

Research Paper

Acceptability of cancer chemoprevention trials: impact of the design

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Background: Chemoprevention could significantly reduce cancer burden. Assessment of efficacy and risk/benefit balance is at best achieved through randomized clinical trials.

Methods: At a periodic health examination center 1463 adults were asked to complete a questionnaire about their willingness to be involved in different kinds of preventive clinical trials.

Results: Among the 851 respondents (58.2%), 228 (26.8%) agreed to participate in a hypothetical chemoprevention trial aimed at reducing the incidence of lung cancer and 116 (29.3%) of 396 women agreed to a breast cancer chemoprevention trial. Randomization would not restrain participation (acceptability rate: 87.7% for lung cancer and 93.0% for breast cancer). In these volunteers, short-term trials (1 year) reached a high level of acceptability: 71.5% and 73.7% for lung and breast cancer prevention respectively. In contrast long-term trials (5 years or more) were far less acceptable: 9.2% for lung cancer (OR=7.7 CI_{95%} 4.4-14.0) and 10.5 % for breast cancer (OR=6.9 CI_{95%} 3.2-15.8). For lung cancer prevention, the route of administration impacts on acceptability with higher rate 53.1% for a pill vs. 7.9% for a spray (OR=6.7 CI_{95%} 3.6-12.9).

Conclusion: Overall healthy individuals are not keen to be involved in chemo-preventive trials, the design of which could however increase the acceptability rate.

Key words: Research Design, Randomized Controlled Trials, Behavior, Attitude, Preventive Health Services, Prevention & Control, Neoplasms, Breast, Lung

Introduction

Cancer control requires therapeutic and preventive innovations. Biomedical ‘upstream’ actions like vaccination [1] or chemoprevention [2] could significantly reduce cancer burden.

Efficacy, risks and benefits of such interventions are currently assessed by different means, of which randomized clinical trial is the gold standard. For preventive purposes this methodology requires (with respect to the annual rate of end-points) a large number of person-years in order to reach a fair discriminatory power.

In an ongoing randomized trial comparing two screening strategies we observed that 1000 persons had been interviewed in order to enroll 1.4 persons where 9 were eligible [3]. Based-on that experience we wanted to have more information on critical factors

that will help to increase that (low) acceptance rate. We decided to come back to the same population having been offered an actual screening trial asking them their opinion about different modalities of a future preventive trial. When considering the feasibility of such trials in the general population, information regarding the absolute and differential rates of acceptability according to different study designs represent valuable data.

Survey based on questionnaire or observed participation rate usually focused on patient perspectives: the impact of actual and perceived risk of being affected [4], the fear of side effects [5], psychological factors among which “worry” [6], demographic [7], and socio cultural or ethnic criteria [8]. The effect of physician recommendation also had been assessed [6,9]. All these factors impact on persons’ decision and multiple barriers exist [8]. We assumed that besides

these characteristics, different study designs are also relevant factors to consider.

Materials and Methods

The administrative organization within France relies on Regions: 25 with a mean population of about 2 400 000 inhabitants; range: 160 000 (Guyane)-11 000 000 (Ile de France). In almost every Region, the French National Health Insurance (Caisse National d'Assurance Maladie) set up a "Health Center" ("Centre de Sante") to promote prevention and screening of diseases. Once every 5 years, these centers sent invitations to all affiliated persons (working people, former or retired workers and their families). For 8 years now, invitations are extended to the whole population living in France through the Universal Health Coverage System ("Couverture Medicale Universelle").

We carried out a descriptive survey in the periodic health center located in Marseilles France. Between January 2003 and May 2003, we included consecutive clients (both women and men) over the legal age of 18 who agreed to participate in the survey.

Subjects were given a written description of the survey and were asked to complete, on site, a three part self-administrated questionnaire. The responses were elicited on a sheet of paper.

The first part recorded the socio-demographic variables and some general information (familial history, belief in the efficacy of treatments...). The second investigated the willingness to participate in a lung cancer chemoprevention trial depending on different design options: randomization, trial duration (years), and route of administration for lung cancer prevention (pill versus spray). The third part, intended for women only, investigated the willingness to participate in a breast cancer chemoprevention trial with the same design options. The questionnaire was built after a pilot phase with a face-to-face interview of 98 persons (these questionnaires were not used in the analysis presented).

