

Preventive Therapy for Cancer

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Summary. Therapeutic cancer prevention is a new field that can learn a lot from the successes in the prevention of cardiovascular diseases. While weight control and physical activity are important for both, preventive therapies have much to add. Low dose aspirin for cancer prevention stands out as the most important agent in terms of population benefit, and should be offered to most people above the age of 50 years who do not have hypertension or risk factors for gastrointestinal bleeding. Universal vaccination against the human papillomavirus, ideally with the 9-valent vaccine, also offers clear benefits for the whole population if given before infection occurs (typically at age 12-14y). Other therapies, notably anti-oestrogen drugs for breast cancer prevention need to be targeted to high risk groups to maintain a favourable benefit-risk ratio. Better algorithms for their identification and better platforms for reaching them, eg. as part of a screening visit remain a key priorities if the discoveries made to date are to have an important impact on public health. Many other promising agents have been identified, often as components of food, but negative experiences with beta-carotene and vitamin E, indicate that they need rigorous evaluation before acceptance.

Introduction. Cancer prevention is a large field comprising lifestyle changes to reduce risk, screening interventions to detect early lesions and preventive interventions aimed at more actively interrupting the carcinogenic pathway. Here we only consider the later. Compared to cardiovascular disease where preventive treatments are firmly established, the development of therapies to prevent cancer is still in its infancy. This in part reflects the fact that cancers

are more heterogeneous and biologically complex than cardiovascular diseases, and causal pathways are less well understood. Good biomarkers for identifying individuals at increased risk for specific cancers are missing and even less is known about predictive factors for response to specific treatments.

The balance of risks and benefits is also inherently more challenging for preventive than for therapeutic interventions. Only a small fraction of the apparently healthy people who receive a preventive treatment would develop the specific type of cancer being targeted and lack of cancer is not apparent at an individual level, whereas all will incur some risk of side effects which are identifiable on an individual basis. This also leads to challenges in evaluating new agents as trials need to be larger in order to have enough endpoints points, and also longer as preventive effects often take more time to appear, as early stages of the carcinogenic process are targeted. Fear of cancer also has a greater impact on the human psyche leading to unsupported claims and wishful expectations for preventive efficacy for a plethora of unproven agents.

Here I review interventions for which there is good evidence of efficacy, those with promising but not fully convincing findings, and those for which there is a substantial amount of evidence of no benefit and in some cases even harm. Assessments are my subjective personal views based on the available data, but are not formal reviews such as those conducted by IARC, NICE or the USPSTF, which are only available for a limited number of agents. However, they are cited when available.

Effective Agents

Surgery. Prophylactic surgery is an appropriate option for a small number of cases where the risk of disease (usually genetically based) is strong – typically above 50%. There are two notable examples: colectomy for individuals with polyposis coli which is caused by a mutation in the *apc* gene and occurs in about 1 in 7000 to 23 000 people depending on the population^{1,2}. About 25-30% of these mutations are thought to be *de novo* with no affected family members. Surgery often takes place before age 25y at which time, a large number of polyps are already present, and is virtually 100% effective if undertaken before cancer is present. The other well-known example is women with a mutation in the BRCA1 or BRCA2 gene, which gives rise to a greatly increased risk of breast cancer (about 60% lifetime risk) and ovarian cancer (55% for BRCA1 and 16.5% for BRCA2)³. Removal of the ovaries around age 35-40y is common for BRCA1 and up to 5 years later for BRCA2. It not only eliminates ovarian cancer but also reduces breast cancer risk by about half⁴, whereas bilateral mastectomy eliminates 90-95% of breast cancer risk⁵. There is increasing evidence that most ovarian cancers initially arise in the fallopian tubes and only removing them could prevent this disease, and would result in fewer side effects⁶. Mutation in other rare genes can also lead to consideration of prophylactic surgery, although it is important reserve this extreme option for the very highest risk women, as above as some of these mutations only carry at 20-30% lifetime risk.

Vaccination. Vaccination against the human papilloma virus is likely to have a major impact on cervical and some other cancers. Vaccination before infection has been shown to virtually eliminate persistent infection and precursor cervical lesions (CIN) due to the HPV types contained in the vaccine, but longer follow up is needed before an effect on cancer becomes apparent. Two vaccines have been widely used – Gardasil⁷ containing virus like particles

(VLPs) as antigens against HPV types 16 and 18, which cause cancer, as well as types 6 and 11 which protect against genital warts. Cervarix⁸ only contains VLPs for types 16 and 18. Recently a new 9-valent HPV vaccine which contains VLPs against 31,33,45,52 and 58 as well as 6, 11, 16 and 18 has shown very high efficacy against all 9 types if given before infection⁹.

