Research Article

Cancer Epidemiology, Biomarkers & Prevention

Overdiagnosis in Mammographic Screening because of Competing Risk of Death

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Abstract

Background: Different definitions and estimates of overdiagnosis in mammographic screening reflect a substantial need to investigate and understand the complexity of the issue. This modeling study aims to estimate the number of overdiagnosed women, defined as those diagnosed with breast cancer who die from any cause within the lead-time period.

Methods: We used numbers from incidence and death statistics available online and published estimates of lead-time. Postulated cohorts of screened and not screened women ages 50 to 51 were followed for a period corresponding to 10 biennial screening exams during 20 years, and a further 10 years, to ages 78 to 79. The increase in breast cancer incidence because of screening was estimated based on lead-time. The proportion of women diagnosed with breast cancer who died within the lead-time period was assessed based on the differences in the cumulative number of breast cancer diagnosed in a nonscreened and screened cohort.

Results: The proportion of inevitable overdiagnosed women in a screened versus nonscreened cohort was 1.9% for England and Wales and 1.8% for Norway. Sensitivity analyses using various assumptions increased the estimates up to a maximum of 4%.

Conclusion: The proportion of women with breast cancer diagnosed after participation in a screening program who died within the estimated lead-time period was less than 4%. This inevitable proportion of overdiagnosis should be emphasized in the definition and communication of the issue.

Impact: The issue of overdiagnosis is complex and estimates should be interpreted with substantial care. *Cancer Epidemiol Biomarkers Prev; 25(5); 759–65. ©2016 AACR.*

Introduction

The reported estimates of overdiagnosis in mammographic screening vary from 0% to 75% (1, 2). Different study designs, age groups included, follow-up time, comparison groups, inclusion of ductal carcinoma *in situ* (DCIS), time span, choice of estimator, and adjustments for lead-time are examples of reasons for the varying estimates (1, 3–10).

As researchers in mammographic screening we have struggled with the issue of overdiagnosis for many years. However, we have realized that the vast majority of the definitions of this dispute include a time aspect related to death. Overdiagnosis can be divided into two components based on the time at which death occurs among women diagnosed with breast cancer; women dying from all causes within the period corresponding to the lead-time, and women dying after the estimated lead-time. Lead-time is defined as the time from detection of preclinical breast cancer by screening to detection of clinical cancer in the absence of screening. The first component is related to potentially progressive preclinical breast cancer. Such cancers are destined to cause symptoms and thus defined to have finite lead-time. Woman diagnosed with first scenario breast cancer is expected to die of other causes before the cancer would have given rise to clinical symptoms, within the lead-time period. The second component assumingly relates to slow- or nonprogressive preclinical cancer that never would have resulted in symptoms or death. The latter is an extreme form of length bias where the lead-time, in theory, is infinitive.

One of the main challenges when estimating overdiagnosis is how to take the lead-time into account. Most studies have used estimates of mean lead-time based on models that assume all preclinical cancers to be progressive. This assumption could potentially yield a large bias (11). Separating the two components is thus essential in the estimation of overdiagnosis. As far as we know, only one study including such a separation has been published (12). That study used the sojourn time to separate the estimated incidence of overdiagnosis into potentially progressive and less or no progressive tumors by applying Markov Chain Monte Carlo estimation on data from two randomized controlled trials. Sojourn time is defined as the time between the point at which a lesion can be found by screening until it is clinically detectable (13). The study concluded that progressive tumors dominated the overdiagnosed cases and only a small fraction consisted of tumors with infinite length bias and thus less or no potential to progress (12).

In principle, all screening programs will detect breast cancer among women who die of other causes in the near future since there exist competing risk of death among women targeted by screening. Although the all-cause mortality rates are low, it is inevitable. In this study, we focus on the first component of overdiagnosis in mammographic screening by using a modeling approach. We aimed to estimate the number of women diagnosed with breast cancer who died within the estimated lead-time period caused by screening.