One critical ethical issue about clinical trials is the acceptability of randomization and how lay people understand it [10]. In our questionnaire that issue was framed as: "To test the actual efficacy of a drug among 100 persons, 50 will receive the drug and 50 will receive a drug without effect (i.e. a pill that looks the same but is ineffective). Knowing that, would you still agree to participate in this trial?" This wording had been upheld after the pilot phase designed to increase actual understanding and to decrease the impact of how the question was phrased [11]. Information about the meaning of randomization was also disclosed in the initial informa-

tion sheet that described the offer to participate in the survey.

Social desirability bias cannot however been excluded [12].

CHI2 statistic tests (two-sided) and logistic regression were computed using SPSS v11.0. For women, willingness to participate in a trial (breast or lung cancer prevention) has been tested for correlation with willingness to participate in the other study (lung or breast), to have a quantitative assessment of this relationship and also, due to the concept of preferential risk aversion, whereby some individuals may be reluctant to participate in some kinds of trial but agree for different circumstances [13]. The other main *a priori* was that family history of a cancer might be an impetus to become involved in a preventive clinical trial.

The aim of this survey was to obtain descriptive data, and the results should be seen as preliminary but, from our perspective, will help to raise hypotheses deserving to be tested. Since no explicative goals were pursued no sample size was calculated [14].

The survey has been carried out according to the French legislation related to medical research and did not require a National or local IRB approval since data were strictly anonymous. Taking in account the advice of a local Ethical Board, an information sheet was delivered to the clients of the Periodic Health Center. The client returned (or didn't) the questionnaire filled or unfilled without any intervention of the staff aiming at increasing the response rate.

Results

During the recruitment period, 1463 questionnaires were distributed at the health examination center, 545 questionnaires were not returned or blank (without either explication or comment from the non-responding individuals), 918 (63%) were completed. Partial respondents and subjects who declared a personal cancer history were excluded. The statistical analysis was carried out on 851 questionnaires (response rate 58 %). The main characteristics of the sample are: 429 male (50.5%); mean age: 45.2 y; 36.5% with college graduation or higher and 234 current smokers (27.8%).

Among the 851 respondents, 228 (26.8%) would agree to participate in a lung cancer chemoprevention trial. Men (31.9%) agreed more often than women (21.4%) OR=1.7 95%CI 1.2-2.4. Using univariate analysis among men, tobacco exposure was the only factor associated with the willingness to participate (OR=2.3 95%CI 1.4-3.9). In a multivariate analysis among women, for lung cancer two factors were associated with a higher rate: agreement to participate in breast

cancer prevention trial (OR=84.3 95%CI 36.6-193.8) and being single (OR=2.2 95%CI 1.1-4.6).

Among 396 women, 116 (29.3%) declared agreement to participate in a breast cancer chemoprevention trial. Three factors were associated with agreement: willingness to participate in a lung cancer prevention trial (OR=103 95%CI 43-247), positive familial history of breast cancer (OR=3.2 95%CI 1.4-6.9), and trust in therapeutic efficacy (OR=2.1 95%CI 1.0-4.2) (table 1).

Table 1 Individual factors associated with the willingness to be involved in a preventive clinical trial. (Multivariate analysis using logistic regression)

Options	Person's positions	Lung cancer prevention male N=429 *	Lung cancer prevention female N=378	Breast cancer prevention N=373
Tobacco exposure	Yes versus no	OR 2.3 (1.4-3.9)	NS	NS
Willingness to be involved in an other preventive trial	Yes versus no	NA	OR 84.3 (36.6-193.8)	OR 103 (43-247)
Familial history of related cancer	Yes versus no	NS	NS	OR 3.2 (1.4-6.9)
Trust in the therapeutic efficacy	Yes versus no	NS	NS	OR 2.1 (1.0-4.2)
Being single	Yes versus no	NS	OR 2.2 (1.1-4.6)	NS
Older Age **	Yes versus no	NS	NS	NS
Higher Educational level ***	Yes versus no	NS	NS	NS

* Univariate analysis (Chi2), since only one factor was found significant, no multivariate analysis was carried out

**1 Above the lower quartile i.e. above 29 y old for the pooled population and above 31 y for female population (the case of breast cancer prevention)

***2 College or higher

The main result of this survey was that the level of acceptability exhibits huge differences according to the design of the trial (table 2). In the sub-group of volunteers, we observed a high acceptability rate for randomization: 87.7% for lung cancer and 93.0% for breast cancer. Short term trials (1 year) reached a high level of acceptability with 71.5% and 73.7% for lung and breast cancer prevention respectively, while long term trials (5 years or more) were far less acceptable: 9.2% for lung cancer (OR=7.7 95%CI 4.4-14.0) and 10.5% for breast cancer (OR=6.9 95%CI 3.2-15.8).

