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Commentary

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Surgery and cancer promotion: are we trading beauty for cancer?

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Summary

It is well-known that cancer surgery can actually promote the growth of some tumors by a variety of mechanisms. There are observational data suggesting that surgery *per se* can increase the risk of cancer among individuals without a history of clinical cancer. Occult microscopic cancers are exceedingly common in the general population and are held in a dormant state by a balance between cell proliferation and cell death and also an intact host immune surveillance. The catecholamine surge from the stress of surgery and resulting β_2-adrenergic signaling culminates in a transient and robust increased vascular endothelial growth factor expression locally and systemically that is enough to start tumor angiogenesis and end dormancy. The same catecholamine surge and β_2-adrenergic signaling impairs cell-mediated immunity at a crucial time. Elegant animal studies have demonstrated that perioperative nonselective β-blockade abrogates surgical stress-induced angiogenesis and tumor growth. Prospective human trials are desperately needed and clinical implications are discussed.

Although surgery continues to be the most effective treatment for cancer in the USA, about one-third of the patients will ultimately have local or systemic recurrence of disease.[1] For more than a century, it has been widely discussed that cancer surgery can actually promote the growth of some tumors, thus making surgery a double edged sword for the treatment of cancer.[2,3] However, one might ask if surgery *per se* can increase subsequent cancer risk among individuals without a history of clinical cancer? Disturbingly, the answer might be affirmative.

A retrospective cohort study of 13 488 women who had augmentation mammoplasty and were followed for 12 years revealed a 21% increase in overall cancer rates based on expected population cancer rates.[4] Among the implant patients, there was a significant and more than doubled risk for stomach cancer, brain cancer and leukemia. Another observational study involving 3473 women with cosmetic breast implants followed for 10 years was notable for a significant and nearly tripled rate of lung cancer based on expected population lung cancer rates, although all cause cancer rates were unchanged.[5] Interestingly, observational data have shown that the risk of renal cell carcinoma is nearly doubled over the decades following hysterectomy, particularly among women undergoing hysterectomy before 44 years of age.[6,7] It has been reported that a history of tonsillectomy is associated with a significant increase in breast cancer among premenopausal women [odds ratio

(ORs) = 1.5].[8] Among Swedish men hospitalized for benign prostatic hyperplasia, those having transurethral resection of the prostate had a significant increase in bladder cancer risk of ~50% over 10–26 years of follow-up.[9] Even though observational data have not shown an overall increase of cancer risk following total joint arthroplasty, interesting and concerning patterns emerge;[10–13] >10 years of follow-up reveals a significant increase in the risk of prostate cancer,[10–13] bladder cancer and melanoma.[11,13] Since all of the aforementioned observational data are only hypotheses generating, they should be of major public health concern since there are millions of inpatient[14] and outpatient[15] surgeries performed annually in the USA and outpatient cosmetic surgeries continue to be exceedingly popular.[16] Largely driven by gynecologic surgeries, significantly more inpatient and outpatient surgeries are performed on women compared to men[14,15] and >90% of all cosmetic surgeries are done on women.[16] In the USA, cancer is the leading cause of death in men and women aged 40–80 years; notably, the death rate from melanoma is increasing.[17]

Imaging[18] and autopsy studies[19,20] demonstrate that occult cancers are extremely prevalent in the population. For example, a study of 110 consecutive medical–legal autopsies on Caucasian women in Denmark revealed that 39% of women aged 40–49 years had evidence of microscopic breast cancer,[19] but only ~2% of women are diagnosed with clinical breast cancer in that same age group.[20] A very high prevalence of other occult cancers is also common in the population; for example, a majority of men in their 60s have microscopic evidence of prostate cancer.[20] Therefore, a large proportion of healthy individuals without a history of clinical cancer harbor microscopic cancers that may never become clinically apparent; the cancers remain dormant. Moreover, it is becoming apparent that metastases occur very early in cancer progression and commonly occur well before the discovery of the primary tumor.[21,22] Even after successful treatment of the primary tumor, micrometastatic cancers may remain dormant for decades by maintaining a balance between cancer cell proliferation and cancer cell death[23,24]

