Costs and Benefits of Extended Endocrine Strategies for Premenopausal Breast Cancer

Janice S. Kwon, MD, MPH, FRCSC^a; Gary Pansegrau, MD, FRCPC^b; Melica Nourmoussavi, MD, FRCSC^c; Geoffrey L. Hammond, PhD^d; and Mark S. Carey, MD, FRCSC^a

Abstract

Background: After completing 5 years of adjuvant tamoxifen, women with estrogen receptor (ER)-positive breast cancer benefit from 5 more years of endocrine therapy, either with tamoxifen or an aromatase inhibitor (AI). For premenopausal women, ovarian ablation (OA) would be required before starting an AI (OA/AI). According to the SOFT/TEXT studies, OA/AI improves 5-year disease-free survival compared with tamoxifen alone, suggesting that OA/AI could be superior to tamoxifen as extended endocrine therapy. The long-term costs and consequences of premature menopause from OA are unknown, but could be estimated through a cost-effectiveness analysis. **Methods:** A Markov chain Monte Carlo simulation model estimated the costs and benefits of 3 extended endocrine strategies in a hypothetical cohort of premenopausal women with ER-positive early breast cancer: (1) no further treatment; (2) tamoxifen for 5 years (extended tamoxifen); or (3) OA/AI for 5 years. Effectiveness was measured in years of life expectancy gain. Sensitivity analyses accounted for uncertainty surrounding various parameters. Monte Carlo simulation estimated the number of adverse events and deaths from each strategy in the US population over a 40-year period. **Results:** Extended tamoxifen yielded a higher average life expectancy gain than OA/AI (17.31 vs 17.06 years) at lower average cost (\$3,550 vs \$14,312). For 18,000 premenopausal ER-positive women, the simulation estimated 13,236, 12,557, and 11,338 deaths with no further treatment, extended tamoxifen, and OA/AI, respectively, but an additional 1,897 deaths from OA, for a total of 13,235 deaths associated with OA/AI. After 24.6 years of follow-up, more women are expected to die from OA/AI than extended tamoxifen. **Conclusions:** For premenopausal women with ER-positive cancer who have completed adjuvant tamoxifen, another 5 years of tamoxifen is the preferable extended endocrine strategy. The potential long-term health consequences of OA could affect overall survival when it precedes the use of an AI.

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Background

Recent evidence suggests that extending endocrine therapy for another 5 years after the initial 5 years of tamoxifen is beneficial for premenopausal women with estrogen receptor (ER)-positive breast cancer. In the ATLAS (Adjuvant Tamoxifen: Longer Against Shorter) and aTTom (Adjuvant Tamoxifen: To offer more?) trials, 10 years of tamoxifen was superior to 5

years in terms of decreasing recurrences and mortality in premenopausal and postmenopausal women.^{1,2} In the MA.17 trial, use of an aromatase inhibitor (AI; letrozole) for 5 years significantly reduced recurrences and mortality compared with placebo after 5 years of initial tamoxifen,³ and this effect was greater in premenopausal compared with postmenopausal women.⁴ No clinical trials compare additional tamoxifen with an AI after the first 5 years of tamoxifen in premenopausal women. Re-

From the ^aDepartment of Obstetrics and Gynecology, Division of Surgical Oncology, University of British Columbia, and BC Cancer Agency, Vancouver, British Columbia; ^bDepartment of Medical Oncology, Fraser Valley Cancer Centre, BC Cancer Agency, Surrey, British Columbia; ^cDepartment of Obstetrics and Gynecology, Division of Gynecologic Oncology, McGill University, Montreal, Quebec; and ^dDepartment of Cellular and Physiological Sciences, University of British Columbia, Vancouver, British Columbia, Canada.

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Correspondence: Janice S. Kwon, MD, MPH, FRCSC, University of British Columbia, 2775 Laurel Street, 6th Floor, Vancouver, BC, Canada V5Z 1M9. E-mail: Janice.kwon@vch.ca

sults of the TEXT/SOFT trials have raised interest in the use of AI in premenopausal women with ER-positive breast cancer. Although an improvement in 5-year disease-free survival (DFS) was seen when AI was compared with tamoxifen alone (89.0% vs 84.7%), no difference in overall survival (OS) was observed between the treatment strategies.⁵

