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Article type : Original Article

Manuscript Title: Breast Cancer Deaths Averted Over Three Decades

Running Title: Breast Cancer Deaths Averted Over 3 Decades

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Text pages Including title page, text, references and figure captions: 16

Tables: 3

Figures: 4

Funding: No specific funding source

Precis: Since the mid-1980s, mammography screening has become widespread in the U.S., currently screening about half of U.S. women either annually or biennially. Since 1989, between 384,000 and 614,500 breast cancer deaths have been averted by mammography screening and improved breast cancer treatment.

Conflicts of Interest: Dr. Hendrick has been a paid consultant for GE Healthcare for work performed outside of the current study. Dr. Helvie was supported by institutional grants from GE Healthcare and IBM Watson for work performed outside of the current study.

Abstract (247 words)

Background

From 1975 to 1990, female breast cancer mortality rates in the United States increased by 0.4% per year. Since 1990, breast cancer mortality rates have fallen between 1.8% and 3.3% per year, attributed to increased mammography screening and improved treatment.

Methods

We use age-adjusted SEER female breast cancer mortality rate and population data to estimate the number of breast cancer deaths averted by screening mammography and improved treatment since 1989. Four different assumptions about background mortality rates (in the absence of screening mammography and improved treatment) are used to estimate deaths averted for women ages 40-84 years by taking the difference between SEER-reported mortality rates and background mortality rates for each 5-year age group, multiplied by the population for each 5-year age group. We use SEER data to estimate annual and cumulative breast cancer deaths averted in 2012 and 2015 and extrapolated SEER data to estimate deaths averted in 2018.

Results

Single-year breast cancer deaths averted range from 20,860 to 33,842 in 2012, from 23,703 to 39,415 in 2015, and from 27,083 to 45,726 in 2018. Breast cancer mortality reduction ranges from 38.6% to 50.5% in 2012, from 41.5% to 54.2% in 2015, and from 45.3% to 58.3% in 2018. Cumulative breast cancer deaths averted since 1989 range from 237,234 to 370,402 in 2012, from 305,934 to 483,435 in 2015, and from 384,046 to 614,484 in 2018.

Conclusion

Between 384,000 and 614,500 breast cancer deaths have been averted by mammography screening and improved treatment since 1989.

Key Words: Breast cancer, female, screening mammography, mortality rate, treatment, therapy, United States

Author Contributions: R. Edward Hendrick: Conceptualization, methodology, data curation, formal analysis, software, writing - original draft, review and editing. Jay A. Baker: Conceptualization, methodology, writing - review and editing. Mark A. Helvie: Conceptualization, methodology, writing - review and editing.

Introduction

Since 1969, the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results Program (SEER) has collected breast cancer incidence and mortality data for the United States.[1] The most recent data extend to 2015. Analysis by the NCI indicates that breast cancer mortality rates for U.S. females of all ages increased by a statistically significant 0.4% per year from 1975 to 1990.[2] Mortality rates then decreased by a statistically significant 1.8% per year from 1990 to 1995, 3.3% per year from 1995 to 1998, and 1.8% per year from 1998 to 2015.[2] From 1989 to 2015, age-adjusted female breast cancer mortality rates among women ages 40-84 years have decreased by 41.6% (**Figure 1**).[3] This decrease has been attributed to increased use of screening mammography combined with improved breast cancer treatment.[4-6]

Screening mammography became widely available in the mid-1980s and its use increased until the early 2000s.[4-7] According to self-reported data collected in the Center for Disease Control's National Health Interview Survey,[7] in 1987 29% of women over 40 years of age reported having mammography in the previous 24 months. This figure rose to 70% in 2000, then dropped to 64% in 2015. The National Health Interview Survey overestimates screening mammography use for 2 reasons: i) it does not distinguish between screening and diagnostic mammography. According to U.S. Breast Cancer Surveillance consortium data collected between 1994 and 2009, 17% of mammography exams were performed for reasons other than screening.[8] ii) According to Cronin et al,[9] self-reported mammography use in the previous 2 years overestimated screening mammography use in that period by 14-27%. Adjusting for such factors, Berry et al estimated that when screening mammography use was at its peak in the year 2000, approximately 25% of U.S. women over age 40 years received annual screening mammography, another 25% received biennial screening mammography, and the remaining 50% had irregular screening or no screening at all.[4]