Infant vaccination against Hepatitis B in Taiwan, where it is the major causative factor for hepatocellular cancer, has led to a more than 60% reduction in this cancer below the age of 20y¹⁰. The main reasons for failure were active infection in the mother and incomplete vaccination. Further follow up will be needed to see if this protection continues into adulthood. Preventing Hepatitis C induced cancer remains a major challenge, as no effective vaccine has yet to be developed¹¹ although expensive treatments are now available to clear infections¹².

Pharmacologic Drugs initially used for other purposes.

The greatest impact on the field of preventive therapy has been the use of drugs initially developed for other indications. This approach has been especially effective for demonstrating the preventive effect of anti-oestrogenic agents for breast cancer and aspirin for the gastrointestinal cancers, and is likely to lead to further important discoveries. One further discovery is that oral contraceptives have been clearly shown to reduce the risk of ovarian cancer by 27% for ever use and more than 50% for 10 years or longer use¹³, although it is difficult to imagine how this might be used in a targeted way.

Breast cancer. Breast cancer prevention has been facilitated by the fact that drugs evaluated for their ability to prevent recurrence of a breast cancer also provide reliable evidence for a preventive effect on new tumours in the contralateral breast. Table 1 shows a variety of agents that have been evaluated for primary prevention.

Tamoxifen was the first such agent to illustrate this. Based on data from the CRC-II adjuvant trial, Cuzick and Baum¹⁴ published the first report of a preventive effect for tamoxifen. A meta-analysis of 20 randomized clinical trials of five-year treatment with tamoxifen as adjuvant therapy in 15 000 women documented an approximately one-third reduction in contralateral breast tumours¹⁵. Four prevention trials have subsequently confirmed this finding in high risk women without breast cancer (Table 1). Overall, these trials show a 38% reduction in breast cancer incidence¹⁶, resulting from a 50% reduction of oestrogen receptor positive breast cancers but no effect on oestrogen receptor negative tumours. These trials have shown that the protection from tamoxifen persists after stopping the medication. In fact, for the two trials with the longest follow up^{17,18}, a greater reduction in breast cancer incidence was observed in the follow up period than during active treatment (cumulative risk 4.6% vs 6.3% in years 0-10; 3.3% vs 6.3 % in years 10-20), and this has persisted for 15 years after treatment completion (Figure1).

The two major side effects of tamoxifen are endometrial cancer and venous thromboembolism. (Table 2). Endometrial cancer was increased by approximately 2.5 fold above the baseline rate of about 60 per 100 000 per year at age 60, whereas venous thromboembolism was found about twice as often in the tamoxifen arm compared to placebo. Recent reports have shown that the excess of thromboembolic events is limited to the active treatment period, whereas the excess of endometrial cancer appears to continue after cessation. Less serious but more common side effects of tamoxifen include vasomotor symptoms such as hot flushes, night sweats and gynecologic symptoms such as bleeding and uterine polyps¹⁹. Topical formulations of tamoxifen metabolites applied directly to the breast are now under study with the hope that the local dose will be high enough to maintain its preventive effects, but the systemic dose will be reduced enough to limit its side effects⁸⁴. Tamoxifen has now been approved for

use in breast cancer prevention for high risk women in the USA by FDA and recommended in the UK by NICE.

Three other selective oestrogen receptor modulators (SERMs) have now been evaluated in addition to tamoxifen. Raloxifene is a second generation SERM originally developed to prevent osteoporosis in postmenopausal women. It has oestrogenic effects on bone and lipid metabolism, and anti-estrogenic effects on the endometrium and breast tissue. Because of this tissue selectivity, raloxifene has fewer side effects than tamoxifen. Three trials have evaluated raloxifene as a preventive agent for breast cancer in postmenopausal women (Table 1) and all have shown efficacy. In the MORE trial a 65% reduction in breast cancer was found after 4 years of treatment, which led to its continuation as the CORE trial with breast cancer as a primary endpoint²⁰, where a 50% reduction in breast cancer was seen. A second study known as RUTH²¹ evaluated the impact of raloxifene in women with increased cardiovascular risk as the primary endpoint and found a 44% reduced incidence of invasive breast cancer.

