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Chemoprevention: From research to clinical oncology

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Abstract

Chemoprevention is by now an emerging area of clinical oncology addressed to healthy individuals at higher risk for cancer, subjects with precancerous conditions, and patients who are at risk for a second primary cancer. The important results of large trials with various agents and the more accurate methods of risk assessment have already had implications in clinical practice. Recently, a number of compounds have shown to be clinically effective at various organ levels, often covering all the three settings of primary, secondary and tertiary prevention.

There is proof today that at least 3 of the 4 'big killers' in oncology – breast, colon and prostate cancer – and oral cancer are to a certain extent preventable by chemopreventive drugs. The missing piece so far is lung cancer.

The expanding molecular drug development is providing the tools for a more effective and safer molecular-targeted prevention. Combination chemoprevention and the use of agents with multiple effects are other particularly promising chemoprevention strategies.

Keywords: Chemoprevention; Clinical trials; Breast neoplasm; Colorectal neoplasm; Prostate neoplasm

1. Cancer prevention strategies

Cancer prevention and control is unquestionably a major health issue. The burden of some of the 'big killers' – such as breast, colon and prostate cancer – has recently been reduced by means of early diagnosis and screening; and more effective and tailored surgical, medical and radiation therapy. Nonetheless, a significant proportion of cancers still elude our ultimate control. This limitation could be substantially corrected by increased research and clinical applications of cancer prevention.

The significant results of numerous basic, translational, epidemiological and clinical studies have already led not only to substantial changes in practical medicine by health providers, but also to a rising awareness of the importance and a growing demand of cancer prevention in the general population.

Recognition of the emerging field of cancer prevention is increasing world-wide [1]. In the USA, this involves intensifying the activities of the NCI (National Cancer Institute) prevention branch, and a stronger commitment to prevention by ASCO (American Society of Clinical Oncology) and AACR (American Association of Cancer Research). A similar interest is growing in Europe as well and prevention is already a core policy of most of the important scientific centres and strategic plans of the European Union (EU) for the next years.

Cancer prevention has improved significantly over the last decade and the chemopreventive efficacy and safety of many compounds has been repeatedly documented. Pharmacological prevention of cancer is a relatively

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new field in clinical oncology, but it represents a very promising approach to reducing the incidence and burden of cancer. It follows the example of other medical disciplines, such as cardiology where it is common practice to treat subjects at higher risk for cardiovascular disease long before clinical evidence and that has definitely contributed to decreased mortality. A similar strategy can be adopted for prevention of cancer in subjects with various conditions of higher risk [2,3].

The peculiarity of carcinogenesis is that it is a multistep, multipath and multifocal process, involving a series of genetic and epigenetic alterations that leads the initial status of genomic instability up to the final development of cancer [3]. This is the key notion that supports the rationale for intervening in early steps of the process (*i.e.* before or at the stage of *intraepithelial neoplasia* or *IEN*), using natural or synthetic agents potentially able to delay, arrest or even reverse the pathogenesis of cancer. Since the process is mostly very long (10–20 years, sometimes more), there is potentially a lot of time to implement risk assessment and to intervene with nutrients and/or pharmacological agents in order to interrupt the chain of molecular events long before the onset of clinical symptoms. This may be especially useful in the case of solid tumours, which are often characterised by multifocality and metachronous growth of lesions as the results of the biologically plausible concept of field carcinogenesis and intraepithelial clonal spread [4–6].

Recently, a number of compounds have shown to be clinically effective at various organ levels, covering all the three settings in which prevention may be typically divided into: primary, where the goal is to prevent the onset of the disease, selecting healthy cohorts at high risk for environmental or lifestyle or familial/genetic factors; secondary, aimed at treating a population with a premalignant condition or an *in situ* neoplasia thereby blocking its evolution to cancer; and tertiary, which intends to protect against second primary tumours in subjects previously cured for a cancer.