The Cancer Intervention and Surveillance Modeling Network (CISNET), a consortium of NCI-sponsored investigators, has attempted to use models of breast cancer incidence and mortality, along with mammography screening and treatment trends, to separate the effects of screening mammography and adjuvant therapy on the reduction in breast cancer deaths.[4-6] Their models estimated that screening mammography was responsible for 28% to 65% of the reduction in breast cancer deaths in the year 2000, with a median estimate of 46%, the remainder due to advances in treatment.[4] These estimates assumed that nearly all women diagnosed with breast cancer underwent treatment, but only about half of women ages 40 years and over underwent screening mammography annually or biennially.[4,5] Based on two CISNET models, Munoz et al estimated that in the year 2000, with 100% compliance to screening mammography, screening would be responsible for 69% to 74% of breast cancer deaths averted.[6] A 2018 CISNET update by Plevritis et al, based on an assumed 50-55% compliance rate with either annual or biennial screening mammography, estimated that in 2012 screening mammography was responsible for 37% of the estimated mortality reduction (range over 6 models: 26% to 51%).[5] Clearly, the relative contribution of screening to mortality reduction estimates depends strongly on assumed screening mammography (and treatment) compliance rates.

DeSantis et al estimated the number of female breast cancer deaths averted because of screening and improved treatment from 1989 to 2012 at 249,000, based on the assumption that, absent increased screening or improved treatment, the death rate would have remained at 1989 levels.[10] While this assumption is the simplest in assessing changes since 1989, it ignores the steadily increasing background mortality trends prior to 1989. Just as estimates of overdiagnosis over the past three decades are highly sensitive to assumptions of background breast cancer incidence rates,[11,12] estimates of breast cancer deaths averted since 1989 are similarly sensitive to assumptions about breast cancer mortality rates in the absence of screening mammography and improved treatment, referred to here as background mortality rates.

The goal of this paper is to estimate the number of breast cancer deaths averted since 1989 due to the collective effects of both screening mammography and improved treatment. Our analysis extends estimates of DeSantis et al by using several different methods to estimate background breast cancer mortality rates, including methods based on mortality rate trends prior to 1989. We also estimate percent mortality reductions for U.S. women overall and by 5-year age groups. Our analysis does not attempt to estimate the separate contributions of mammography screening and adjuvant treatment to breast cancer deaths averted.

Methods

All data used in this analysis are anonymized, publicly available data and, hence, required no institutional review board approval. Breast cancer deaths averted in U.S. women since 1989 were estimated by using age-specific 5-year breast cancer mortality data and female population data for U.S. women 40 to 84 years of age. Female age-adjusted breast cancer mortality rates (**Figure 2**) and population data for each 5-year age group are available from 1969 to 2015 from the latest SEER database mortality tables (SEER*Stat Software, Version 8.3.5).[3] For the years 2016-2018, a linear least squares fit to breast cancer mortality rates from the previous 10 years, 2006-2015, was used to extrapolate mortality rates for 3 additional years, 2016-18, for each 5-year age group. Analysis of residuals was performed to establish that linear fits were appropriate. Extrapolated mortality rates are included as the last 3 data points for each age group in **Figure 2**. Female population data for 2016 for each 5-year age group ages 40-84 years were taken from U.S. Census estimates as of July 1, 2016,[13] and for 2017 and 2018 from U.S. female population estimates by age.[14]

Four different methods were used to estimate background female breast cancer mortality rates from 1990-2018:

1) following DeSantis et al.[10], background mortality rates were assumed to be flat since 1989. This simple assumption assesses change since 1989, when breast cancer mortality rates were at their peak, but ignores background mortality rate trends prior to 1989. Prior to 1989, background mortality rates increased overall, likely due to preceding increases in breast cancer incidence rates. The 3 assumptions below attempt to account for those increasing background mortality trends, although in different ways.