The STAR trial²² is the only randomized clinical trial that has directly compared raloxifene with tamoxifen. It found that the reduction in breast cancer risk from raloxifene was about 25% less than for tamoxifen. In contrast to tamoxifen, no excess of endometrial cancer or other gynaecological problems were observed. However like tamoxifen it was associated with an increase of thromboembolic events, although the magnitude of the increase appears to be smaller. While raloxifene is less effective than tamoxifen, it may be more acceptable for postmenopausal women, where it is already widely used for osteoporosis. Raloxifene has now been approved for use in breast cancer prevention for high risk postmenopausal women in the USA by FDA and recommended in the UK by NICE.

Two other SERMs (lasofoxifene and arzoxifene) have been investigated in osteoporotic postmenopausal women with reduction in fractures as the primary endpoint. The PEARL trial²³ evaluated two doses of lasofoxifene vs placebo and based on 49 breast cancers incidence was significantly reduced by 79% with the higher 0.5 mg/day dose when compared to placebo. Furthermore, although there was a significant increase in thrombotic events, lasofoxifene significantly reduced major

coronary events, strokes and both vertebral and non-vertebral fractures and so it may be ideal for prevention, where the total benefit–harm balance is particularly important.

The GENERATIONS trial²⁴ evaluated arzoxifene (20 mg/day) versus placebo in 9,354 postmenopausal women with osteoporosis (Table 1). It reduced all breast cancer events by 58% and vertebral fractures by 41%, but increased the incidence of thromboembolic events, hot flushes, muscle cramps and gynecological events, as with other SERMs (except gynecologic events for raloxifene).

Aromatase Inhibitors

The third generation aromatase inhibitors (AI) anastrozole, letrozole and exemestane have been found to be more effective than tamoxifen for the treatment of oestrogen receptor positive breast cancer in postmenopausal women²⁵ and are now routinely used for this indication. Contralateral breast tumours, a good surrogate for new cancers, were also reduced by a further 50% compared to tamoxifen in these trials²⁶.

Two large breast cancer prevention trials have reported on the use of AIs in high risk women without cancer. The MAP3 trial randomized 4560 postmenopausal women to receive either exemestane or placebo for 5 years. A 65% reduction of invasive breast cancers was seen²⁷. No reduction was observed for ER-negative disease, but the effect on ER-positive disease was even greater (HR=0.27 (0.12-0.60), P<0.001). No statistically significant differences were found between treatment arms for adverse events, suggesting a good benefit-risk profile. However, these conclusions are limited by the short follow-up period of only 35 months.

The IBIS-II trial compared anastrozole to placebo in postmenopausal women at increased risk of breast cancer²⁸. After a median of 5 years of follow-up a highly significant 53% reduction of invasive breast cancer and DCIS combined (primary endpoint) was seen (HR = 0.47, 95% confidence interval (0.32-0.68), P<0.0001), which was similar to the results reported in the MAP3 trial. For oestrogen receptor positive invasive cancer the reduction was 58% (HR=0.42 (0.25-0.71), P<0.001), but as in the MAP3

trial no effect was found for ER-negative breast cancer. Vasomotor and musculoskeletal side effects were increased with anastrozole, but only by 10-15%, and these adverse events were also reported by many women receiving placebo. Thus most of these events were not attributable to anastrozole, but reflect a high incidence of them for all women in their early postmenopausal years. This illustrates the need to have a placebo arm to accurately assess subjective side effects. The risk of fractures was slightly but non-significantly increased by 11% (8.5% vs 7.7%) for anastrozole. This was much less than the 50% increase seen in a previous adjuvant trial²⁹, mostly likely due to the use of bone density (DXA) scans at entry, and appropriate bisphosphonate prophylaxis for women with low bone density. Blinded long-term follow-up is continuing in IBIS-II, so that the long-term efficacy and side effects of anastrozole can be evaluated.

Overall, the reported reductions in breast cancer incidence for both exemestane and anastrozole were larger than those seen for tamoxifen or raloxifene, and indicate that these two drugs are an attractive option for breast cancer prevention in postmenopausal women at increased risk of the disease. NICE have recently issued draft guidelines for consultation for the use of anastrozole in postmenopausal women in the UK (<https://www.nice.org.uk/guidance/GID-NG10010/documents/short-version-of-addendum>). For premenopausal women the only current option remains tamoxifen.

None of these anti-oestrogen agents have had any impact on oestrogen receptor negative breast cancer, which remains an unmet need.