Important practical advances have been reached after the results of big randomised clinical trials, which have significantly reduced cancer risk of the breast, colon and prostate. Remarkably, in the USA the results of the NSABP P-1 breast cancer prevention trial have led the FDA (Food and Drug Administration) to extend the approval for the use of tamoxifen in all the three prevention settings, *i.e.* not only for prevention of contralateral cancer and for prevention of DCIS (ductal carcinoma *in situ*), but also as a chemopreventive agent in women at high risk for breast cancer [7,8]. Another major change for public health has come from PCPT (prostate cancer prevention trial) results where finasteride, drug that is largely used for benign prostatic hypertrophy, was shown to reduce prostate cancer risk by 25% [9, see also Mellon, this issue]. Other important clinical trials has led FDA to approve the use of celecoxib as adjunct treatment of FAP (familial adenomatous polyposis) [10] and have shown the efficacy of NSAIDs (non-steroidal antinflammatory drugs) and micronutrients, like aspirin, sulindac and calcium in reducing sporadic and hereditary colorectal adenoma and carcinoma [10–12].

None of the above trials are without defects of course. For instance, the fact that the striking effects of tamoxifen in the NSABP P-1 have only been partially confirmed by the European studies, and the increased number of prostate cancers with a high Gleason score in the PCPT treated arm are much debated issues and present current limitations to widspread clinical application of these drugs. However, what is becoming evident is that many – and possibly all – cancers may be preventable. The complex aspects of the risk/benefit ratio of the use of the drugs, the appropriate dose and duration of treatment and the choice of subjects at high risk who can benefit most by it are still unresolved issues and will require additional research.

The reduction in cancer incidence and mortality, which is ultimately needed to show the chemopreventive efficacy of an agent, unfortunately requires phase III studies with large numbers of patient participation that can last for several years and are extremely costly. These studies are especially problematic for academic research centers and no-profit organisations and are not appealing to pharmaceutical companies. This issue is becoming crucial at the present time and severely limits the number of compounds that can be studied by the scientific community.

To overcome these difficulties, an additional strategy has been encouraged. This aims to search and develop intermediate endpoints of intervention efficacy, or SEBs (surrogate endpoint biomarkers) [2,13]. SEBs can include specific molecular pathways, levels of circulating proteins, expression of histological markers, the presence of atypia in cytological samples, detection of genomic DNA from malignant cells in the peripheral blood, or other events that may be assessed in the pre-clinical phase of cancer and are associated with its development. The use of SEBs may substantially reduce sample size, time, and costs of chemoprevention studies. The studies on SEBs may be particularly useful when used according to a step-by-step, sequential strategy that is able to confirm the efficacy and safety of a drug on subsequent intermediate endpoints in phase II trials. SEBs can also be studied in a presurgical model of research, *i.e.* the use of one or more drug treatments for few weeks before surgery in patient candidates for surgical treatment of early stage primary cancer and who are not suitable for neoadjuvant therapy. The presurgical approach has already been successfully applied in breast cancer chemoprevention to test the effects of SERMs on various biological markers (Ki-67, ER, PgR, Her-2/neu) [14]. The series of results on intermediate SEBs may then be used more

efficaciously and rapidly to reach the ultimate clinical endpoint of cancer reduction in a wider population.

A large amount of studies on SEBs have been implemented and some of them (particularly those on colorectal adenoma reduction) have already shown the efficacy of this research model in clinical cancer prevention. In other organs like breast, no definitive SEB has been demonstrated so far as to be able to explain the intervention effect to a completely significant degree in the same way as, for instance, the variation of cholesterol levels subsequent to lipid lowering treatment (*e.g.* with statins) in cardiovascular medicine [15]. However, several putative SEBs are very promising, such as IGF-I (insulin-like growth factor-I) and its main binding protein BP-3 [16], some hormones (*e.g.* free oestradiol) [17], atypical cells in cytological samples [18, see also Ranger-Moore *et al*., this issue] and high mammographic density studied with computerised techniques [19].

Importantly, the last generation of cancer chemoprevention studies, both phase III and phase II trials, are also providing data on biomarkers for cardiovascular and bone risk. The demonstration of a solid risk/benefit ratio for a drug should involve all the most frequent health risks, not only cancer. This is particularly true in the prevention setting and it is interesting to observe that some of the most effective drugs used in breast cancer treatment and prevention (*e.g.* tamoxifen and other SERMs at the right dose) have shown, so far, this positive balance [8,20].