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Materials and Methods

We postulated a cohort of 100,000 women ages 50 until age 79 according to death statistics. We used numbers from national statistics from England and Wales (14) and Norway (15). From the interim life tables, we found that the yearly decrement of death in the period 2008 to 2010 increased from 2.3 per 1,000 at age 50 to 38.2 per 1,000 at age 79 in England and Wales (14) and from 1.9 per 1,000 to 34.0 per 1,000 in 2010 to 2012 among Norwegian women (15). Yearly decrement was defined as the all-cause mortality rate between age x and $(x + 1)$, which is the probability that a woman at age x will die before reaching age $(x + 1)$. The expected remaining lifetime, the number of years the woman will live thereafter, decreased from 34 years at age 50 to 17 years at age 69 in both England and Wales (14) and in Norway (15). Based on these numbers, women 50 to 69 years are expected to live until age 85. The majority would thus live beyond any realistic lead-time period (9, 16).

Nonscreened cohort

The incidence rates of invasive breast cancer in England and Wales (late 1980s) were adapted from Duffy and Parmar (3). The rate increased from 158.4 per 100,000 women years at age 50 to 272.7 per 100,000 at age 79. Data from Norway was adapted from the Cancer Registry of Norway. The smoothed incidence rate (three-year moving average) of invasive breast cancer increased from 114.1 per 100,000 at age 50 to 234.5 per 100,000 women years at age 79 in 1980 to 1984. The reference incidence was consciously chosen from periods not influenced by opportunistic or organized screening.

Screened cohort

We assumed biennial mammographic screening for women ages 50 to 69 years, following the recommendation of 10 screening rounds. Furthermore, we calculated the proportion of breast cancer diagnoses advanced by screening according to the formulae given by Duffy and Parmar (3), which assume an exponentially distributed lead-time. We applied the rate of progressive cancers as exponential distributed with λ equal to 0.34 as given by Duffy and colleagues (12). These figures correspond to an average lead-time of 3.2 years, ranging from 1 to 10 years (Table 1).

Table 1. Proportion of the breast cancer advanced to the year of screening by year at which the diagnosis would have taken place in the absence of screening

Years after screen	Average lead-time of 3.2 years ($\lambda = 0.34$)	Average lead-time of 4.7 years ($\lambda = 0.22$)
1	85%	90%
2	60%	71%
3	43%	58%
4	31%	47%
5	22%	38%
6	16%	30%
7	12%	25%
8	9%	20%
9	7%	16%
10	5%	14%
11		11%
12		10%
13		8%
14		7%
15		6%

NOTE: λ is the instantaneous rate in the exponential distribution of transition time from progressive preclinical screen-detectable breast cancer to symptomatic disease.

Analysis

We followed two cohorts of women, 50 and 51 years old, for a period corresponding to 10 biennial screening exams during 20 years, and a further 10 years after screening, to 78 and 79 years old. We compared the cumulative number of women diagnosed with breast cancer in the nonscreened and screened cohort and applied the decrement mortality to estimate the proportion of women diagnosed with breast cancer who died within the estimated lead-time period (first component). We called this measure the inevitable proportion of overdiagnosed women. Calculations were made for England and Wales and for Norway, separately. Sensitivity analyses were performed to study the influence of the yearly decrement in mortality, the lead-time distribution, and the incidence of DCIS and/or breast cancer in the prescreening period.

This is a modeling study and thus no ethical approval or consent was required. Microsoft Excel was used for calculations.

Results

The estimated number of breast cancers diagnosed in a postulated cohort of 100,000 women 50 years old, screened prevalently at age 50 to 51 and screened subsequently at age 52 to 68 and 53 to 69, and followed for a further 10 years in England and Wales is given in Table 2 and Supplementary Table S1. In the absence of screening, the number of women diagnosed with breast cancer was calculated as the breast cancer incidence multiplied by the decremented population. In the screened 50-year old cohort (upper diagonal in Supplementary Table S1), the number of women with breast cancer was affected by lead-time, that is, the number of diseased women aged 50 was calculated as $158 + 0.85 \times 162 + 0.60 \times 165 + \ldots + 0.05 \times 196 = 650$; and for women aged 51 the number was calculated as $(1 - 0.85) \times 162 = 25$. For the subsequent screening exams, we multiplied the lead-time coefficient with the remaining number of breast cancer cases. For women aged 52, the number was 448 $[(1 - 0.60) \times 165 + (1 - 0.43) \times 169 \times 0.85 + \ldots + 0.05 \times 206]$. For those aged 53, the number was 15 $[(1 - 0.85) \times (1 - 0.43) \times 169]$. Similar calculation was performed for the screened 51-year-old cohort (lower diagonal in Supplementary Table S1). The effect of the biennial screening interval is clearly visible in the fluctuating number of breast cancers diagnosed during the age range 50 to 69 in the screened cohort. The cumulative number of women with breast cancer observed during the 30 years period was equal in the nonscreened and screened cohort, but the internal distribution differed. Because of lead-time, there are more women at risk of dying after a diagnosis of breast cancer in the screened compared with the nonscreened cohort. Applying the mortality rates yields an excess of 223 deaths among women with breast cancer in the screened cohort (Table 2). The inevitable proportion of overdiagnosed women in the screened versus nonscreened cohort was thus 1.9% (223/11,474) for England and Wales.