Aspirin and other NSAIDs

There is now overwhelming evidence for an approximately one-third reduction in colorectal cancer incidence and mortality from long term regular aspirin use³⁰. Beneficial effects of a similar size have been seen for oesophageal and gastric cancers, and smaller, less convincing 5-15% reductions for lung, breast and prostate cancers (Table 1) have also emerged over the

past several years^{28,31,32}. There is also a suggestion of a small effect also for ovarian cancer, but this is still uncertain. There appears to be little or no effect on other major cancer sites including pancreatic, endometrial, and haematopoietic tumours. Long term use of about 10 years was estimated to reduce overall cancer incidence by about 10% in men and 7% in women, and overall cancer mortality by 13% in men and 9% in women²⁸. Gastrointestinal and cerebral bleeding are the most important harms associated with aspirin use, and their risk and fatality rate increase with age³³. Use of prophylactic aspirin in the general population aged 50-65y is likely to be beneficial when the reduction in cancer and cardiovascular disease and excess bleeding are all considered. For example for 100 men aged 55y taking low dose aspirin for 10 years, Cuzick et al²⁸ estimated that over the next 15 years there would be 2.29 fewer cancers, myocardial infarctions and strokes and 0.49 more gastrointestinal bleeding events. For women the numbers were 1.32 and 0.25 resp. In terms of deaths in the next 20 years, for men there would be 1.60 fewer deaths from cancer and heart disease and 0.17 more from GI bleeds and strokes. For women these numbers were 0.82 and 0.11, resp. Both benefits and harms increase with age in men and women. Thus the benefit-risk ratio is highly favourable for the general population and is about 5:1 for serious events and at least 7:1 for deaths. This is likely to increase with further treatment duration and follow up. It is also clear that only a small proportion of the population will benefit and identifying which individuals are most likely to do so would allow treatment to be more focussed.

The effects of daily aspirin on cancer incidence are not apparent until at least 3 years after the start of use (Figure 2), with a relative incidence reduction after that time for all cancers of about 24%³⁴, and some benefits appear to be sustained for several years after treatment cessation in long-term users. Relative reductions in cancer incidence appear to be similar in men and women³⁴, although data are less extensive for women, and men have a higher incidence of the cancers reduced by aspirin, leading to greater absolute reductions. Two trials of alternate day

use of 100mg - the Women's Health Study (WHS)³⁵ and the Physicians' Health Study (PHS) did not show any cancer reduction within 10 years of follow-up, although a 43% reduction in colorectal cancer after 10 years has been observed in the WHS³⁵. No differences between low and standard doses of aspirin have been observed either for efficacy or side effects, but there are no direct comparisons. Higher doses above 325mg/day do not appear to confer additional benefit but do increase toxicities.

The impact of aspirin on cancer mortality appears to be larger than for incidence³⁶. The mechanisms by which aspirin prevents cancer incidence and mortality are poorly understood. Rothwell et al³⁰ suggested that the greater effect on mortality is due to a reduction in metastatic spread, possibly through a platelet mediated mechanism, with benefits both before and after the diagnosis of cancer^{37,38}. Trials are underway to examine aspirin as an adjuvant treatment for individuals with colorectal, gastric, oesophageal, breast and prostate cancer³⁹. A recent review by the US Preventive Services Task Force (USPSTF) has given limited support for a preventive effect of aspirin on colorectal cancer incidence and possibly mortality⁸².

Data on other NSAIDs such as ibuprofen, sulindac or celecoxib are less extensive and there are no trials with long term follow up, except for studies of colorectal adenomas. However observational studies have found similar overall effects on cancer incidence^{40,41}.

Agents with preliminary evidence for cancer prevention

Evidence for a potential preventive effect comes from two main sources, with very different limitations and potential confounding factors. One source is epidemiologic cohort and case-control studies. These have the advantage of looking at exposure in human populations, but can only establish an association between exposure and reduced disease incidence. Confounding of the association by other concomitant exposures, lifestyle or socioeconomic factors is a challenging issue, and randomised prevention trials offer the only certain protection against this. While epidemiologic studies have provided some important leads, such as for aspirin and colorectal cancer, there are also some serious examples where epidemiologic studies have suggested a preventive effect which was later disproved in randomised trials are indicated below.

The other approach which has generated or supported preventive effects is mechanistic laboratory studies. While understanding mechanisms is very important, the main limitation here is that tissue culture or animal models cannot fully reproduce the human environment, and there are several examples where convincing evidence of a mechanistic effect in the laboratory has not translated into a preventive effect in humans.