2) background mortality rates after 1989 were assumed to continue their previously steady 0.4% per year increase that was observed from 1975 to 1990, based on joinpoint analysis by Noone et al.[2] Extrapolation of joinpoint trends to estimate mortality rates has precedent in peer-reviewed literature.[15,16]

3) background mortality rates after 1989 were estimated for each 5-year age group using the change in mortality rates for that age group prior to 1990. Specifically, for each 5-year age group from ages 40-84 years, the trend over the previous 11 years, 1979-1989, was determined by a best linear fit to SEER mortality rate data and the resulting background trend was assumed to persist from 1990 to 2012, 2015, and 2018.[15,16]

4) following Cronin et al,[17] which used seven CISNET models to estimate background mortality rates in the absence of screening or treatment, we assumed that background mortality rates increased by 0.94% per year since 1989. Their seven models estimated that between 1975 and 2000, in the absence of screening or treatment, breast cancer mortality rates would have increased by a mean of 12.7 deaths per 100,000 women (median: 14.7, range 5.6-15.9, per 100,000 women) compared to a 1975 breast cancer mortality rate of 48.2 per 100,000 women. Their mean background mortality rate estimate was

an increase of 26.2% over 25 years or 0.94% per year. We extrapolated this result to extend to 2012, 2015 and 2018.

Figure 3 illustrates these four different background mortality rate assumptions for one 5-year age group, women ages 65-69 years. For each of these four methods, we assumed that the background mortality rate change continued from 1989 to different end dates of 2012, 2015, and 2018. Estimates for 2012 and 2015 are based entirely on SEER breast cancer mortality rate and population data. Estimates for 2018 are based on extrapolations of SEER breast cancer mortality rates and census projections of U.S. female population data from 2016 to 2018.

Breast cancer deaths averted in a given year for each 5-year age group were determined by taking the difference between background mortality rates and measured rates for years 1990-2015 (or extrapolated rates for years 2016-18) per 100,000 women and multiplying by the U.S. female population that year (in 100,000s) in that 5-year age group. Breast cancer deaths averted in a given year were determined by summing over all 5-year age groups between ages 40 and 84 years. Cumulative breast cancer deaths averted since 1989 were determined by summing deaths averted in each year from 1990 to endpoints of 2012, 2015, and 2018.

Percent mortality reductions in 2012, 2015, and 2018 were determined by dividing the estimated breast cancer deaths averted in a given year by the total estimated breast cancer deaths without screening or improved treatment (the sum of known breast cancer deaths in a given year plus the estimated breast cancer deaths averted in that year) times 100%:

% Mortality Reduction = (BC Deaths Averted x 100%)/(Known BC Deaths + BC Deaths Averted)

Known breast cancer deaths each year for women ages 40-84 years were taken from the SEER mortality database up to 2015.[3] For the year 2018, breast cancer deaths in each 5-year age group were estimated by multiplying the linearly extrapolated breast cancer death rate for 2018 for each 5-year age group by the 2018 estimated female population for each 5-year age group.[13]

Results

Single-year breast cancer deaths averted in U.S. women ages 40-84 years by both mammography screening and improved treatment since 1989 are shown in **Table 1** for the years 2012, 2015, and 2018. In 2018, estimates range from 27,083 to 45,726 breast cancer deaths averted. Also shown in **Table 1** are percent mortality reductions for 2012, 2015, and 2018, based on SEER-reported breast cancer deaths specific to each of those 3 years. In 2018, percent mortality reduction estimates for women ages 40-84 years range from 45.3% to 58.3%.

Cumulative breast cancer deaths averted in U.S. women ages 40-84 years by both screening and improved treatment beginning in 1990 and ending in 2012, 2015, and 2018 are shown in **Table 2**. In 2018, estimates range from 384,046 to 614,484 breast cancer deaths averted. **Figure 4** illustrates estimated cumulative breast cancer deaths averted by year since 1989 for the four different assumptions about background breast cancer mortality trends. **Table 2** and **Figure 4** show that the assumption of a flat background since 1989 yields the lowest estimate of breast cancer deaths averted by screening and improved treatment. **Table 2** and **Figure 4** show roughly similar results for breast cancer deaths averted since 1989 based on a background trend of a 0.4% per year increase and a background trend based on individual 5-year age group mortality trends prior to 1990.