There are numerous ways by which surgery can activate the growth of clinically unapparent dormant micrometastatic cancers that eventually develop into clinical disease. The acceleration of metastatic cancer growth after excision of the primary tumor can be attributed to the removal of source of anti-angiogenic factors, such as angiostatin, that were made by the primary tumor.[25,26] Furthermore, surgery itself is a potent stimulator of tumor angiogenesis and tumor cell proliferation both at local and distant sites[27–30] by triggering the rapid production of various growth factors and proangiogenic factors used in healing wounds, such as vascular endothelial growth factor (VEGF) which is made by a variety of cells including endothelial cells, tumor cells, macrophages, immune cells and fibroblasts. Serum VEGF levels can increase more than double in a matter of hours after surgery and remain elevated for several days;[28,29] and intuitively, major surgical procedures result in increases of serum VEGF levels significantly more than minimally invasive procedures.[31] It is believed that the transient burst of angiogenic factors, as seen after surgical procedures, is enough to start the growth of dormant nonangiogenic tumors, thus converting them to proliferating angiogenic tumors.[32,33]

Catecholamine release from surgical stress is the spark that ignites tumor angiogenesis.[34–36] Norepinephrine binds to β_2-adrenoceptors on tumor cell membranes and results in the activation of the cyclic adenosine monophosphate/protein kinase A signaling pathway which culminates in VEGF production and angiogenesis. In an animal model of ovarian carcinoma, surgical stress-induced angiogenesis and tumor growth was completely abrogated by perioperative nonselective β-blockade with propranolol.[34] This has enormous clinical significance, since most women with ovarian carcinoma have advanced disease at the time of diagnosis and frequently undergo several surgical procedures throughout the course of their treatment; perhaps, those individuals might benefit from perioperative nonselective β-blockade. In an animal model of breast cancer, stress-induced β_2-adrenergic signaling culminated in a 30-fold increase in metastasis, but not growth of the primary tumor.[35] Interestingly, these consequences were mediated by increased macrophage infiltration into the primary tumor parenchyma and the expression of a robust prometastatic and proinflammatory gene signature by the macrophages, which included *Vegf* along with many other genes.[35] In this animal model of breast cancer, propranalol treatment of the stressed animals abolished the stress-induced macrophage infiltration into the primary tumor and metastasis. On the other hand, the β-agonist, isoproterenol, increased metastasis compared to saline-treated controls by 22-fold;[35] this might have clinical significance, if β-agonists are used in the perioperative period. In an animal model of prostate cancer, catecholamine driven metastasis was inhibited by nonselective β-blockade.[37] It is interesting that observational studies have shown β-blocker treatment has been associated with a significantly decreased risk of all-cause cancer,[38] prostate cancer[39] and breast cancer.[40]

Surgery suppresses cell-mediated immunity (CMI), particularly natural killer (NK) cell responses, for up to a week and the amount of suppression correlates directly with the amount of surgical trauma and tissue damage.[41,42] This might be particularly important after the removal of a primary tumor if the immune surveillance of remaining micrometastatic lesions is impaired. Theoretically, the micrometastatic lesions are not large enough to show immunoescape mechanisms that the primary tumor exhibited and the primary tumor is removed and no longer expressing immunosuppressive compounds systemically;[41] therefore, the remaining microscopic residual disease might be particularly susceptible to a robust host immune response. Catecholamines and prostaglandins are key mediators of surgical stress-induced suppression of CMI (NK cells and other lymphocytes express receptors for catecholamines and prostaglandins) and β-blockers and cyclooxygenase-2 (COX-2) inhibitors might attenuate perioperative CMI suppression.[41] The anesthetic drugs ketamine, thiopental and halothane suppress NK cell activity whereas propofol does not and regional and local anesthesia is preferred to general anesthesia for the preservation of immune function.[43] Additionally, hypothermia leads to an impairment of CMI and should be avoided.[43] Moreover, melatonin levels are decreased the first day after surgery[44] and this might add to impaired NK cell function[45,46] in the vulnerable perioperative period.