Several compounds have demonstrated both epidemiologic and laboratory evidence for a preventive effect. Of these metformin, a drug used to treat type 2 diabetes, is among the most promising. Early interest was sparked by a study using the UK General Practice Research Database⁴², suggesting a more than 50% reduction in breast cancer. That was followed by other studies from this resource suggesting reductions in ovarian cancer. However no other cancers were reduced. Concerns have been raised about potential confounding with diabetes and especially the other medications used for this condition⁴³. In an overview of 65 540 cancer cases in 47 studies of diabetic women, metformin was found to have a beneficial effect on a range of cancers leading to an overall 31% reduction in incidence and 34% reduction in

mortality⁴⁴. Some of the concerns raised previously were addressed in this review and some of the differences appeared to be related to differences in BMI and time related factors (adjusted incidence reductions 18% and 10%, resp). Significant reductions were only seen for lung and liver cancer. This remains an active area of research and a range of mechanisms have been suggested for metformin's action including activation of the AMPK pathway or a direct effect on the insulin levels via the liver⁴⁵.

There are a vast range of agents, many of which are food constituents or their derivatives, which have shown anti-cancer effects in laboratory systems but for which evidence in humans is lacking or very minimal. It is not possible to review them all here. The US National Cancer Institute has a long standing and active programme in evaluating such agents. They periodically publish a compendium of drugs undergoing evaluation as potential cancer-preventive agents⁴⁶. Most of these are still being investigated in laboratory systems, but some are also undergoing early Phase 1 and Phase 2 studies⁴⁷, where biomarkers are also being studied as early indicators of treatment response.

Dietary components

Many studies have suggested a protective effect of consumption of fruits and vegetables, with a stronger effect seen in vegetables⁴⁸. Specific potential ingredients include sulphoraphane found in cruciferous vegetables⁴⁹ and lycopene, which is particularly high in cooked tomatoes, but is also found in other fruits and vegetables. High tomato consumption was initially linked to reduced prostate cancer risk by Mills et al⁵⁰. A recent overview found no overall effect but a suggestion it might protect against high grade or fatal disease⁵¹.

A number of spices have also been proposed to have protective effects⁵². Curcumin which comes from turmeric has been most studied, but there is still very limited human data for cancer prevention⁵³. Of the many hundreds of other compounds⁵⁴, resveratrol, which mostly comes from red wine and berries^{55,56}, green tea polyphenols⁵⁷, and pomegranate⁵⁸ have received much attention but again convincing human evidence of efficacy is lacking.

The evidence for a role of vitamin D with or without calcium is very mixed but overall there is currently no compelling evidence that it has an effect on any cancer site either for incidence or mortality^{59,82}.

Agents that haven't worked

Epidemiologic and laboratory evidence suggested a potential anti-cancer effect of Vitamin A, beta carotene and their analogues^{60,61}. Despite randomised evidence of a benefit of beta carotene, vitamin E, and selenium in a severely deficient population in Linxian, China⁶², subsequent studies in the West have been negative. Two large studies of beta carotene in heavy smokers and asbestos exposed workers^{63,64} found it actually lead to increases in the incidence of lung cancer and Omenn et al⁶³ found an increase in all-cause mortality. In an overview of all randomised trials of β -carotene Druesne-Pecollo et al⁶⁵ confirmed an increase in lung cancer incidence, and also found an increase in gastric cancer and no significant effect on other cancers, either individually or overall.

Trials of vitamin E, and selenium, both of which were thought to have a beneficial effect on prostate cancer, have also been negative. In particular neither selenium nor vitamin E supplementation reduced the incidence of prostate cancer in the SELECT trial, in which prostate cancer was the primary endpoint. Klein et al⁶⁶ reported that in 35 533 men with a PSA

of 4 ng/mL or less and a negative digital rectal examination, the incidence of prostate cancer increased by 17% with vitamin E supplementation. Other studies have not shown any effects of supplementation on the incidence of prostate cancer⁶⁷, colorectal cancer⁶⁸ or cause specific mortality⁶⁹.

