.2191

COMMENTARY

Overdiagnosis in breast cancer chemoprevention trials

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Several randomized controlled trials have demonstrated that the preventive use of an antiestrogen agent such as tamoxifen[1–4], raloxifene[5–7], anastrozole[8], or exemestane[9] will reduce the incidence of estrogen receptor (ER)–positive breast cancers by 50% or more. The reduction in risk becomes apparent shortly after tamoxifen initiation[10]. However, no mortality benefit has yet been demonstrated with tamoxifen or any other agent, an effect that might be statistical: that is, the statistical power to detect a difference in mortality could be lacking because deaths from breast cancer are far fewer in number than cases of breast cancer, and because the average time to cancer is much shorter than the time to death[11]. In other words, it could be too early to see an effect. However, the lack of an observed survival benefit might also be a result of chemoprevention agents preferentially preventing cancers that would rarely lead to death. That paradigm extends the (controversial) concepts of overdiagnosis and of the potential for spontaneous regression of some low-grade breast cancers[12].

Overdiagnosis is a problem associated with mammography-detected breast cancers[13–15], and some authors suggest that overdiagnosis helps to explain why the reduction in mortality associated with screening mammography might be less than expected[16–18]. In the report of the 25-year follow-up of the Canadian National Breast Screening Study, the authors concluded that 50% of all nonpalpable mammography-detected cancers are overdiagnosed (22% of all mammography-detected cancers)[17]. Breast cancers that are most likely to be nonprogressive (or regressive) and to be detected by mammography are ER- or progesterone receptor–positive, small, node-negative, and nonpalpable[19–21].

The phenomenon of breast cancer regression was also observed in the wake of the widespread discontinuation of hormone replacement therapy around 2000, after hormone replacement therapy was reported to increase the risk of breast cancer[22]. A rapid decline in breast cancer incidence quickly followed the reduction in the use of hormone replacement therapy, and the immediacy of the effect suggests the disappearance of established subclinical cancers rather than the prevention of new cancers[23–25]. The complementary observations concerning the immediate effects of tamoxifen chemoprevention and hormone replacement withdrawal suggest that a slowly growing ER-positive cancer might be induced to regress based on the sudden removal of an estrogenic signal.

We question whether that paradigm is relevant for evaluating antiestrogen-based chemoprevention studies—in particular if the cohorts under study were being followed for incident cancers with annual mammography. If the paradigm were to hold true for patients assigned to an antiestrogen arm in the screening trials, then removal of the estrogen signal might provoke the regression of some ER-positive nonpalpable tumours, while similar cancers in the placebo arm might remain detectable—but would not threaten survival (and might eventually regress). If all incident breast cancers in the chemoprevention trials were to have been diagnosed by mammography, overdiagnosis would be a concern. In contrast, if the great majority of cancers were detected by clinical breast exam or self-exam (being therefore palpable), overdiagnosis would be less of an issue. However, when the relevant studies were initiated, overdiagnosis was not a recognized phenomenon.

We therefore reviewed the incidence and mortality data from the breast cancer prevention trials, seeking to determine whether breast cancers were detected only by mammography or were palpable. A preventive effect restricted to women with cancers detected only by mammography would raise the question of whether the observed incidence benefit could be expected to translate into a mortality benefit. If so, then an excess of nonpalpable mammography-detected ER-positive breast cancers would be expected in the placebo arm compared with the treatment arm, and restriction of the analysis to palpable cancers would attenuate or eliminate the

effect. In the absence of data on palpability (or detection method), ER status and lymph node status might to some extent indicate whether the incident cancers could be examples of overdiagnosis—under the assumption that most overdiagnoses are to be found in the node-negative luminal subgroup.

Table I summarizes ER status, nodal status, mortality, and detection method (mammography-detected vs. palpable) of incident breast cancers diagnosed in the trials. No trial demonstrated a significant (or borderline significant) reduction in mortality, and in all trials, the benefit was restricted to the ER-positive subgroup. The detection method of incident cancers was reported only in the 1998 report of the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial. In that report, tamoxifen was shown to reduce the occurrence of ER-positive tumours by 69%[26]. In 2008, Shen *et al.* reported the detection method of the cancers, identifying mammography-only detection of 54 ER-positive cancers in the placebo arm and 19 in the tamoxifen arm[27]. Removing those nonpalpable breast cancers from the analysis resulted in a significant risk estimate of 0.29 ($p < 0.0002$), suggesting that overdiagnosis