Furthermore, despite the potential benefits of AI use in premenopausal women, there are long-term risks of ovarian ablation (OA), which is a necessary additional intervention in women who still have ovarian function. A recent study found that OA preceding an AI (OA/AI) was more costly and less effective in terms of overall life expectancy compared with tamoxifen alone for low-risk premenopausal women with ER-positive breast cancer.⁶ However, for high-risk women requiring chemotherapy, OA/AI was more costly but more effective than tamoxifen alone, although the incremental cost-effectiveness ratio (ICER) reached the upper threshold for acceptability within our healthcare system. The assessment of such long-term outcomes remains impractical in the context of most clinical trials. Recognizing the limited improvements in DFS and OS from extended endocrine treatment strategies and the potential detrimental impact of premature menopause from OA/AI, a decision analytic model is the most feasible strategy to evaluate long-term survival associated with extended endocrine strategies in women with premenopausal breast cancer. We conducted a cost-effectiveness analysis to compare these strategies for premenopausal women with ER-positive breast cancer who have completed 5 years of tamoxifen therapy and are eligible for additional endocrine therapy.

Methods

A Markov chain Monte Carlo simulation model evaluated 3 strategies in a hypothetical cohort of women with ER-positive early-stage breast cancer who have completed 5 years of initial tamoxifen therapy, similar to those in ATLAS. However, unlike the patient population in ATLAS, the women in our hypothetical cohort were exclusively premenopausal. The treatment options were (1) no further treatment; (2) 5 additional years of tamoxifen (extended tamoxifen); or (3) OA accomplished by outpatient laparoscopic bilateral salpingo-oophorectomy (BSO), followed by 5 years of an AI. We

did not model the use of gonadotropin-releasing hormone (GnRH) agonist as a method of OA/AI, because there is no evidence that hormone levels are different between the 2 interventions. GnRH agonist is also more costly than outpatient laparoscopic BSO because it requires multiple physician visits and injections.⁷

The benefit of each strategy was calculated in terms of average discounted years of life expectancy gained relative to an alternate strategy. Average lifetime costs were estimated in US dollars (\$USD) in 2016. All costs for services and medications were derived from the Healthcare Bluebook.⁸ We assumed that patients used generic forms of tamoxifen and letrozole as the AI. The primary outcome measure was the ICER, defined as the additional cost divided by the incremental health benefit compared with an alternate strategy. If the ICER was <\$100,000 per year of life gained, this strategy would be considered cost-effective, a commonly accepted threshold for healthcare measures.⁹ A strategy that was less effective and more costly than an alternative would be considered “dominated” (ie, inferior, and therefore excluded). As per recommendations of the US Public Health Service Panel on Cost-Effectiveness in Health and Medicine, a societal perspective was adopted and all costs and benefits were discounted at a rate of 3% per year.¹⁰

We assumed that women entered the model at an average age of 45 years after having completed 5 years of initial tamoxifen therapy, and had not yet become menopausal. The women were comparable across all treatment strategies in demographic and tumor characteristics. Risks of coronary heart disease (CHD), stroke, fracture, pulmonary embolism (PE), and endometrial cancer associated with tamoxifen and AI were estimated from the ATLAS and MA.17 trials, respectively.^{1,11} Ten-year overall mortality rates associated with placebo (5 years of tamoxifen) and extended tamoxifen (10 years of tamoxifen) for ER-positive women were 24.7% and 22.4%, respectively, in the ATLAS trial.¹ These 10-year mortality rates were converted to 1-year mortality probabilities. Ten-year mortality rates were not available from MA.17; however, at 4 years, the hazard ratio for overall mortality between AI (letrozole) and placebo was 0.82 (95% CI, 0.57–1.19). This hazard ratio was applied to the placebo subgroup of ATLAS to extrapolate the mortality rate in a comparable age-

and disease-matched subgroup of women using an AI. Consequently, AI would yield a lower mortality (20.5%) than extended tamoxifen (22.4%) at 10 years.