Research into behavioural and nutritional sciences is of great importance in cancer prevention and is strictly correlated to chemoprevention. Obesity and tobacco use are two largely avoidable causes of cancer and their control will rely much on public education and health policies and also on research on the basic biology and susceptibility genes for smoking and eating behaviour. In the mean while, much can and should be done to avoid smoke and to modify patterns of diet and, possibly more importantly, to increase physical exercise. Among risk markers, and strictly correlated to obesity and other behavioural issues, are hormonal factors. Research on the complex endocrine mechanisms of tumourigenesis and their modulation by drugs are ongoing and may be crucial for prevention of many cancers, such as breast and prostate. Another great cause of cancer, which is susceptible to control, is represented by infections. Typical examples of correlation are HBV (hepatitis B virus), HPV (human papilloma virus), and *Helicobater pylori*, for liver, cervical and gastric cancer, respectively. Here, screening and early detection programmes, and vaccines may have a huge impact. However, chemoprevention may be important too in at-risk subjects. In the case of the cervix, for instance, vaccines will not cover the whole problem, and HPV positive subjects with cervical IEN should be the focus of increased chemoprevention research [21,22].

Importantly, many recent studies on obesity and inflammation are showing more clearly the role of inflammation in the aetiology of cancer. This is very much in accordance with the pathogenesis of other chronic diseases, such as atherosclerosis that start as an inflammatory disorder. Obesity is a major cause of inflammation and many inflammatory conditions are well known cancer precursors (Barrett's oesophagus, chronic gastritis, hepatitis and pancreatitis, ulcerative colitis). Recently, the presence of chronic inflammation and atrophy at the same time has been described, for instance, in prostate. So, early correction of inflammatory conditions by chemoprevention may be very useful.

The enormous advances in molecular biology and molecular drug development are providing an invaluable support to cancer prevention. Fundamental advances have been made after major studies with molecular targeted drugs, such as tamoxifen, celecoxib and finasteride [8–10]. Now, thanks to multiplying molecular studies, we are facing a time in which a potentially very wide range of targeted drugs may reveal an excellent risk/benefit balance. Potential molecular targets include tyrosine kinases, RAR/RXR, AIB1, mediators of angiogenesis like VEGFR, hystone deacetylase, 15-LOX, COX-2, PPARs, HMG-CoA and many others. The potential benefit by targeted drugs, such as NSAIDs or statins, may cover a very large spectrum of conditions, from early IEN to invasive cancer, and this really contributes to reduce and to re-think the traditional distinction between prevention and therapy [1, see also Thierry-Vullemin *et al*., this issue].

An essential aspect of chemoprevention is the definition of the appropriate target population by selecting and identifying the criteria for high-risk subjects in order to positively increase the risk/benefit ratio of the intervention treatment. Risk assessment is in fact an integral part and the first phase of cancer prevention management. It is clearly more reasonable, ethically acceptable and cost-effective to address active prevention to selected subjects and categories with varying degree of increased risk rather than to general population at average risk.

Important target groups include those who are at high-risk for familial and genetic factors. Carriers of gene mutations are numerically a small proportion of all at-risk cohorts, but their risk is particularly high for one or more malignancies and they may frequently develop them at a much younger age than is the case for sporadic cancer [23]. Knowledge of various aspects of cancer genetics has grown enormously, and the recent possibility of genetic testing those predisposed to breast, ovarian, colorectal or other cancers has lead to an increasing impact of molecular data on the clinical management of selected mutation carriers [24]. However, we must be aware of the current limitations of the molecular diagnosis and the complexity of the multidisciplinary management of genetically predisposed individuals. The

combination of the main preventive strategies (intensive surveillance, pharmacological prevention and surgical prophylaxis) in these individuals at high-risk is a very complicated issue and should always be modulated and tailored to every subject and family, and constantly revised in light of new research data.

Besides genetic mutations, there are a number of other conditions for higher risk, which we are able to recognise. Current biostatistical models such as the Gail model, although still imperfect, are of great help to clinicians, especially in the presence of tissue and circulating risk markers. Molecular diagnostics, imaging modalities, endoscopy and sampling modalities like needle biopsies and breast ductal lavage (DL) are practically very useful to confirm the level of risk deriving from the presence of different types of IEN, such as colorectal adenomas or breast AH (atypical hyperplasia) or LIN (lobular intraepithelial neoplasia) or atypical cells in fine needle aspirations and DL. There are also highest-risk IEN, like oral IEN with aneuploidy or FAP (familial adenomatous polyposis). All these conditions of higher risk are targets for specific risk-reducing drug treatment. Biology and molecular studies (*e.g.* on polymorphisms) are already offering new models of risk estimation and may help in predicting response to drugs. An increased use of these molecular tools will be very helpful for the more sophisticated clinicians' decision-making process and will definitely favour the acceptability of chemoprevention, especially in unaffected individuals.