Among the 851 males and females, only 21 persons (2.5%) would agree to be randomized in a clinical trial looking at lung cancer prevention lasting 5 years or more. Among the 396 women in our sample only 12 (3.0%) would agree with a similar long-term trial for breast cancer prevention.

For lung cancer the route of administration of the active product made a difference, with a higher acceptability rate of an "ubiquitous" pill: 53.1%, far higher than the "disease-specific" spray 7.9% (OR=6.7 95%CI 3.6-12.9).

Table 2 Impact of the design of the trial on the acceptability rate in volunteers for a chemo-preventive trial.

Options	Person's positions	Lung cancer prevention N=228	Breast cancer prevention N=114*
Randomization	Agree	200 (87.7%)	106 (93.0%)
	Disagree	22 (9.6%)	8 (7.0%)
Time length (Trial duration)	1 y or less	163 (71.5%) **	84 (73.7%) ***
	2-3 y	24 (10.5%)	10 (8.8%)
	5 y or more	21 (9.2%)	12(10.5%)
Kind of treatment (Route of administration)	Pill	121 (53.1%) ****	-
	Spray	18 (7.9%)	-
	Indifferent	77 (33.8%)	-

* Among the 116 women who agreed to be involved in a chemo-preventive trial, 114 filled the part of the questionnaire regarding the trial options.

* for lung cancer prevention. Difference between 1 year or less and 5 years or more OR=7.7 95% CI 4.4-14.0

** for breast cancer prevention. Difference between 1 year or less and 5 years or more OR=6.9 95% CI 3.2-15.8

*** for lung cancer prevention. Difference between "a pill" and "a spray" OR=6.7 95% IC 3.6-12.9

Discussion

On average, regardless the kind of survey, acceptability rate is low and may even be lower in the non-respondents group due to psychological or social differences [15]. This low rate has been reported in various survey, 34.0% for breast cancer prevention (actual trial) [6] or even lower 22.1% (willingness to participate) [7].

These data contrast with highly accepted and performed chemoprevention of cardiovascular diseases [16]. Already in the late eighties, 84% of the persons with hypertension were aware of it, 73% under treatment and 55% controlled [17]. However looking backward in the past, drug management of risk was not that easy to achieve. Indeed, in the early sixties 48% of the persons with hypertension were aware of it, 30% under treatment and only 12% controlled [17]. As far as cancer prevention is concerned, it is not possible to know yet whether a similar shift towards higher acceptability will occur as preventive action takes time to implement (education, information, communication) or if cancer risk mitigation is under different decision-making pattern.

Randomization has been reported to reduce the willingness of patients to be involved in clinical trials [18]. Interestingly, our results show a high acceptability rate for randomization. Three hypotheses may ex-

plain this opposition. First a cultural difference [19] could steer the meaning of randomization and its connection with fate. Second the difference between attitudes and behaviors [20]. Lastly maybe some participants didn't really understand the meaning of the question, despite the fact that it was the item on which attention had been focused on during the pilot phase of that survey. An argument against this last hypothesis is that there was no statistical difference in the rate according to the level of education (data not shown).

If confirmed, the major result of our survey is the huge impact of the duration of the trial on the acceptability rate. People agree with short-term trials of one year or less and disagree strongly with longer trials. These data are coherent with the observed drop-out rates in preventive trials [21]. If confirmed, this provides advice to "clinical trial designers" and pharmaceutical companies to look for intermediate end points [22,23] or short-term interventions, which could be recurrent. In this respect, for the targeting of apoptosis [24], a kind of 'wash-out' intervention could therefore be both efficient and acceptable.

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Conflict of Interest

The authors have declared that no conflict of interest exists.

