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Commentary

Fall in US cancer death rates: Time to pop the champagne?

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The fall in mortality rates for cancer in the US between 2016 and 2017, as reported by the American Cancer Society (ACS) in a recent publication, urged a big debate about who or what deserved the credit for such progress [1]. Researchers found that since 1991 the cancer death rate has dropped 29% but the 2.2% decline in mortality rates from 2016 to 2017 was the largest single-year decline in cancer mortality ever reported, compared against the 1.5% decline per year for the decade 2008−2017. Who deserves credit for this success? Since this fall was primarily driven by lung cancer, many experts speculated that this was the success story of treatment advances which has dramatically changed over the decade with the introduction of genomic and immunotherapy-based drugs.

Without a doubt, the fall in cancer mortality is a welcome news to everyone in the oncology community. However, before getting too excited, it is important to look at the trends in cancer mortality over many years (Fig 7 of the original publication) [1]. Although this study cannot prove whether the fall in mortality in 2016−2017 is statistically better than previous years, we see that the graphs do not reveal a dramatic drop and are in the general downward trend for both cancer mortality and lung cancer mortality rates for each gender. Thus, in our opinion, this downward trend of mortality graphs serves more as a reassurance than a cause for celebration.

What indeed contributed to the fall in lung cancer mortality rates? A combination of all efforts, including continued decline in smoking rates across both the genders, better treatment, improved surgery and radiation techniques, improved supportive care and screening may have had an impact. There is clear relationship of reduced smoking with improvement in cancer mortality rates over last few decades, and this is visible in the mortality graphs. If we consider the reduced incidence and mortality from lung cancer [2] and decades-long latency

period between smoking initiation and lung cancer occurrence [3], it seems that the success of tobacco control policies and cancer prevention programs could be a major contributor to the decline in cancer deaths. Furthermore, a decline in the rates of smoking from 20.9% in 2005 to 15.1% in 2015 support the *continued* role of tobacco control in reduced lung cancer incidence and mortality [4].

While the contribution of screening is probably minimal given the low uptake of lung cancer screening, the improvement in diagnostics could have some positive effect on mortality. The contribution of improved surgery and radiation cannot be discounted as well. Interestingly, all four cancers where mortality rates are dropping (lung, colorectal, prostate, breast) are the cancers where all three modalities of treatment are an important component of care. The improvement in supportive care should have an impact across all tumor types broadly.

Finally, the billion-dollar question, how much contribution to this fall in mortality rates is due to advances in cancer drugs? We do not intend to discount the substantial impact advancement in cancer drugs have made to the lives of patients with cancer. However, have these effects been big enough to change mortality rates at the population level?

The advances in drugs have exclusively occurred in the advanced setting which accounts for 57% of all lung cancers in the US [1]. Of these, 15% are patients with small cell lung cancer where no therapeutic advances have been made over the years. Furthermore, most therapeutic advances are applicable only to certain subgroup of patients with lung cancer.

Important advances in genomic targeted therapy in lung cancer happened in 2004 (erlotinib approval) and 2011 (crizotinib approval) begging the question why fall in mortality rates would be delayed until 2016−2017. Newer targeted drugs such as osimertinib and alectinib were approved first in late 2015 and after 2017 and thus, wouldn't be able to affect mortality rates in 2016−2017. Other genomic directed therapies approved on the basis of smaller single arm trials like BRAF and MEK inhibitors in lung cancer are applicable for fewer patients and are approved in or after 2017.

What about immunotherapies? The only immunotherapies in lung cancer approved before 2016 shown to have an effect on mortality rates between 2016 and 2017 are pembrolizumab monotherapy 2nd line, pembrolizumab monotherapy 1st line and nivolumab 2nd line. Other immunotherapy advances in lung cancer such as pembrolizumab combination therapy or durvalumab in stage III occurred

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after this period. The pembrolizumab approvals were limited to PDL1 positive tumors, further restricting the patient pool eligible for this treatment.

Furthermore, FDA approval doesn't immediately translate to real-world adoption since only half of patients in the US eligible for targeted therapies were receiving such treatment [5]. Notwithstanding the beneficial effect genome based and immunotherapy drugs may have provided, the benefits would be too small and cannot explain such a difference in mortality rates at the population level, more so when clinical adoption is an issue.

Therefore, based on the timing of drug approvals, as well as the fraction of patients eligible for and ultimately receive these drugs, the contribution of drug innovation to fall in population mortality rates in lung cancer and thereby overall cancer mortality rates is very low. An exception is probably melanoma, where drugs may have contributed to improving mortality rates; however, one fact that is often overlooked in such reports is the effect of overdiagnosis. Indeed, examining Fig. 2 of the ACS report reveals continued increase in incidence of melanoma coinciding with the continued decrease in mortality from melanoma [1].

The ACS report also found that black men were twice as likely to die of cancer as Asian/Pacific Islander men and 20 percent more likely to die than white men. Furthermore, men and women living in certain states are also more likely to develop and succumb to risk reducible cancers such as lung cancer, cervical cancer and melanoma [1]. These did not make much news, because these are stories of failure that do not make us feel as good as the stories of success, but are vital to our continued progress. Indeed, we completely support the conclusions made in a different analysis of the same ACS report, "Public-health policies are not personalized to any individual but can promote longevity for all of us" [6]. We hope that our comment provides complementary analysis to contribute to this debate.

Finally, it is important to remember that the ACS report is an ecological analysis and cannot prove any causal relations. The key take-home from this study for us is reassurance that we are moving in the right direction but not necessarily a cause for celebration yet. Unsurprisingly, the low-hanging fruit to achieve better outcomes overall seems to be equitable access to cancer care, which is in line with our argument for cancer groundshot parallel to cancer moonshot [7]. Paraphrasing Robert Frost:

The woods are lovely, dark and deep,
But we have promises to keep,
And miles to go before we sleep,
And miles to go before we sleep.

Declaration of Competing Interest

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