Table 3 shows percent mortality decreases for each 5-year age group and the entire age range of women ages 40-84 years based on our four different assumptions about expected background mortality in the absence of screening or advances in treatment. The first assumption of mortality rates being unchanged since 1989 represents the known mortality decrease since 1989 in 2012 and 2015, and the estimated decrease since 1989 in 2018.

Discussion

This study demonstrates that estimates of the number of breast cancer deaths averted due to screening and improved treatment depend strongly on specific assumptions about background mortality rate trends in the absence of screening and advances in treatment. For example, estimates of mortality reduction in 2015 range from 41.5% to 54.2% and estimates of breast cancer deaths averted in that single year range from 23,703 to 39,415 across our four different assumptions about background mortality rates. Likewise, cumulative breast cancer deaths averted from 1990 to 2015 range from over 305,000 women to over 483,000 women depending on background mortality assumptions. Extrapolating results to 2018 shows cumulative breast cancer deaths averted since 1989 range from over 384,000 to over 614,000.

Assuming that background mortality rates are flat in the absence of screening mammography and improved treatment since 1989 likely underestimates breast cancer deaths averted. This is because

U.S. breast cancer mortality rates, like breast cancer incidence rates, were increasing prior to 1990.[2] Background mortality rate estimates of methods 2 and 3 may also underestimate the background rate since modern treatment advances with adjuvant chemotherapy and hormonal therapy had already entered clinical practice in the 1980s.[4,5] Both treatments had likely begun to suppress mortality rates by 1989. The successful application of hormonal therapy and adjuvant chemotherapy in the 1980s likely began reducing mortality shortly after their introduction among women already diagnosed with breast cancer. Screening mammography, although entering widespread clinical practice in the mid-1980s, was shown by RCTs to require 5-7 years until mortality reduction was evident, due to the longer interval between screen detection and prevented death.[18]

Most other developed countries also had increasing breast cancer mortality rates prior to adoption of widespread screening mammography in the 1980s and '90s.[19] We believe the best estimates of breast cancer deaths averted are those that take into account these background increases. Thus, we estimate that over the last 3 decades, in excess of half a million breast cancer deaths have been averted by screening mammography and improved treatment.

CISNET modeling results reported in Plevritis et al estimated that in 2012, mortality reduction due to both mammography screening and advances in treatment for U.S. women ages 30-79 years was 49%.[5] Our estimate for mortality reduction in 2012 for women ages 40-84 years based on 5-year age group background trends is 45.6%, in reasonable agreement with Plevritis et al. If we assume the same 0.94%/year background mortality increase that was the mean estimate by CISNET models in Cronin et al,[17] our estimated mortality reduction in women ages 40-84 years in 2012 is 50.5%, in good agreement with the CISNET estimate for women ages 30-79 years. Our estimate of 237,234 deaths averted from 1990-2012 assuming a flat background is also in good agreement with the DeSantis et al estimate of 249,000 deaths averted during the same period.[10] The difference between these two estimates is that DeSantis et al estimated breast cancer deaths averted in U.S. women of all ages, while we restricted our estimate to women ages 40-84 years.

One limitation of this study is that SEER breast cancer incidence data do not specify whether a woman attended mammography screening within the year that her breast cancer was diagnosed. While almost all U.S. women diagnosed with breast cancer receive treatment, only about half of U.S. women over 40 years of age undergo either annual or biennial screening.[4,5,9] Thus, this analysis does not estimate breast cancer deaths averted from screening all age-eligible U.S. women, as other works have.[6,20] In addition, this analysis makes no attempt to estimate the separate contributions of screening versus advances in treatment, as others have.[4-6]

Another limitation of our study is that it estimates the number of breast cancer deaths averted and percent mortality reduction since 1989, not the full number of breast cancer deaths averted by screening mammography and treatment. While the onset of widespread screening mammography in the mid-1980s did not begin to affect breast cancer mortality rates until the early 1990s, treatment improvements such as tamoxifen and advances in surgical therapy were ongoing and averting breast cancer deaths prior to 1989.

We know from SEER mortality data and the estimates in this paper, however, that hundreds of thousands of women's lives – likely in excess of half a million by 2018 – have been saved by the use of screening mammography and new developments in breast cancer treatment since 1989.