A more sophisticated ability to select at-risk individuals as targets for preventive interventions is by now fortunately accompanied by an ever increasing number and quality of compounds which are confirming their preventative potential in the clinical setting (see also Crowell, this issue).

Impressive results have been reached especially in chemoprevention of breast, colorectal and prostate cancer. Significantly, the possibility of molecular-targeted prevention is confirmed at these sites by the beneficial effects of compounds targeting ER (oestrogen receptor), COX-2 (cyclooxygenase-2), and 5αR (5-α-reductase), respectively [8–10].

2. Breast cancer

Some of the major achievements have been reached in breast cancer (BC) chemoprevention (see also [14]). Tamoxifen studies have proven that chemoprevention can successfully cover all the targets of the three settings of prevention: healthy women at increased risk using the Gail model; patients with ductal carcinoma *in situ*; and definitively treated breast cancer patients.

A recent meta-analysis has been conducted [25] on all four major primary prevention trials of tamoxifen involving 28,406 healthy subjects [8,26–29], the multiple outcome raloxifene endpoint (MORE) study in 7705 osteoporotic women [30] and the 14,170 patients participating in adjuvant trials where the effect on contralateral breast cancer was assessed. The tamoxifen prevention trials showed a 38% (95% CI 28–46) reduction of breast cancer incidence. There was no effect on ER negative breast cancer, HR ratio 1.22 [0.89–1.67], but ER-positive cancers were decreased by 48% (36–58; $P < 0.0001$) in the tamoxifen prevention trials. Age had no apparent effect on tamoxifen efficacy. Rates of endometrial cancer were increased in all tamoxifen prevention trials, RR 2.4 [1.5–4.0] and the adjuvant trials (RR 3.4 [1.8–6.4], while no increase has been seen so far with raloxifene. Venous thromboembolic events were increased in all tamoxifen studies (RR 1.9 [1.4–2.6] in the prevention trials; $P < 0.0001$) and with raloxifene.

The evidence now clearly shows that tamoxifen can reduce the risk of ER-positive breast cancer. A point of debate involving the results of preventive tamoxifen is: is it really prevention or treatment of early breast cancer, *i.e.* delaying it? Keeping in mind that the curves of the incidence of carcinoma and DCIS in the 2 arms of the NSABP P-1 separate early and continue to separate after treatment cessation, what is really important is that even a delay of 10–30 years may well be considered prevention. New approaches are now needed to prevent ER-negative breast cancer and to reduce tamoxifen's adverse events, including employment of a lower dose of tamoxifen and the use of aspirin to reduce the risk of VTE. Newer agents such as raloxifene and aromatase inhibitors need to be evaluated.

A simple and economic approach to retain tamoxifen efficacy while reducing its risks may be a dose reduction. Recent phase II trials have shown that doses as low as a twentieth of the standard daily dose are able to beneficially influence a wide spectrum of markers of breast carcinogenesis (including cell proliferation by Ki-67%, IGF-I, IGFBP-3, estrogens, mammographic density) and cardiovascular risk (*e.g.* ultrasensitive C-reactive protein) [14,31]. Provided that lower doses of the drug do not increase the risk of endometrial proliferative lesions and venous thrombosis while confirming the effect on breast cancer incidence, the rationale for wider use of low-dose tamoxifen in high-risk cohorts should provide a better risk/benefit ratio.

The analysis of the Italian Tamoxifen Study has shown that tamoxifen also appears to be beneficial in women at increased risk for ER-positive breast cancer arising from hormonal and reproductive factors such as early menarche, delayed first pregnancy, preserved ovarian function and height [32]. Notably, previous studies have shown that the combination of HRT and tamoxifen does not adversely affect their biological effects, including bone density and clotting factors [33,34], and there is evidence for a negative interaction between tamoxifen and ERT on VTE in the IBIS trial [29]. Apparently, for

all three major endpoints (breast cancer, endometrial cancer and VTE) the combination of HRT and tamoxifen seems to reduce risks while retaining benefits of either agent alone [26,29]. All these findings strongly justify studying the effect of the combination of HRT and tamoxifen in order to reduce the risks while retaining the benefit of either agent. To this aim, the H.O.T. study (HRT Opposed by Tamoxifen at low dose), a multicentric phase III trial of tamoxifen 5 mg/day vs. placebo in HRT users, is ongoing in Italy [35].