The use of 5 α -reductase inhibitors either for prevention or management of early prostate cancer has produced complex outcomes, with substantial reductions in low Gleason grade disease but an apparent increase in high grade cancers. The Prostate Cancer Prevention Trial (PCPT)⁷⁰ investigated finasteride in men with low PSA (≤ 3 mg/mL) and no evidence of disease. After 18 years of follow-up, a 30% (95%CI 24-35%) reduction was observed in all prostate cancers based on a 43% reduction in low Gleason grade tumours but a 17% increase in high grade (Gleason 7 or higher) cancers. No impact on death from prostate cancer was seen. Similar results were reported in the REDUCE trial⁷¹, which assessed dutasteride, another 5 α -reductase inhibitor, in a high-risk population of men with a PSA concentration between 2.5 ng/mL and 10 ng/mL and a negative initial prostate biopsy. After 4 years of follow-up, a 23% reduction in overall prostate cancer incidence was reported compared with controls who received placebo, but there was no effect on cancers with Gleason score 7 or higher, and an increase in Gleason 10 tumours. Although both drugs have a beneficial effects on benign prostatic disease, the apparent increase in risk of high-grade tumours is of major concern. It has been suggested that this may be a result of detection bias. An increase in the sampling accuracy of the prostate with the then common six-needle biopsy, because of smaller total prostate size after 5 α -reductase inhibitor therapy, has been offered as an explanation for this finding. Overall the evidence for a detrimental or protective effect on the incidence of high grade prostate cancer or prostate cancer specific site-specific mortality remains inconclusive⁷², and neither finasteride nor dutasteride have been approved by the Food and Drug Administration for cancer prevention.

There has also been much interest in the role of statins for cancer prevention, but the overall evidence is largely negative⁷³.

Conclusions

Despite its early stage of development, preventive therapy already has made important discoveries which have the potential to make useful reductions in cancer incidence. Of these low dose aspirin stands out as having the largest potential impact on the population at large. This is because it has a major impact on three common gastrointestinal cancers – colorectal, gastric and oesophageal, and potentially provides small reductions in 3 other major cancers – lung, breast and prostate. In terms of relative overall importance for cancer prevention tobacco cessation remains the most important factor, and Parkin⁷⁴ have estimated that tobacco use is responsible for 19% of all cancers. However they have calculated that no other activity is responsible for more than 10% of cancers, and the estimate that between 7-10% of cancers could be avoided by taking a daily low dose aspirin for 10 years between ages 50-65y with a larger 9-13% reduction for mortality²⁸ makes this a key element of any cancer prevention strategy. Other preventive activities such as eating more vegetables, reducing obesity, and taking more exercise are much harder to achieve⁸¹, and obtaining the full cancer reduction benefit identified from controlling these factors is unrealistic. While we are a long way from achieving the full benefit of preventive therapy, widespread use of aspirin is likely to be more acceptable, and other more toxic agents can be targeted to high risk individuals where there is a greater possibility of acceptance. Clearly a strategy that uses both approaches is needed.

Several major challenges remain however. Key among these is to find ways to encourage more widespread use of agents with established utility. Uptake of tamoxifen in women at high risk of breast cancer is only 10% at best and much of this is due to a lack of knowledge and interest

in prevention from health professionals. Aspirin has suffered from earlier recommendations from professional bodies against using it in the general population⁷⁵. However these recommendations were based on comparing cardiovascular benefits to bleeding risks, and now need updating in view of the much larger benefits seen for cancer prevention than for cardiovascular disease. These have only appeared more recently, largely due to the fact that they were not apparent until after 3-5 years of aspirin use.

There are several areas where further work is needed to focus the use of prevention agents. Key among these is risk assessment. This is less critical for aspirin as benefits are for a range of cancers, and we still do not understand the mechanisms behind its cancer prevention effects. Knowing these may help to focus use on those most likely to benefit, but a more immediate need is to understand who is at greatest risk of bleeding side effects, so that avoidance of use or treatment predisposing factors such as helicobacter infection can be employed. For the use of anti-oestrogen agents to prevent breast cancer, serious side effects are more common and risk in the general population is lower so targeting therapies to high risk individuals is essential to achieve a favourable benefit-risk ratio. Classical factors as combined in risk scores^{76,77}, mammographic breast density⁷⁸ and a panel of individual SNPs that are common but individually have low predictive power but in combination appear useful⁷⁹ all are useful in risk assessment. Finding the best way to combine these factors to produce a more comprehensive risk model is needed.

A similar need is to find biomarkers which not only accurately predict risk, but also response to treatment, as LDL cholesterol and blood pressure provide for cardiovascular disease. Changes in mammographic breast density have been shown to predict response to endocrine agents both in the preventive⁸⁰ and adjuvant treatment settings, but 6-12 months of treatment is needed to detect this, and earlier markers of effect are desirable.