TABLE I Estrogen receptor (ER) status, mortality, nodal status, and detection method of incident breast cancers detected in tamoxifen, anastrozole, and exemestane prevention trials

Reference	*Variable*	*Subject group*					
		Overall		*ER-positive*		*ER-negative*	
		Placebo	*Treatment*	*Placebo*	*Treatment*	*Placebo*	*Treatment*
Tamoxifen							
National Surgical Adjuvant Breast and Bowel Project (P-1)							
1998 Report (4-year follow-up)[26]							
2005 Report (7-year follow-up)[2]							
	Study subjects	13,338		6,599		6,576	
	Invasive breast cancer						
	1998 Report	175	89	130	41	31	38
	2005 Report	250	145	182	70	42	56
	Deaths from breast cancer						
	1998 Report	6	3				
	2005 Report	11	12				
	Nodal status						
	1998 Report						
	Positive	36	14				
	Negative	116	60				
	2005 Report						
	Positive	70	48				
	Negative	162	91				
	Detection method						
	1998 Report	163	80	132	42	31	38
	Mammogram only	64	31	54	19	10	12
	Palpable	99	49	78	23	21	26
	2005 Report	NA					
International Breast Cancer Intervention Study (IBIS-I) (8-year follow-up)[1]							
	Study subjects	7,154		3,575		3,579	
	Invasive breast cancer	168	124	132	87	35	35
	Deaths from breast cancer	13		11			
	Nodal status						
	Positive	49	37				
	Negative	114	83				
	Detection method	NA					

TABLE I Continued

Reference	*Variable*	*Subject group*					
		Overall		*ER-positive*		*ER-negative*	
		Placebo	*Treatment*	*Placebo*	*Treatment*	*Placebo*	*Treatment*
Tamoxifen (continued)							
Royal Marsden Trial (20-year follow-up)[3]							
	Study subjects	2,494		1,244		1,250	
	Invasive breast cancer	104	82	86	53	17	24
	Deaths from breast cancer	9	12				
	Nodal status	NA					
	Detection method	NA					
Italian Randomized Tamoxifen Prevention Trial (11-year follow-up)[4]							
	Study subjects	5,408		2,708		2,700	
	Invasive breast cancer	66	53	52	40	19	21
	Deaths from breast cancer	2		2			
	Nodal status						
	Positive	18	10				
	Negative	56	52				
	Detection method	NA					
Exemestane							
NCIC Clinical Trials Group Mammary Prevention 3 (3-year follow-up)[9]							
	Study subjects	4,560		2,275		2,285	
	Invasive breast cancer	32	11	27	7	5	4
	Deaths from breast cancer	0	1				
	Nodal status						
	Positive	9	3				
	Negative	22	7				
	Detection method	NA					
Anastrozole							
International Breast Cancer Intervention Study (IBIS-II) (5-year follow-up)[8]							
	Study subjects	3,864		1,920		1,944	
	Invasive breast cancer	64	32	47	20	14	11
	Deaths from breast cancer	0	2				
	Nodal status						
	Positive	16	12				
	Negative	44	18				
	Detection method	NA					

NA = data not available.

had not unduly inflated the results. However, the data came from only 4 years of follow-up[26], and it would be useful to have data for the palpability of incident cancers reported in the long-term follow-up from 2005. Contrary to the 1998 report, the long-term follow-up identified a higher reduction in node-negative breast cancers and more breast cancer deaths in subjects assigned to tamoxifen than to placebo (12 vs. 11)[2].

The remaining trials have published no information about the palpability or detection method

of incident cancers. All trials (except the raloxifene trials) reported on the nodal status of incident breast cancers and show a reduction of both node-positive and node-negative breast cancers with the chemoprevention agent, but in all trials except one[4], the reduction was more profound for the node-negative cancers[1,2,8,9]. Based on the data reported so far, the evidence that overdiagnosis might explain the discordance between cancer incidence ratios and cancer mortality ratios in the breast cancer prevention studies is insufficient—but overdiagnosis might still be a contributing factor. Unfortunately, the trials do not have adequate power to detect a small reduction in mortality (20% for example). However, this issue appears to be of increasing relevance, and we would be grateful if the authors of future study reports would provide data concerning the mammography detection and palpability of incident cancers in addition to ER status and nodal status. It is commendable to prevent the occurrence of breast cancer, but ultimately, the greatest value of tamoxifen chemoprevention will come from its ability to prevent deaths from breast cancer.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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