Raloxifene is another SERM used for treatment of osteoporosis that is potentially less hazardous than tamoxifen, since it has not been shown to induce endometrial cancer; however, it still may produce blood clots, and its long-term efficacy and safety profile are still unknown [25]. In the MORE study, raloxifene has shown a consistent 62% reduction of invasive breast cancer in postmenopausal women over a four-year period (RR = 0.38; CI = 0.24–0.58). Raloxifene had a marked effect on ER-positive tumours, reducing incidence by 72% (RR 0.28, 95%; CI 0.17–0.46) with no effect on the incidence of ER-negative tumours [30]. In the five-year STAR study, raloxifene is being evaluated in comparison with tamoxifen 20 mg/day. This is a large primary prevention trial in postmenopausal high-risk women based on the Gail model or women with previous lobular carcinoma *in situ*. A total of 19,000 patients will be recruited to assess the non-inferiority of raloxifene over tamoxifen. The main outcome measure is breast cancer and the results are expected in June 2006.

One of the less toxic vitamin A analogues studied for breast cancer chemoprevention is (*N*-4-hydroxyphenyl) retinamide or fenretinide. A phase III trial has been completed in 2972 women with a history of stage I breast cancer randomised to fenretinide 200 mg/day or no intervention for 5 years. The primary endpoint was the occurrence of contralateral breast cancer. The analysis after a median of 8 years has shown that fenretinide significantly reduced the rate of local recurrence in premenopausal women but not in postmenopausal women [36].

The new third generation aromatase inhibitors (AIs) have shown good efficacy in advanced breast cancer and have a low toxicity profile. Some large randomised trials have also shown the significant efficacy in the adjuvant setting of anastrozole, letrozole and exemestane [37–39]. They offer another approach to local control, prevention of recurrence and possibly prevention of primary breast cancers, which may be superior and/or complimentary to the use of SERMs. However, they have caused significant increases in musculo-skeletal disorders, primarily arthralgia, bone fractures and lipid disorders, which partly question their overall therapeutic index [40]. A large international trial (IBIS II) has recently started to test the chemopreventive effect of anastrozole in postmenopausal high-risk subjects and DCIS patients.

A high scientific and clinical priority is represented by ER-negative breast cancers, which account for a significant proportion of breast cancers and whose incidence is not affected by SERMs or AIs. Strategies to prevent ER-negative tumours are actively being sought using many potentially active drugs: tyrosine kinase and cyclin-dependent kinase inhibitors, PPARγ ligands (glitazones), RXR selective ligands (rexinoids), COX-2 inhibitors, statins, demethylating agents, histone deacetylase inhibitors, Vit D3 derivatives and many others.

3. Colorectal cancer

Colorectal cancer (CRC) represents an optimal model for primary and secondary prevention, given the availability of effective screening procedures and of a well-defined multi-step carcinogenic pathway with adenomatous polyp as an intermediate step and a very good surrogate biomarker [41]. Regular screening with examination of faecal occult blood and additional intermittent endoscopy may reduce the mortality up to 33% [42,43]. Nevertheless, the real role and the best method for a screening program is still uncertain, due also to the relatively poor compliance to such programs [44].

A huge number of observational and randomised trials have shown the preventive properties of various drugs and micronutrients: aspirin, sulindac, anti COX-2 and other NSAIDs, calcium and vitamin D, selenium, folic acid, HRT (hormone replacement therapy), soy, curcumin (see also Sharma *et al.*, this issue) and green tea polyphenols [45–47].

The potential preventive effect of dietary agents may be very appealing to many. However, studies on diet changes and specific supplementations have not yet shown significant efficacy. While reduction in fat, supplements of fiber, beta-carotene, vitamin C and E have failed to reduce recurrence of adenoma or CRC [48–50], four other groups of compounds have indeed demonstrated significant efficacy in randomised trials: NSAIDs, calcium, selenium and HRT.