We did not use mortality estimates from the SOFT trial because tamoxifen was compared with AI as initial endocrine therapy, not as extended endocrine therapy. We assumed that women continued to die of breast cancer^{12,13} and other age-associated causes according to US life tables¹⁴ after the reported trial end points. Risks of tamoxifen-associated thromboembolic events and endometrial cancer and of AI-associated fractures were increased during endocrine therapy but returned to baseline risks after completion of treatment. Alternately, risks associated with premature menopause from OA persisted for many years after treatment and were estimated from the Nurses' Health Study subgroup of women who had undergone oophorectomy without estrogen replacement therapy. According to that large prospective cohort study with 28 years of follow-up, 20% of deaths are expected within the first 15 years after oophorectomy, and the remaining 80% of deaths after 15 years.¹⁵ The Markov model structure is illustrated in Figure 1. All women enter the model "at risk" of an event (adverse event, dying of cancer, dying of another cause), the probabilities for which are governed by age and type of treatment. If they do not experience one of these events at the end of one annual cycle, they return to the "at risk" state. The time horizon for this model was 40 years (cycles).

The model was programmed using TreeAge Pro 2014 (TreeAge Software, Inc., Williamstown, MA), with extensive sensitivity analyses around variables, including age at starting extended endocrine therapy, length of follow-up, and healthcare costs. Selected data for the base case of the model are provided in Table 1. Monte Carlo simulations estimated the number of women experiencing adverse events

attributable to extended endocrine treatment, including CHD, fracture, stroke, PE, and endometrial cancer, as well as the number of deaths in each treatment group.

Results

Extended tamoxifen for 5 years after the initial 5 years yielded a higher average life expectancy and at acceptable cost compared with no further treatment, with a favorable ICER of \$4,042 per year of life gained. Extended tamoxifen yielded a higher average life expectancy and at lower average cost compared with AI preceded by OA (17.31 vs 17.06 years, and \$3,550 vs \$14,312, respectively). Therefore, extended tamoxifen is the dominant (preferred) strategy as the second course of endocrine therapy after initial tamoxifen for premenopausal women. Table 2 summarizes the average discounted costs and life expectancy gains associated with each strategy.

Our results were sensitive to the length of follow-up time. If we compare the strategies at only 10 years after the start of extended endocrine therapy, AI is predicted to yield a higher average life expectancy than extended tamoxifen. However, our model estimated outcomes to 40 years, and after 24.6 years from starting extended endocrine therapy (ie, after 69.6 years of age, assuming that the average age at the start of extended endocrine therapy is 45 years), the life expectancy curves cross and extended tamoxifen is predicted to yield a higher life expectancy than OA/AI (Figure 2).

Our results were stable over a wide range of parameters, including age at starting extended endocrine treatment. If women are aged 30 years at treatment initiation, they have a higher overall life expectancy gain if they continue tamoxifen for another 5 years rather than undergoing OA followed by treatment with an AI. The survival difference between the extended endocrine strategies is greatest for younger women, as seen in Figure 3. Our results were also stable to a wide range of costs, including estimates for tamoxifen and AI, and treatment-related complications including CHD, stroke, fracture, PE, and endometrial cancer. Although the annual cost of tamoxifen in the model was greater than that of letrozole, the lifetime cost of the extended tamoxifen strategy was still lower than that of the OA/AI strategy.

Figure 1. Markov model transition states.

Table 1. Selected Data for Base Case

	No Further Endocrine Therapy	Tamoxifen for 5 Additional Years (Extended Tamoxifen)	AI for 5 Additional Years (Preceded by OA)
Mortality risks (range)			
Overall mortality (10 year) ^{1,3}	24.7% (24%–26%)	22.4% (21%–23%)	20.5% (19%–21%)
Additional mortality attributable to premenopausal OA ¹⁵	–	–	12.5% (HR, 1.41; 95% CI, 1.04–1.92)
Adverse event risks (range) ^{4,20}			
Fractures	1.1% (0.5%–1.5%)	4.9% (3.6%–6.4%)	6.8% (5.8%–7.9%)
VTE	0.4% (0.2%–0.8%)	2.2% (1.4%–3.3%)	1.0% (0.7%–1.5%)
Cardiac ischemia/infarction	0.5% (0.2%–1.2%)	0.5% (0.2%–1.2%)	0.7% (0.4%–1.1%)
Stroke	0.2% (0.1%–1.0%)	0.6% (0.2%–1.3%)	0.2% (0.1%–1.5%)
Endometrial cancer	1.6% (1%–2%)	3.1% (2%–5%)	0.2% (0.1%–1.0%)
Average costs ^{8,21,22}			
	Base case (\$USD)		Range (\$USD)
Outpatient laparoscopic BSO for OA	6,951		1,900–7,900
AI (letrozole) for 1 year	158		158–2,737
Tamoxifen for 1 year	280		120–520
CHD (myocardial infarction)	9,055		9,055–21,720
Fracture (repair hip fracture)	12,295		12,295–28,081
Pulmonary embolism	10,482		10,482–23,099
Stroke	8,388		2,606–21,635
Endometrial cancer (hysterectomy and subsequent care)	20,235		14,918–20,390

Abbreviations: AI, aromatase inhibitor; BSO, bilateral salpingo-oophorectomy; CHD, coronary heart disease; HR, hazard ratio; OA, ovarian ablation; VTE, venous thromboembolism.