We used the same approach for Norway (Table 3 and Supplementary Table S2). The prescreening incidence of breast cancer was somewhat lower for Norway compared to England and Wales. The age slope was about the same for both populations. The mortality decrement had the same curve in Norway as in England and Wales, but on a slightly lower level in Norway. The inevitable proportion of over-diagnosed women because of implementation of organized mammographic screening in a Norwegian setting was estimated to be 1.8% (160/8,993).

Table 2. Breast cancer cases in the screened and nonscreened cohort, and the inevitable proportion of overdiagnosis in England and Wales

Age, years	Mortality rate 2008–2010 (per 1000)[14]	Population (*n*)	Breast cancer incidence (per 100,000 women-years)[3]	Breast cancer, population (*n*)	Breast cancer, screened cohort (n)	Breast cancer, nonscreened cohort (*n*)	Cumulative no of breast cancer, screened cohort (*n*)	Cumulative no of breast cancer, nonscreened cohort (*n*)	Difference in the cumulative no of the screened and nonscreened cohort (*n*)	Mortality (*n*)	Over-diagnosis (%)
50	2.3	100,000	158.4	158	650	158	650	158	491	1.1	
51	2.4	99,768	162.2	162	688	324	1,337	482	855	2.1	
52	2.8	99,525	166.0	165	473	330	1,810	812	997	2.7	
53	3.0	99,251	169.8	169	471	337	2,281	1,150	1,132	3.3	
54	3.4	98,959	173.5	172	414	343	2,695	1,493	1,202	4.1	
55	3.5	98,622	177.3	175	419	350	3,114	1,843	1,271	4.5	
56	3.9	98,272	181.0	178	399	356	3,513	2,198	1,315	5.1	
57	4.2	97,892	184.8	181	406	362	3,919	2,560	1,359	5.7	
58	4.6	97,482	191.0	186	402	372	4,321	2,933	1,389	6.3	
59	5.1	97,037	197.2	191	408	383	4,729	3,315	1,414	7.2	
60	5.5	96,545	203.3	196	411	393	5,141	3,708	1,433	7.8	
61	6.0	96,019	209.5	201	415	402	5,556	4,110	1,446	8.6	
62	6.3	95,446	215.7	206	418	412	5,974	4,522	1,452	9.2	
63	7.0	94,843	218.1	207	420	414	6,394	4,936	1,459	10.3	
64	7.8	94,176	220.5	208	422	415	6,816	5,351	1,465	11.4	
65	8.4	93,441	222.9	208	424	417	7,240	5,767	1,472	12.4	
66	9.3	92,653	225.3	209	426	417	7,665	6,185	1,481	13.8	
67	10.1	91,792	227.7	209	427	418	8,093	6,603	1,490	15.0	
68	11.3	90,867	232.7	211	428	423	8,521	7,026	1,495	16.9	
69	12.5	89,837	237.7	214	428	427	8,948	7,453	1,495	18.7	
70	14.1	88,714	242.7	215	55	431	9,003	7,884	1,119	15.7	
71	15.2	87,466	247.7	217	122	433	9,125	8,317	808	12.3	
72	16.8	86,138	252.7	218	188	435	9,313	8,752	561	9.4	
73	19.0	84,694	255.6	216	247	433	9,560	9,185	375	7.1	
74	21.3	83,083	258.4	215	293	429	9,853	9,615	239	5.1	
75	23.4	81,312	261.3	212	329	425	10,182	10,040	142	3.3	
76	26.7	79,411	264.1	210	354	419	10,536	10,459	77	2.0	
77	29.7	77,294	267.0	206	371	413	10,906	10,872	35	1.0	
78	33.7	74,996	269.9	202	381	405	11,287	11,277	10	0.4	
79	38.2	72,468	272.7	198	187	198	11,474	11,474	0	0.0	
										222.7	1.9