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Figure Legends:

Figure 1: Age-adjusted U.S. breast cancer mortality rates (per 100,000) for women ages 40-84 years by year from 1969 to 2015. From SEER database.

Figure 2: Age-adjusted breast cancer mortality rates (per 100,000) by year for each 5-year age group of women ages 40-84 years. Rates for 2016-18 in each age group are linear extrapolations of mortality rate trends for that age group from 2006 to 2015.

Figure 3: SEER age-adjusted mortality rates (per 100,000) for women ages 65-69 years by year from 1975 to 2015 (blue data points). Dark red data points represent linear extrapolation of the mortality rate to 2016-18 based on the trend from 2006 to 2015. Solid lines represent the four different assumptions about background mortality rate trends since 1989: increasing by 0.94% per year since 1989 (blue), based on a linear fit to mortality rates from 1979 to 1989 (red), increasing by 0.4% per year (green), constant since 1989 (orange).

Figure 4: Cumulative breast cancer deaths averted for women ages 40-84 years under four different assumptions about background mortality rate trends since 1989.

Tables

Table 1: Single-year breast cancer deaths averted and percent mortality reduction in U.S. women ages 40-84 years

	Single-year Breast Cancer Deaths Averted, Women Ages 40-84 Years			
Deaths Averted % Mortality Reduction	Background Mortality Rate Flat Since 1989	Background Mortality Rate Increase 0.4%/yr Since 1989	5-year Age Group Background Mortality Rate Trends '79-'89	Background Mortality Rate Increase 0.94%/yr Since 1989
In 2012	20,860 38.6%	26,060 44.0%	27,801 45.6%	33,842 50.5%
In 2015	23,703 41.5%	29,943 47.3%	32,329 49.2%	39,415 54.2%
In 2018	27,083 45.3%	34,424 51.3%	37,769 53.6%	45,726 58.3%

Table 2: Cumulative breast cancer deaths averted in U.S. women ages 40-84 years since 1989

	Breast Cancer Deaths Averted, Women Ages 40-84 Years			
Year Range	Background Mortality Rate Flat Since 1989	Background Mortality Rate Increase 0.4%/yr Since 1989	5-year Age Group Background Mortality Rate Trends '79-'89	Background Mortality Rate Increase 0.94%/yr Since 1989
1990-2012	237,234	291,579	312,788	370,402
1990-2015	305,934	377,933	405,499	483,435
1990-2018	384,046	476,947	513,320	614,484

Table 3: Percent mortality reduction in 2012, 2015, and 2018 by 5-year age groups and ages 40-84 years based on four different assumptions about expected background mortality rates in the absence of screening and advances in treatment.

Age Range	Background Flat Since 1989			Background Increase 0.4%/yr Since 1989			Background with 5-year Age Group Trends			Background Increase 0.94%/yr Since 1989		
	2012	2015	2018*	2012	2015	2018*	2012	2015	2018*	2012	2015	2018*
40-44	47.0%	51.9%	52.7%	51.6%	56.7%	57.8%	44.5%	49.7%	50.3%	57.2%	62.3%	63.9%
45-49	43.9%	49.4%	53.0%	48.8%	54.4%	58.1%	42.9%	48.4%	52.0%	54.8%	60.4%	64.2%
50-54	46.4%	48.4%	50.9%	51.1%	53.5%	56.3%	36.2%	37.0%	38.6%	56.8%	59.5%	62.6%
55-59	43.6%	45.5%	51.5%	48.6%	50.9%	56.8%	40.6%	42.1%	48.0%	54.6%	57.3%	63.1%
60-64	41.5%	44.8%	50.2%	46.6%	50.3%	55.6%	52.8%	56.4%	61.4%	52.8%	56.7%	62.0%
65-69	38.3%	42.2%	45.3%	43.7%	47.9%	51.3%	46.3%	50.6%	54.1%	50.2%	54.7%	58.3%
70-74	35.6%	37.2%	40.1%	41.2%	43.4%	46.7%	51.7%	54.4%	57.8%	48.0%	50.7%	54.4%
75-79	30.4%	33.2%	37.1%	36.5%	39.8%	44.0%	46.2%	50.0%	54.3%	43.9%	47.6%	52.0%
80-84	22.5%	26.3%	30.8%	29.3%	33.6%	38.4%	39.7%	44.3%	49.1%	37.5%	42.2%	47.3%
40-84	38.6%	41.5%	45.3%	44.0%	47.3%	51.3%	45.6%	49.2%	53.6%	50.5%	54.2%	58.3%