This remained true even if the cost of letrozole was reduced to one quarter of the baseline cost.

We conducted a Monte Carlo simulation to estimate the total number of treatment-related complications, including endometrial cancer, fracture, CHD, stroke, and PE in each strategy, as well as the number of deaths attributable to OA/AI. In the United States, approximately 246,660 women were diagnosed with breast cancer in 2016.¹⁶ An estimated 10.7% of these women were aged <45 years and 70% of these had ER-positive tumors¹⁷; if we assume that they are still premenopausal after completing 5 years of initial tamoxifen therapy and are eligible for a second 5-year course of endocrine therapy, this is approximately 18,000 women. By simulating this cohort, our model estimates 13,236, 12,557,

and 11,338 cancer- and age-related deaths associated with no further treatment, extended tamoxifen, and OA/AI, respectively, over a period of 40 years. However, the model also estimates 1,897 additional deaths in the OA/AI group attributable to adverse events associated with premature menopause from OA, for a total of 13,235 deaths in this group. This is just less than the number of deaths associated with no further treatment, but more than those associated with extended tamoxifen. Although extended tamoxifen was associated with a higher number of cases of endometrial cancer and PE, AI preceded by OA was associated with a higher number of fractures, strokes, and CHD. We also modeled a cohort of 1 million premenopausal women with ER-positive early-stage breast cancer because the annual US co-

Table 2. Average Discounted Costs and Life Expectancy Gains

Strategy	Average Discounted Costs in \$USD	Average Discounted Life Expectancy Gain in Years	Incremental Cost- Effectiveness Ratio
No additional therapy	\$1,074	16.69	–
Extended tamoxifen	\$3,550	17.31	\$4,042
Ovarian ablation (BSO) then AI	\$14,312	17.06	Dominated

Abbreviations: AI, aromatase inhibitor; BSO, bilateral salpingo-oophorectomy.

Premenopausal Breast Cancer Therapy

Figure 2. One-way sensitivity analysis of number of years of follow-up after starting extended endocrine therapy.
Abbreviations: AI, aromatase inhibitor; OA, ovarian ablation.

Figure 3. One-way sensitivity analysis of the age at diagnosis.
Abbreviations: AI, aromatase inhibitor; OA, ovarian ablation.

hort of 18,000 women is comparably small; results are consistent between both cohorts. The estimated numbers of select adverse events in each group are summarized in Table 3.

Discussion

There are long-term consequences of premature menopause that must be considered when young women with ER-positive breast cancer are contemplating OA with an AI as extended endocrine therapy. Our model predicts that OA with an AI has the potential to be harmful if offered to women who are still premenopausal after completing initial tamoxifen therapy. For women who have completed 5 years of tamoxifen therapy, 10-year OS rates will be close to 80%, regardless of whether they use tamoxifen for another 5 years.¹ For women considering 5 more years of tamoxifen, the improvement in survival at 10 years is only 2.3% compared with no additional therapy based on the ATLAS trial. Furthermore, based on results of the SOFT trial, use of OA/AI as a primary endocrine strategy did not improve OS over tamoxifen alone, although follow-up is still limited.⁵ Nonetheless, most premenopausal women with ER-positive early breast cancer have the potential to live long-term, irrespective of treatment, and many will survive another 40 years given the average life ex-

pectancy of 81 years in the United States.¹⁴ Based on these data, women who are still premenopausal after the first 5 years of tamoxifen therapy should be counseled about the health consequences of OA if an AI is being considered, and that this intervention may actually compromise long-term survival even if there is a short-term DFS benefit from the AI. Our model predicted that AI would be superior up to 24.6 years after starting extended endocrine therapy; however, after this time, AI will contribute to a higher number of deaths than tamoxifen.