There is still a long list of promising agents that need further investigation. Full scale prevention trials are expensive and require long term follow up. They probably are unavoidable for agents in which widespread use is proposed, but we need better biomarkers and greater understanding of mechanisms to ensure we target the large prevention trials on agents very likely to be effective.

We also need to integrate activities to promote preventive therapy with those to encourage a healthy lifestyle. Neither of these alone will eliminate cancer, and adoption of one does not obviate the need for the other. In this regard we need to better integrate preventive therapy with other activities. Linking it with screening, especially breast screening where women attend a dedicated screening centre, is an obvious but undeveloped approach. However, this will require specialist staff in the screening clinics to be effective. Consideration of renaming breast screening programmes as breast cancer prevention programmes has merit, especially as mammographic breast density is an important risk factor which needs to be combined with a risk assessment based on family history and other classical risk factors, and possibly including a SNP risk score from blood or saliva. Advice from a trained nurse about what can be done to lower risk not only for breast cancer but other cancers and diseases is also needed to make this effective.

In addition to developing and publicizing effective agents we also have an obligation to debunk claims for ineffective agents. Cancer is such an emotional issue that people can often be misled by unsubstantiated claims for prevention or cure and part of a programme for cancer prevention needs to also make clear when evidence for an effect is very limited, non-existent or even clearly negative.

Prevention has become an integral part of cardiovascular medicine where risk factors such as high cholesterol or hypertension have been raised to the level of diseases in their own right.

Although preventive therapy for cancer is still in its early days, we have already identified agents which if fully used would have an important impact on incidence and mortality. Because of the site specific nature and mechanistic complexity of cancer, progress will be challenging but there are already sufficient leads to feel confident that more can be achieved.

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Tables

Table 1. Established methods for cancer prevention

Agent	Type of study	Relevant studies	Number evaluated	Key findings
Surgery				
Colectomy for polyposis coli	Danish nation cohort	Bisgaard ¹ Half ²		Surgery almost 100% effective if before cancer
Oophorectomy for BRCA mutant carriers	Expert review of cohorts	Guillem ⁴		100% for ovary ~50% for breast
Bilateral Mastectomy for BRCA mutant carriers	Meta –analysis of cohorts	Ludwig ⁵		90-95% effective
HPV vaccination	3 major RCTs of VLP based vaccines (16,18), (6,11,16,18), (6,11,16,18,31,33,45, 52, 58)	Paavonen ⁸ Ault ⁷ Joura ⁹	43 442	>95% protection against CIN lesions due to vaccine types if given before infection. Some cross protection against other HPV types.
HPB Vaccination	Taiwan National cohort	Chang ¹⁰	1509 cases of HCC of which 166 vaccinated	76% reduction of hepatocellular cancer in those vaccinated
Pharmaceutical agents				
Aspirin	RCTs and observational studies	Rothwell ³⁰ Algra ³¹ Bosetti ³² Cuzick ²⁸	69 224 RCT 52 926 CC	7-10% reduction in all cancer incidence and 9-12% in mortality in 10y users. Mostly colorectal, gastric and oesophageal cancer (30% each) with smaller and less certain reductions in breast, prostate and lung (5=15%)
Anti-oestrogen compounds				
SERMs				
Tamoxifen	4 RCTs in high risk women	Powles, Fisher,Cuzick,	28 193	33% reduction in all BC based on 44% of ER+

		Veronesi as summarized in Cuzick ¹⁶		invasive and no effect on ERneg
Raloxifene	3 RCTs (one vs tamoxifen in high risk women)	Martino ²⁰ Barrett-Connor ²¹ Vogel ²²	37296	34% reduction overall with 56% reduction of ER+ invasive. 25% less effective than tam in direct comparison in high risk women
Lasofixifene	1 RCT in osteoporotic women	LaCroix ²³	8856	79% reduction in all BC for higher dose 18% reduction for lower dose
Arzoxifene	1 RCT in osteoporotic women	Powles ²⁴	9354	58% reduction for all BC 70% reduction for ER+ BC
Aromatase Inhibitors				
Anastrozole	1 RCT in high risk women; contralateral tumours in RCTs in adjuvant setting	Cuzick ²⁸	3864	53% reduction in all BC 58% reduction in ER+ invasive BC
Exemestane	1 RCT in high risk women; RCT of contralateral tumours in adjuvant setting	Goss ²⁷	4560	53% reduction in all BC 73% reduction in ER+ invasive BC
Oral Contraceptives	Meta-analysis of 24 case control and Cohort studies	Havrilesky ¹³		27% reduction for any use >50 % reduction for > 10y use

Table 2. Potential common or major side effects of pharmacologic agents considered for cancer prevention.