Table 3. Breast cancer cases in the screened and nonscreened cohort, and the inevitable proportion of overdiagnosis in Norway

Age, years	Mortality rate 2010–2012 (per 1000)[15]	Population (*n*)	Breast cancer incidence (per 100,000 women-years)	Breast cancer, population (*n*)	Breast cancer, screened cohort (*n*)	Breast cancer, nonscreened cohort (*n*)	Cumulative no of breast cancer, screened cohort (*n*)	Cumulative no of breast cancer, nonscreened cohort (*n*)	Difference in the cumulative no of the screened and nonscreened cohort (*n*)	Mortality (*n*)	Over-diagnosis (%)
50	1.9	100,000	114.1	114	458	114	458	114	344	0.6	
51	2.2	99,814	114.5	114	481	229	939	343	596	1.3	
52	2.1	99,597	115.7	115	331	230	1,270	573	696	1.5	
53	2.4	99,388	117.7	117	330	234	1,600	807	793	1.9	
54	2.9	99,148	117.4	116	292	233	1,892	1,040	852	2.5	
55	3.0	98,856	121.6	120	299	241	2,191	1,280	910	2.8	
56	3.5	98,556	127.0	125	288	250	2,479	1,531	948	3.3	
57	3.8	98,210	134.4	132	294	264	2,773	1,795	978	3.7	
58	3.8	97,836	135.9	133	293	266	3,066	2,061	1,006	3.8	
59	4.3	97,464	140.4	137	300	274	3,366	2,334	1,032	4.5	
60	5.1	97,041	144.4	140	306	280	3,673	2,614	1,058	5.4	
61	5.1	96,550	151.1	146	314	292	3,987	2,906	1,080	5.5	
62	6.0	96,055	153.3	147	321	295	4,308	3,201	1,107	6.6	
63	6.1	95,479	155.2	148	330	296	4,638	3,497	1,140	6.9	
64	7.1	94,901	159.0	151	339	302	4,976	3,799	1,177	8.3	
65	7.8	94,230	167.6	158	348	316	5,324	4,115	1,209	9.4	
66	8.1	93,496	175.0	164	355	327	5,679	4,442	1,237	10.0	
67	9.4	92,742	182.6	169	361	339	6,040	4,781	1,259	11.8	
68	10.6	91,874	187.5	172	366	345	6,406	5,125	1,281	13.6	
69	10.5	90,901	197.4	179	369	359	6,775	5,484	1,291	13.6	
70	11.6	89,943	204.8	184	47	368	6,822	5,853	969	11.3	
71	13.1	88,898	212.7	189	106	378	6,928	6,231	698	9.2	
72	15.1	87,730	210.8	185	160	370	7,088	6,601	488	7.4	
73	16.8	86,406	213.5	184	210	369	7,299	6,970	329	5.5	
74	18.4	84,956	216.4	184	251	368	7,550	7,337	212	3.9	
75	21.0	83,397	226.0	188	292	377	7,841	7,714	127	2.7	
76	23.7	81,645	228.8	187	315	374	8,156	8,088	69	1.6	
77	25.8	79,712	232.6	185	333	371	8,490	8,459	31	0.8	
78	29.7	77,652	230.5	179	336	358	8,826	8,817	9	0.3	
79	34.0	75,345	234.5	177	167	177	8,993	8,993	0	0.0	
										159.6	1.8

Sensitivity analyses

We applied mortality statistics from the prescreening period to study the influence of the yearly decrement in mortality. For England and Wales, the mortality rates increased from 3.3 to 58.5 per 1,000 for age 50 to 79 in the prescreening period 1985 to 87. Using these numbers resulted in a 3.2% inevitable overdiagnosis (Supplementary Table S3). For Norway, the mortality rates increased from 3.0 to 55.6 per 1,000 for women 50 to 79 years in the prescreening period 1980 to 1984, which resulted in 2.6% inevitable overdiagnosis (Supplementary Table S4).