*** Percent mortality decreases for 2016-18 are based on linear extrapolations of mortality rate trends from 2006 to 2015.**

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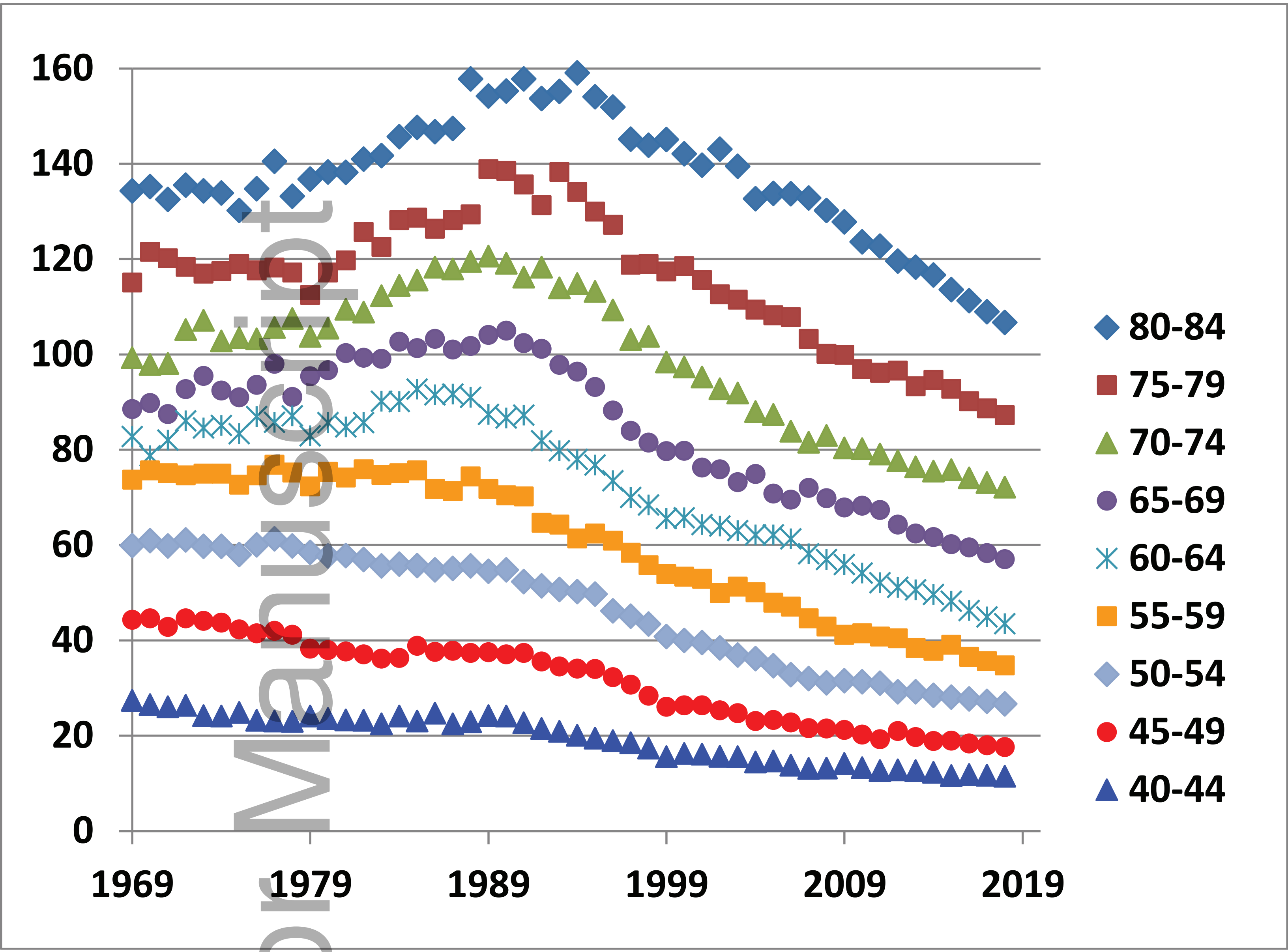