Calcium carbonate supplement has shown a moderate but consistent reducing effect on adenoma recurrence in two randomised trials [11,51]. The Nutritional Prevention of Cancer trial [52] revealed a significant 58% reduction in CRC incidence with selenium supplementation, and this has prompted further investigation in the SELECT trial and in another ongoing specific study of selenium in colorectal chemoprevention.

A meta-analysis of 18 epidemiological studies have evidenced that current HRT use (*i.e.* oestrogens alone or combined with progestins) reduces CRC risk by 20% [53]. The WHI study, the largest randomised trial of HRT so far, has shown a significant 37% decrease in CRC incidence with the use of HRT, with the exception of women who had used oestrogen alone [54,55].

This chemopreventive effect on colon is important because it may influence the therapeutic index of HRT, counterbalancing its risks on breast and the cardiovascular system in the long-term period.

NSAIDs are well-established molecular-target compounds with chemopreventive efficacy in various organs, including colon. Their activity involves the inhibition of COX-1 and/or COX-2, which are overexpressed in many precancers and cancers, thus reducing cell proliferation and neo-angiogenesis and increasing apoptosis [56, see also Hull, this issue]). Their COX-independent effects have been described too [57]. Many epidemiological studies have provided solid evidence of the beneficial and durable effects of aspirin and other NSAIDs on adenomas, cancers, and CRC-associated mortality, and of sulindac, celecoxib and other NSAIDs in FAP patients [58]. In the clinical setting, although aspirin in one study did show a null effect [59], more recently three other randomised trials of aspirin did show significant chemopreventive effects on adenoma and CRC recurrence [12,60,61]. It is interesting to observe that in Baron's study the best effects were observed in the group treated with the lowest dose of aspirin [12]. The super-selective COXIBs, such as celecoxib, have already revealed interesting preventive properties in FAP and sporadic adenomas [10,62], but their therapeutic index has been recently revised after the data on cardiovascular events in some randomised trials involving in particular rofecoxib.

Other promising compounds deserve further investigation in colorectal prevention. NO-aspirin (nitric oxide-releasing aspirin) has shown so far an increased anti-inflammatory activity compared to the parental aspirin, without any apparent gastric toxicity [63–65]. Nimesulide, although it is defined as a preferential rather than a selective COX-2 inhibitor, was among the most potent COX-2 inhibitors among a panel of NSAIDs tested for the COX-1 and -2 inhibition and selectivity. It exhibited a COX-2 selectivity ranging from 5 to 50-fold, which was comparable to celecoxib and just inferior to rofecoxib [66,67]. In addition, the incomplete COX-2 selectivity of nimesulide allows maintenance of its favourable effects such as lack of fluid retention, and probably protects against cardiovascular side effects [68]. The huge post-marketing surveillance provides an extended knowledge of nimesulide safety with respect to COXIBs. Given it is far less expensive than the newer drugs of the same class, nimesulide could represent a cost effective alternative strategy to be extended to a large population at higher risk for CRC.

4. Prostate cancer

Prostate cancer (PC) is another hormone-related cancer occurring after a long period of latency, thus potentially an ideal object of chemoprevention with agents antagonising the effect of androgens on the gland tissue. An important step forward in genetic epidemiology has been recently done and some genetic polymorphisms are intensively studied: these regard especially CYP17, SRD5A2 (steroid 5-α-reductase type II), and the AR gene [69]. The most promising, in order to develop a polygenic model of PC susceptibility, seems to be SRD5A2 [70]. SRD5A2 polymorphisms are common and are likely to strongly influence the effect of specific chemopreventive agents such as finasteride. This drug, administered daily for 7 years in a very large randomised trial in over 18,000 men (the PCPT trial) has caused a remarkable 25% reduction in PC prevalence [9]. However, this striking result has yet to be transferred to practical PC prevention due to concerns about sexual side effects and an increase in the risk of high-grade PCs by finasteride (280 cancers with Gleason score 7–10 in the treated arm of the PCPT versus 237 in the placebo arm; RR = 1.27, 95% CI, 1.07–1.50). The latter issue is the object of an extensive analysis of the trial pathology outcomes: so far it is not clear what is the real biological relevance and potential of this "grade effect". Further molecular studies in and out the PCPT will be of great use to tailor the profile of men who are most likely to benefit from SRD5A2 inhibition. This will add significantly to the current criteria we may use to identify candidates to PC chemoprevention (men at high PC risk, *i.e.* with first degree family history of PC, >64 years age, of black race, and with PSA level >2.0 ng/mL) and to the studies on chronic inflammation and atrophy especially in obese individuals in whom an association of BMI with higher PC mortality and grade has been shown.