Furthermore, it is noteworthy that stress and depression in the remote postoperative period might promote cancer progression and metastasis which appears to be driven by β_2-adrenergic signaling.[47,48] This raises the possibility that long-term nonselective β-blockade would be beneficial in this setting, but this needs to be proven by prospective trials. It is worth mentioning that oral nicotine administration has been shown to stimulate the proliferation of human colon cancer xenograft in an animal model by promoting angiogenesis via β-adrenergic activation and β_2-blockade abrogated this action; nicotine activated β-adrenoceptors on colon cancer cells resulted in VEGF production and angiogenesis.[49] Disturbingly, in an immunocompetent mouse model of lung cancer, over-the-counter transdermal nicotine patches promoted tumor growth and metastasis.[50] These data have rather significant clinical consequences since nicotine in any form might synergize with catecholamines in promoting angiogenesis[49] and thus, hasten the growth of colon cancer or other cancers, particularly in the perioperative period.

Additionally, the vitamin D status of an individual might play a role in surgery-induced cancer promotion. The biologically active form of vitamin D (1α,25-dihydroxyvitamin D) has been shown to abrogate angiogenesis *in vitro* and *in vivo* by an inhibitory effect on VEGF.[51] There is a wealth of epidemiologic evidence suggesting that low vitamin D status is associated with an increased prevalence of a variety of cancers;[52,53] unfortunately, vitamin D insufficiency (usually defined as a serum 25-hydroxyvitamin D level <30 ng/ml) is found in a majority of the US and global population.[54,55] Perhaps, preoperative vitamin D repletion might partially nullify any surgery-induced tumor angiogenesis.

In conclusion, it is well-known that cancer surgery can be a mixed blessing; it can remove the primary tumor but also promote cancer by a variety of mechanisms. Importantly, occult microscopic cancers are exceedingly common in the general population and are typically held in dormancy by a delicate balance between cancer cell proliferation and cancer cell death along with intact host immune surveillance functionality. Of the millions of people that have inpatient and outpatient surgeries, including cosmetic surgeries in the USA each year, presumably many of them have known cancer, have a history of treated cancer and likely dormant micrometastatic cancers, or no known history of clinical cancer but harbor microscopic cancers. As mentioned, it is not uncommon for the same individual to have multiple surgeries over time, particularly cosmetic surgeries. Observational data suggest that surgery done on patients with no known cancer history does indeed lead to increased cancer risk over the ensuing decades. Many animal studies and some human studies have elucidated how this might occur. A recurrent theme is that the abrupt catecholamine surge from the stress of surgery and resulting β_2- adrenergic signaling culminates in a transient increased VEGF expression systemically and in the tumor microenvironment that is enough to start tumor angiogenesis leading to the end of dormancy and the beginning of the sustained proliferation of cancer cells. The same catecholamine surge and β_2-adrenergic signaling impairs CMI at a crucial time that might allow microscopic cancers to escape host immune surveillance.

Many more critical questions are raised than answered. Since nonselective β-blockers are relatively safe and have been shown to abrogate surgically induced tumor growth in animal models and decrease cancer risk in observational studies, it begs the question: Should nonselective β-blockers be given perioperatively, particularly in patients with known cancer, a history of cancer or in general to adults in order to decrease the subsequent risk of cancer? If so, for what duration should they be

given? Should nicotine exposure of any form, including the transdermal nicotine patch and gum used for smoking cessation, be avoided perioperatively and in any patient with clinical cancer? In patients with known cancer, should nonselective β-blockers be continued indefinitely and at what dose? Perhaps, β-blockade will prove to be just as important in the cancer arena as it has been in the cardiovascular arena. On the other hand, should β-agonists be avoided in the perioperative period and in patients with a history of cancer; might they actually promote tumor growth? Is there a role for perioperative COX-2 inhibitors to decrease CMI suppression? What about using perioperative melatonin supplementation to avert CMI suppression? Should we try and use more regional and local anesthesia in place of general anesthesia, particularly in those individuals with known cancer? Also, should the vitamin D status of patients be optimized preoperatively?

Finally, long-term well designed prospective trials are needed to answer these questions. In the meantime, physicians might consider using nonselective perioperative β-blocker therapy and COX-2 inhibition in appropriate patients and long term nonselective β-blockers in patients with a clinical history of cancer, particularly smokers. Anesthesiologists might consider using more regional and local anesthesia, if appropriate. Preoperative vitamin D supplementation might be considered. Most importantly, unnecessary surgery should be avoided. As for the increasing popularity of cosmetic surgeries, hopefully we are not trading immediate beauty for future cancer.

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