Agent	Side effect	Findings
Tamoxifen/SERMs	Endometrial cancer	2-3 fold increase except for raloxifene
	Venous thromboembolic events	73% increase overall; smaller increase with raloxifene
	Vasomotor symptoms	20% increase during treatment; no effect subsequently
Aromatase Inhibitors	Bone Fractures	50% increase in adjuvant trials without baseline bone density scan; NS 11% increase in prevention studies with baseline identification and treatment of women with low bone density
	Musculoskeletal symptoms/ arthralgia	Increase from 58% in placebo to 64% with anastrozole (10% relative increase)
	Carpal tunnel syndrome	3.6 fold increase in adjuvant setting vs tamoxifen (3% v1%) 58% increase (3% vs 2%) in prevention
	Vasomotor symptoms	15% increase overall; 20% increase in severe symptoms
	Vaginal dryness/ Dyspareunia/Libido loss	20% increase (19%v 16%) prevention setting vs placebo (3-fold increase vs tamoxifen in adjuvant setting (1% v 0.3%)
Aspirin/ NSAIDs	Gastrointestinal bleeding	Increase of about 50%, mostly in initial period after starting treatment.
	Haemorrhagic Stroke	35% increase, but larger reduction in occlusive strokes Net decrease in incidence but increase in fatal events

Figure 1. Long term effect of tamoxifen on breast cancer prevention in the IBIS-I trial. From Cuzick²⁸ et al Lancet Oncology 2014.

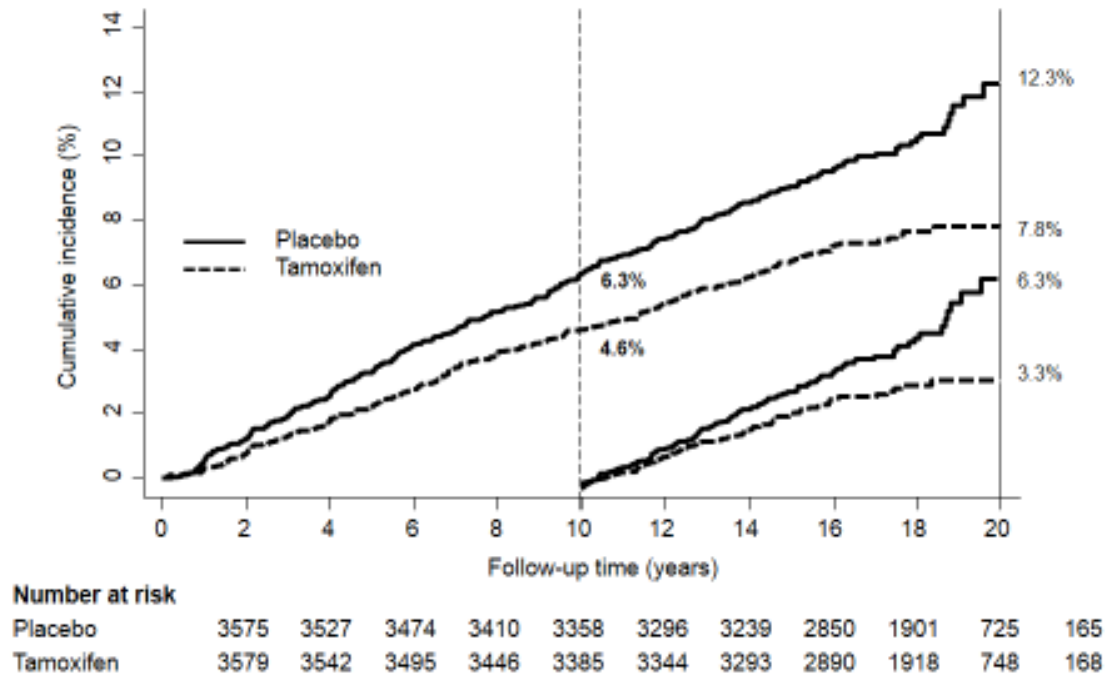


Figure 2. Impact of aspirin on cancer mortality by scheduled duration of treatment. From Rothwell³⁰ et al 2011.