Our results are also substantiated by a recent systematic review and meta-analysis of 4 trials (ABCSG-12, SOFT, TEXT, E-3193) that evaluated the effects of adding ovarian suppression to either tamoxifen or AIs and found fewer DFS events but more deaths associated with ovarian suppression and an AI.¹⁸ The Nurses' Health Study demonstrated that women who underwent oophorectomy (OA) before 50 years of age without subsequent estrogen replacement therapy had a 41% higher risk of mortality from various causes (CHD, stroke, osteoporosis, cancer) based on an adjusted comparison to those who did not have this intervention. At the end of 28 years of follow-up, 1 in 8 patients (12.5%) died of causes attributable to premature menopause from oophorectomy.¹⁵ Although extended tamoxifen may be associated with higher rates of endometrial

Kwon et al

Table 3. Monte Carlo Simulation of Events

Strategy	Deaths From Breast Cancer	Deaths From ASR Causes	Deaths From OA	Total Deaths	Adverse Events				
					EC	PE	Frac	CHD	Stroke
Annual cohort of 18,000 women in United States									
None	7,358	5,878	0	13,236	460	93	542	181	179
Tam	6,227	6,330	0	12,557	883	306	688	400	412
OA/AI	5,504	5,834	1,897	13,235	184	206	977	826	628
Hypothetical cohort of 1,000,000 women									
None	420,868	326,338	0	747,206	25,009	6,188	27,867	9,057	9,062
Tam	352,356	351,156	0	703,512	48,323	17,051	37,841	23,532	23,558
OA/AI	310,559	326,234	105,248	742,041	9,868	12,830	53,808	45,081	35,846

Abbreviations: AI, aromatase inhibitor; ASR, age- and sex-related causes of mortality from US life tables; CHD, coronary heart disease; EC, endometrial cancer; Frac, fracture; OA, ovarian ablation; PE, pulmonary embolism; Tam, tamoxifen.

cancer and PE, the absolute difference in endometrial cancer mortality is estimated at 0.2% between 10 and 5 years of tamoxifen use, with no difference in PE mortality.¹

The absolute benefit of tamoxifen as extended endocrine therapy is arguably nominal. The life expectancy gain of an additional 0.25 years above the OA/AI strategy translates into 3 months; however, this is comparable to the average life expectancy gain associated with adjuvant trastuzumab for HER2-positive metastatic breast cancer.¹⁹ The average life expectancy gain represents the benefit for the entire population at risk, not the benefit realized by an individual. There is a large gain for the women who might have died prematurely as a result of premenopausal OA, offset by the lack of gain by most women who never would have experienced adverse effects from this intervention.

This model has a number of limitations. First, there are no data on long-term OS after premenopausal OA (oophorectomy) and AI, and therefore we extrapolated these outcomes from the Nurses' Health Study, of which only a small proportion of the study cohort had breast cancer. However, most of these premenopausal patients with breast cancer will be expected to survive long after their diagnosis, and therefore it is realistic to expect that a proportion of them will encounter adverse health consequences from OA in the future.

Second, we used survival outcomes and treatment toxicity data from ATLAS and MA.17, which were primarily comprised of postmenopausal women, and therefore survival estimates in our study have likely been underestimated because our hypothetical cohort included only premenopausal women. Furthermore,

these clinical trials were conducted a decade ago and, because systemic therapy has changed since then, survival outcomes may be different from those estimated. However, these 2 clinical trials represent the highest-level evidence relating to the potential benefit of extended endocrine therapy, which appears to be true regardless of menopausal status.⁴ Extended endocrine therapy remains a relevant question in light of the recent SOFT/TEXT trials, which demonstrated a benefit from OA/AI among premenopausal women as first-line endocrine therapy.^{5,20}

Third, we did not model treatment for recurrent or contralateral breast cancer, or second primaries, and therefore we may have underestimated lifetime costs, which would likely be higher in the tamoxifen group. However, the magnitude of difference is probably very small. In MA.17, the absolute difference in events between AI and placebo after 4 years was only 2.4%.¹¹ The difference between AI and tamoxifen as extended therapy is expected to be even smaller than this, and if extrapolated to 10 years, the magnitude of difference might be in the range of 4% to 5%. In contrast, at least 1 in 8 women (12.5%) with premature menopause secondary to OA are ultimately expected to die of CHD, osteoporotic fractures, stroke, or other cancers in the future.¹⁵ Finally, although we did not model quality-adjusted life expectancy, the detrimental impact of premenopausal OA on quality of life would likely yield an even greater difference between the extended endocrine strategies, in favor of tamoxifen.