To study the influence of the lead-time distribution we applied an additional distribution with more years affected (range 1–15; Table 1). This has an average lead-time of 4.7 years ($\lambda = 0.22$), instead of an average of 3.2 years (range 1—10). We were thus able to follow the women until age 84 (within the expected life-time for women aged 50 years). Then the proportion of cancers advanced was 90% for year 1, 71% for year 2, . . ., 6% for year 15 (Table 1). This approach increased the inevitable overdiagnosis estimates to 4.0% for England and Wales (Supplementary Table S5) and to 3.7% for Norway (Supplementary Table S6).

Three different settings were used to study the influence of a rise in the prescreening incidence of DCIS and/or invasive breast cancer. The settings were (1) a fixed increase in incidence of 20% for women aged 50–79 years; (2) an 1% absolute increase for each year of age, starting with a 1% increase in women aged 50, ending up at 30% increase among women aged 79; and (3) 1% absolute decrease for each year of age, starting with a 30% increase in women aged 50 and ending up at 1% increase among women aged 79. The proportion of inevitable overdiagnosis was similar for all of the three settings and the same as the prescreening incidence in England and Wales (1.9%; Supplementary Table S7), and in Norway (data not shown).

Discussion

In this modeling study, 2% to 4% of women diagnosed with breast cancer in a population offered mammographic screening are dying from any cause within the estimated lead-time.

There are at least three factors to consider when estimating the inevitable proportion of overdiagnosed women in this study: the death rates, the lead-time, and the incidence of breast cancer.

First, we used the observed rates of all-cause mortality in England and Wales and in Norway to estimate the competing risk of death. If the rate increases, the inevitable proportion of overdiagnosed women increases and vice versa. The death rates are relatively stable in developed countries, but small differences, as shown for England and Wales and for Norway are of substantial influence for the estimate. The shape of the death curve by age is also of influence for the estimates. In this study, a steep curve indicates a higher mortality among the elderly and thus a higher inevitable proportion of overdiagnosed women among the elderly. The curve is steeper for England and Wales compared to Norway, which partly explain the different outcome for the two places.

Second, the assumption of the lead-time distribution highly influences the results. We based our estimations on the exponential distribution of lead-time given by Duffy and Parmar (3), which presents mathematical details in the calculation of probabilities of cancers shifted by screening. We assumed that lead-time is only related to progressive cancers, thus the instantaneous rate of transition to symptomatic disease was changed to $\lambda = 0.34$ instead of 0.30 (12). However, considerable development of screening equipment, from screen film to full-field digital mammography and further to tomosynthesis has taken place during the last decades, resulting in an increased rate of screen-detected cancer (17–19). The increase is assumingly because of longer lead-time. To quantitatively investigate this bias, we applied an average lead-time of 4.7 years ($\lambda = 0.22$), yielding a two-fold increase of first component overdiagnosed women.

Third, a constant increase in the age-specific prescreening incidence did not influence our estimate of inevitable overdiagnosis. Adding a fixed proportion of DCIS to the incidence did not influence the estimate of the first component of overdiagnosis. Similarly, the inevitable overdiagnosis estimate changed marginally for an age dependent increase. The yearly decrement in death and the lead-time distribution are thus the main contributors in this estimate.

Several assumptions were included in our estimations. Biennial mammographic screening in women ages 50 to 69 years was the basis, which is shown to reduce mortality from breast cancer (20). Furthermore, we assumed an attendance rate of 100%, which probably overestimate the outcome of interest. Compliance in the Norwegian screening program is 84%, which gives a 16% reduction in the estimate (1.5% instead of 1.8%). In addition, the estimates are valid for England and Wales and for Norway. No generalization is thus possible. In particular, the breast-screening program in England and Wales invites the women every 3 years and has now expanded the target age range to cover 47 to 73 years (21).

The strength of the study was using a fixed lead-time distribution to study the impact of organized screening exclusively. The impact of opportunistic screening was evaded by using reference incidences from the period before opportunistic screening was available (1980s). Furthermore, the estimates are based on easy available numbers and numbers from previous published papers. The estimations are explained in detail in the text, which makes the results transparent and easily approvable.