References

- Goldie SJ, Kohli M, Grima D, Weinstein MC, Wright TC, Bosch FX, et al. Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. *J Natl Cancer Inst* 2004;96:604-15.
- Freedman AN, Graubard BI, Rao SR, McCaskill-Stevens W, Ballard-Barbash R, Gail MH. Estimates of the number of US women who could benefit from tamoxifen for breast cancer chemoprevention. *J Natl Cancer Inst* 2003;95:526-32.
- Eisinger F, Giordanella JP, Brigand A, Didelot R, Jacques D, Schenowitz G, et al. Cancer prone persons. A randomized screening trial based on colonoscopy: background, design and recruitment. *Fam Cancer* 2001;1:175-9.
- Bober SL, Hoke LA, Duda RB, Regan MM, Tung NM. Decision-making about tamoxifen in women at high risk for breast cancer: clinical and psychological factors. *J Clin Oncol* 2004;22:4951-7.
- Port ER, Montgomery LL, Heerdt AS, Borgen PI. Patient reluctance toward tamoxifen use for breast cancer primary prevention. *Ann Surg Oncol* 2001;8:580-5.
- Rondanina G, Puntoni M, Severi G, Varricchio C, Zunino A, Feroce I, et al. Psychological and clinical factors implicated in decision making about a trial of low-dose tamoxifen in hormone replacement therapy users. *J Clin Oncol* 2008;26:1537-43.
- Bastian LA, Lipkus IM, Kuchibhatla MN, Weng HH, Halabi S, Ryan PD, et al. Women's interest in chemoprevention for breast cancer. *Arch Intern Med* 2001;161:1639-44.
- Herberman RB, Pearce HL, Lippman SM, Pyenson BS, Alberts DS. Cancer chemoprevention and cancer preventive vaccines--a call to action: leaders of diverse stakeholder groups present strategies for overcoming multiple barriers to meet an urgent need. *Cancer Res* 2006;66:11540-9.
- Rouch D, Mayer I, Truica C. Barriers to chemoprevention of breast cancer with tamoxifen. *J Clin Oncol* 2005;23(suppl 16S):1010.
- Kerr C, Robinson E, Stevens A, Braunholtz D, Edwards S, Lilford R. Randomisation in trials: do potential trial participants understand it and find it acceptable? *J Med Ethics* 2004;30:80-4.
- Singer S, Gaba D, Geppert J, Siniako A, Howard S, Park K. The culture of safety: results of an organization-wide survey in 15 California hospitals. *Qual Saf Health Care* 2003;12:112-118.
- Motl RW, McAuley E, DiStefano C. Is social desirability associated with self-reported physical activity? *Prev Med* 2005;40:735-9.
- Weber E, Blais A-R, Betz N. A domain-specific risk-attitude scale: measuring risk perceptions and risk behaviors. *Journal of Behavioral Decision Making* 2002;15:263 - 290.
- Bacchetti P. Peer review of statistics in medical research: the other problem. *Bmj* 2002;324:1271-3.
- Montano DE, Selby JV, Somkin CP, Bhat A, Nadel M. Acceptance of flexible sigmoidoscopy screening for colorectal cancer. *Cancer Detect Prev* 2004;28:43-51.
- Murphy MJ, Wei L, Watson AD, MacDonald TM. 'Real-life' reduction in cholesterol with statins, 1993 to 2002. *Br J Clin Pharmacol* 2008;65:587-92.
- Shea S. Hypertension Control, 1994. *Am J Pub Health* 1994;84:1725-26.
- Evans D, Laloo F, Shenton A, Boggis C, Howell A. Uptake of screening and prevention in women at very high risk of breast cancer. *Lancet* 2001;358:889-90.
- Eisinger F, Geller G, Burke W, Holtzman N. Cultural Basis for Differences Between US and French Clinical Recommendations for Women at Increased Risk of Breast and Ovarian Cancer. *Lancet* 1999;353:919-20.
- Extermann M, Albrand G, Chen H, Zanetta S, Schonwetter R, Zulian GB, et al. Are older French patients as willing as older American patients to undertake chemotherapy? *J Clin Oncol* 2003;21:3214-9.
- Veronesi U, Maisonneuve P, Costa A, Rotmensz N, Boyle P. Drop-outs in tamoxifen prevention trials. *Lancet* 1999;353:244.
- Greenwald P, McDonald SS, Anderson DE. An evidence-based approach to cancer prevention clinical trials. *Eur J Cancer Prev* 2002;11 (Suppl 2):S43-7.
- Vourlekis JS, Szabo E. Predicting success in cancer prevention trials. *J Natl Cancer Inst* 2003;95:178-9.
- Sun SY, Hail NJr, Lotan R. Apoptosis as a novel target for cancer chemoprevention. *J Natl Cancer Inst* 2004;96:662-72.