In the meanwhile studies with novel compounds are proceeding. The REDUCE clinical trial is assessing the effects of dutasteride, a more potent SRD5A2 inhibitor, in 8000 men [71]. Other studies are investigating the chemopreventive effect and the safer sexual profile of other agents like bicalutamide.

5. Oral cancer

Oral cancer (OC) is another fairly common cancer and its precursor IEN, oral leukoplakia, is well recognised. Surgical resection of this IEN does not avoid oral cancer appearance, since oral cancer is most probably characterised by a process of field carcinogenesis and intraepithelial clonal spread [6]. This is especially important for aneuploid oral IEN [72]. Additional approaches are clearly needed. Recently, the knowledge on molecular markers has greatly improved, and LOH (or allelic imbalance) and aneuploidy are now reliable measures of the cancer risk of an oral IEN [73,74]. The seminal studies on 13cRA (13-*cis*-retinoic acid) [75] and nuclear RARs (retinoic acid receptors) [76] opened the way for a

better understanding of the molecular biology and risk of oral cancer. A number of drugs have then shown their molecular target effects. Fenretinide has shown to reduce OC risk [77]. COX-2 and EGFR are notably overexpressed in oral aneuploid IEN and cancer, and not in normal oral tissue [78,79]. The inhibition of either or both targets are the object of active investigation and studies with EKB-569 (an irreversible EGFR tyrosine kinase inhibitor) and celecoxib alone or in combination are under way in high-risk subjects with oral aneuploid IEN.

Thus, there is proof today that at least 3 of the 4 'big killers' in oncology – breast, colon and prostate cancer – and oral cancer are preventable. The missing piece so far is lung cancer.

6. Lung cancer

The burden caused by lung cancer is enormous worldwide and largely due to tobacco use. So we have the advantage to know that subjects at high-risk are mostly current and former heavy smokers. In Western countries, smoke cessation campaigns and stricter regulations are beginning to multiply. This strategy will surely achieve good results in the future. Still, there are age and gender groups (younger people and women) who are at present more reluctant to avoid smoking, while even more alarmingly the smoking epidemic is hitting the underdeveloped countries. In the meanwhile, new screening modalities are under evaluation: the most promising is currently spiral low-dose CT scan.

Studies on candidate drugs for lung cancer prevention have not provided any striking results. Apart from the disappointing outcome of the Finnish trial with beta-carotene [80,81], all other studies involving retinoids, vitamin A and *N*-acetylcysteine, even if safe, did not show convincing evidence of efficacy [82–84]. The current generation of prevention trials is focusing on the potential drug modulation of two different types of biomarkers: the study of the changes in bronchial dysplasia after drug treatment and the modifications of lung nodules at spiral CT. Some novel drugs are under evaluation in phase II setting. One of the most promising is budesonide, an aerosol corticosteroid that is largely used in the treatment of chronic bronchitis [85]. A phase II study with this drug is going to start shortly.

7. Conclusions

Chemoprevention is by now an emerging area of clinical oncology addressed to healthy individuals at higher risk for cancer, subjects with precancerous conditions, and patients who are at risk for a second primary cancer. The important results of large trials with various agents and with more accurate methods of risk assessment have already had implications in clinical practice. The expanding molecular drug development is providing the tools for a more effective and safer molecular-targeted prevention and producing in fact a convergence of prevention and therapy. The rapid advances in molecular sciences are also showing more and more clearly that many diseases with a long latency period, such as cancer, neurodegenerative conditions, atherosclerosis, and osteoporosis may have a common molecular pathogenesis.

In the near future, a more sophisticated management of individuals at higher risk might benefit from the combination of compounds – such as an endocrine agent and an anti-inflammatory drug – and from agents with pleiotropic effects (on inflammation, angiogenesis, apoptosis and oxidative stress) such as statins. This is likely to be one of the major approaches in the future, not only in cancer prevention, to global preventive medicine.

Conflict of interest statement

None declared.

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