Our estimate is in contrast with the result given by Duffy and colleagues (12). They separated the estimate into potentially progressive and less or no progressive tumors using the sojourn time and concluded that progressive tumors dominated. However, both studies state that the absolute risk of death from other causes in the near future after a diagnosis of breast cancer is a minor phenomenon.

Focusing only on the competing risk of death during the estimated lead-time period (first component of overdiagnosis) represents a limitation of this modeling study. The second component is related to women diagnosed with breast cancer and die from any cause after the estimated lead-time period has passed (i.e., maximum 10 years). These women might be diagnosed with slow- or nonprogressive breast cancer and might thus went through treatment as a result of a breast cancer diagnosis that did not prolong their life. However, we are not able to separate women with an incessant slow- or nonprogressive tumor from tumors with potential to change their growing pattern. The screening might thus save lives by detecting and treating these women for breast cancer in an early stage and it is well known that early diagnosis allows for effective and less toxic treatment with reduced mortality compared with symptomatic breast cancer (22). Hypothetically, a woman with a screen-detected early stage slow growing tumor is treated at age 50 and die at age 85 of other causes. She might be overtreated (i.e., second component), but she might also be saved from breast cancer death because of early diagnosis and treatment. Another woman had the same tumor, but do not attend screening. When she turns 62, she is diagnosed with a late-stage symptomatic cancer and die 3 years later. She got her breast cancer diagnosis 12 years later compared with the first women, but the breast cancer killed her at age 65. Continuous diagnostics and research on these early breast cancer cases is thus of utmost importance to get knowledge and making us able to tailor the treatment. Furthermore, follow-up time after the estimated lead-time period has passed is important to get knowledge about the progression rate and to estimate the percentage of breast cancers that never will cause symptoms or death. Optimally, a cohort of screened women along with an accompanied unscreened cohort should be followed until death, that is use of observational data. Such data are not available of today. To estimate a precise extent of the second component is impossible, because of reasons described above. To get a view about the extent of the second component, estimates of the overall rate of overdiagnosis could be considered. The Independent UK Panel on Breast Cancer Screening (23) estimated the proportion of overdiagnosis to be 10.7% in randomized controlled trials. Observational studies using a compensatory drop represent an appropriate method for estimating the proportion of overdiagnosis (1). Two of the studies included in the review by Puliti and colleagues (1) were from England and Wales, showing a proportion of overdiagnosed invasive cancers among invited women of 10% (24) and 2.3% (25). The latter was recalculated to 3.3% (1). A recent study from Norway showed a proportion of 10% to 11% for the same group of women (5). Using these numbers yield an average of 8% [(10 + 3.3 + 10.5)/3] overdiagnosis. This number represents both the first and second component. Our estimate for the first component was approximately 2%. Subtracting our estimate for the first component leave 6% (8–2%) for the second. It means that 75% (6%/8%) of the overdiagnosed women have a lead-time longer than 3 years on average. Applying a lead-time of 4.7 years on average yields 50% [(8–4%)/8%] of the estimate in the second component. These rough estimates indicate that the major contribution of overdiagnosis is from slow- and nonprogressing tumors. However, our estimates are based on lead-time estimated from tumors detected in the 1970s to 1990s (3). More recent studies and newer technologies indicate a longer lead-time (16). The proportion of women overdiagnosis within the first component might be underestimated in our study. However, we need information about prognostic and predictive characteristics and other biological markers of the tumor to understand this complex issue of overdiagnosis. Such knowledge could help to differentiate the non-progressive from the progressive tumors, and thus make us able to identify the most efficient treatment.

In conclusion, a small proportion of women diagnosed with breast cancer died within a time-period corresponding to the lead-time caused by mammographic screening. The inevitable proportion of overdiagnosis ranged from 2% to 4%. We consider the disadvantage of this component of overdiagnosis negligible when weighted against the mortality reduction because of mammographic screening.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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Authors' Contributions

Conception and design: R.S. Falk, S. Hofvind
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R.S. Falk
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R.S. Falk, S. Hofvind
Writing, review, and/or revision of the manuscript: R.S. Falk, S. Hofvind
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): R.S. Falk, S. Hofvind
Study supervision: S. Hofvind

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