Conclusions

We predict that continuing tamoxifen for another 5 years will be superior to OA followed by AI in terms

Premenopausal Breast Cancer Therapy

of prolonging OS in women with ER-positive breast cancer who remain premenopausal after completing initial tamoxifen therapy. This is a small subgroup, representing only approximately 7.5% of all women with breast cancer. However, the long-term effects of premature menopause associated with OA can be catastrophic for these women, most of whom are still

expected to survive their breast cancer even in the absence of additional endocrine therapy. Long-term health outcomes associated with breast cancer treatment still need to be evaluated prospectively. In the interim, it is important to recognize the potential for harm and to mitigate treatment-related morbidity that could compromise OS.

References

1. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013;381:805–816.
2. Gray RG, Rea D, Handley K, et al. aTTom: long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 in 6,953 women with early breast cancer [abstract]. *J Clin Oncol* 2013;31(Suppl):Abstract 5.
3. Goss PE, Ingle JN, Pritchard KI, et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. *N Engl J Med* 2016;375:209–219.
4. Goss PE, Ingle JN, Martino S, et al. Impact of premenopausal status at breast cancer diagnosis in women entered on the placebo-controlled NCIC CTG MA17 trial of extended adjuvant letrozole. *Ann Oncol* 2013;24:355–361.
5. Francis PA, Regan MM, Fleming GF, et al. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2015;372:436–446.
6. Kwon JS, Pansegrau G, Nourmoussavi M, et al. Long-term consequences of ovarian ablation for premenopausal breast cancer. *Breast Cancer Res Treat* 2016;157:565–573.
7. Halder K, Giamougiannis P, Wilson C, Crawford R. Laparoscopic salpingo-oophorectomy for ovarian ablation in women with hormone-sensitive breast cancer. *Int J Gynaecol Obstet* 2011;113:222–224.
8. Healthcare Bluebook. Fair Price search tool. Available at: https://healthcarebluebook.com/page_ConsumerFront.aspx. Accessed February 28, 2017.
9. King JT Jr, Tsevat J, Lave JR, Roberts MS. Willingness to pay for a quality-adjusted life year: implications for societal health care resource allocation. *Med Decis Making* 2005;25:667–677.
10. Weinstein MC, Siegel JE, Gold MR, et al. Recommendations of the panel on cost-effectiveness in health and medicine. *JAMA* 1996;276:1253–1258.
11. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst* 2005;97:1262–1271.
12. Colleoni M, Sun Z, Price KN, et al. Annual hazard rates of recurrence for breast cancer during 24 years of follow-up: results from the International Breast Cancer Study Group trials I to V. *J Clin Oncol* 2016;34:927–935.
13. Pan H, Gray RG, Davies C, et al. Predictors of recurrence during years 5–14 in 46,138 women with ER+ breast cancer allocated 5 years only of endocrine therapy (ET) [abstract]. *J Clin Oncol* 2016;34(Suppl):Abstract 505.
14. Social Security Administration. Actuarial Life Table. Available at: <http://www.socialsecurity.gov/OACT/STATS/table4c6.html>. Accessed March 9, 2017.
15. Parker WH, Feskanich D, Broder MS, et al. Long-term mortality associated with oophorectomy compared with ovarian conservation in the Nurses' Health Study. *Obstet Gynecol* 2013;121:709–716.
16. SEER. Cancer Stat Facts: Female Breast Cancer. Available at: <http://seer.cancer.gov/statfacts/html/breast.html>. Accessed June 23, 2016.
17. Anderson WF, Katki HA, Rosenberg PS. Incidence of breast cancer in the United States: current and future trends. *J Natl Cancer Inst* 2011;103:1397–1402.
18. Chlebowski RT, Pan K, Col NF. Ovarian suppression in combination endocrine adjuvant therapy in premenopausal women with early breast cancer. *Breast Cancer Res Treat* 2017;161:185–190.
19. Ovarian ablation in early breast cancer: overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 1996;348:1189–1196.
20. Pagni O, Regan MM, Walley BA, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2014;37:107–118.
21. Writing Group Members, Mozaffarian D, Benjamin EJ, et al. Executive summary: heart disease and stroke statistics—2016 update: a report from the American Heart Association. *Circulation* 2016;133:447–454.
22. GoodRx. Available at: <http://www.goodrx.com/>. Accessed February 28, 2017.