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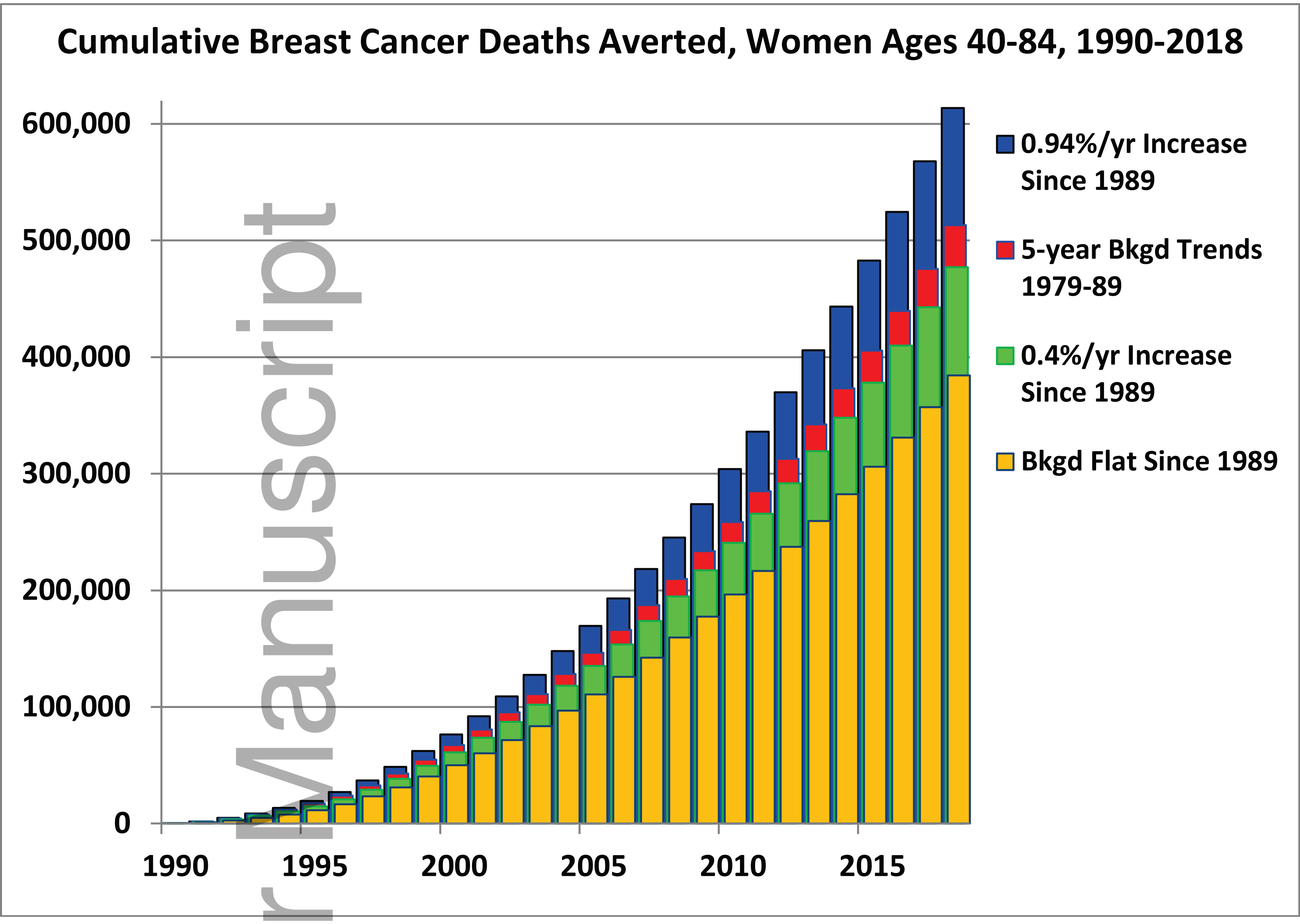

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