Original article

Annals of Oncology 15: 726–732, 2004
DOI: 10.1093/annonc/mdh183

An oncologist-based model of cancer genetic counselling for hereditary breast and ovarian cancer

A. Contegiacomo[1]*, M. Pensabene[1], I. Capuano[1], L. Tauchmanova[1], M. Federico[2], D. Turchetti[2], L. Cortesi[2], P. Marchetti[3], E. Ricevuto[4], G. Cianci[4], S. Venuta[3], V. Barbieri[3] & V. Silingardi[2]
On behalf of the Italian Network on Hereditary Breast Cancer

[1]*Department of Molecular and Clinical Endocrinology and Oncology, University of Naples 'Federico II', Naples;* [2]*Department of Medical Oncological Research, University of Modena and Reggio Emilia;* [3]*Department of Clinical and Experimental Medicine 'G. Salvatore', University of Catanzaro 'Magna Graecia';* [4]*Department of Experimental Medicine, University of L'Aquila, Italy*

Received 22 September 2003; revised 28 November 2003; accepted 21 January 2004

Background: We describe a multistep model of cancer genetic counselling designed to promote awareness, and disease surveillance and preventive measures for hereditary and familial breast and ovarian cancer.

Patients and methods: Step T0 of the model entails information giving; this is followed by pedigree analysis and risk estimation (T1), risk communication and genetic testing (T2), and genetic test result communication (T3). User consent was required to proceed from one step to the next. Surveillance and preventive measures are proposed to at-risk users. Of the 311 subjects who requested cancer genetic counselling, consent data to each counselling step were available for 295: 93 were disease-free, 187 had breast cancer, 12 had ovarian cancer and three had breast plus ovarian cancer.

Results: Consent was high at T0 (98.39%), T1 (96.40%) and T2 (99.65%). Consent decreased at the crucial points of counselling: T2 (87.71%) and T3 [genetic test result communication (85.08%), and extension of counselling to and testing of relatives (65.36%)].

Conclusions: The model fosters the user's knowledge about cancer and favours identification of at-risk subjects. Furthermore, by promoting awareness about genetic testing and surveillance measures, the algorithm enables users to make a fully informed choice of action in case of predisposing or familial cancer risk.

Key words: breast cancer, genetic counselling, ovarian cancer

Introduction

It has been estimated that ~70% of all primary breast cancers are sporadic forms, between 15% and 20% are familial forms and the remaining 5–10% are hereditary [1–4]. In this context, identification of the *BRCA1* and *BRCA2* susceptibility genes [5, 6] provided a molecular basis for genetic testing. This, together with increased breast cancer awareness in the general population, has increased the demand for identification of the hereditary risk, mainly as regards identification of the susceptibility gene. Moreover, the identification of familial risk favours the use of surveillance measures also in relatives at moderate risk of cancer. Consequently, when one of these forms of hereditary or familial breast and/or ovarian cancer is suspected in clinical practice, the general practitioner should address the patient to an oncological centre specialising in cancer genetic counselling for risk identification, definition and management [7–11].

Genetic counselling, defined by the American Society of Human Genetics as 'a *communication process* which deals with the *human problems* associated with the occurrence or risk of occurrence of a genetic disorder in a family' (our italics), involves one or more appropriately trained persons to help the affected individual or family [9, 10, 12, 13]. Genetic counselling in the oncological setting (cancer genetic counselling) should also provide sufficient information to enable the user to make a fully informed choice of action, particularly as regards prevention, in case of identification of a mutation or of a familial cancer risk [11].

In Italy, where health care is mainly a public service, cancer genetic counselling is a relatively new concept and is almost invariably offered within the framework of research projects [14]. The onset of cancer genetic counselling, which at first focused on genetic testing, coincided with a change in the physician/patient relationship as the Italian public became more aware of improvements in cancer treatment, in palliative care and in prevention. In recognition of this new scenario, the Ministry of Research funded a research project entitled the Development of a National Network for the Study of Hereditary Breast Cancer [15]. Five clinically oriented centres of this network (representing northern, central and southern areas of the country) are implementing a multistep

**Correspondence to:* Prof. A. Contegiacomo, Department of Molecular and Clinical Endocrinology and Oncology, University of Naples 'Federico II', Via Pansini 5, 80131 Naples, Italy. Tel/Fax: +39-081-746-2067; E-mail: contalma@unina.it

model of cancer genetic counselling based on the experience initiated and promoted by the Naples Unit.

Given the highly technical expertise required for cancer management, and the need to provide updated information about diagnostic methods and treatment options, the oncologist seems to be the most appropriate professional figure for the role of counsellor. In fact, the oncologist is able to play a comprehensive role in assessing familial cancer risks and in the counselling process starting from risk identification to risk management [16]. Considering the multidisciplinary nature of cancer genetic counselling, our model also foresees close links with the psychologist, geneticist, radiologist, gynaecologist and surgeon during the patient's educational process and as required in the various counselling steps.

The defining features of the model described herein are: (a) it is an educational model; (b) it aims at promoting awareness; and (c) it aims at promoting prevention and surveillance measures in subjects who have been identified as being at hereditary or familial risk. Here we describe this model and report the 'consent' to each counselling step obtained in 311 subjects.

Patients and methods

Subjects who requested counselling were referred by their physician or came spontaneously to the Screening and Follow-up for Hereditary and Familial Tumours Unit (Azienda Ospedaliera Universitaria 'Federico II', Naples), the Centre for the Study of Familial Breast and Ovarian Tumours (Modena Polyclinic), the Medical Oncology Division (University of L'Aquila), and the Regional Reference Centre for Genetic Counselling and High Technology Therapies in Medical Oncology ('Mater Domini' Polyclinic, Catanzaro), between 1999 and 2001. The Ethics Committees of the participating units approved the counselling procedures. Each participating centre adhered to the counselling model proposed by the Naples unit.

Counselling was addressed to: (a) cancer-affected subjects with a personal history suggesting genetic risk (e.g. early onset breast cancer, male breast cancer, breast and ovarian cancer in the same subject and multiple cancers besides breast or ovarian cancer in the same subject), or with a family history of cancer; and (b) disease-free subjects belonging to families with cancer clustering.

The multistep counselling model

The counselling teams included an oncologist/counsellor, psychologist, geneticist, radiologist, gynaecologist and surgeon, except in the Catanzaro unit where there was a psychiatrist instead of a psychologist. The model was designed to promote awareness using a multistep approach in order to allow users to assimilate fully the information given, to adapt to the new reality and to become fully aware of their condition and all its implications. Sessions with a psychologist are structured within the model, and subjects may request a session with the psychologist whenever they want information or need support. Adequate time is set aside for each counselling step, and each subject decides when he/she is ready for the next step. Every effort is made to protect the user's privacy. Easy-to-understand language adapted to each subject is used. The communicative modalities are modelled according to the affected or disease-free condition of the proband and to his/her cultural profile. Interaction between users and the oncologist is informal and respects the communication process typical of the clinical setting.

The steps of the model are shown in Figure 1 and in Table 1. At step T0, the aims and organisation of cancer genetic counselling are explained by the

Table 1. Methodological scheme at the various steps of the model and the professionals involved in each step

Step		Description	Professionals involved
T0	Providing information	Information/education about sporadic, familial and hereditary breast cancers.	Oncologist counsellor; psychologist (psychiatrist at the Catanzaro unit)
		Information about risk assessment procedures.	
		Information/education about preventive strategies, lifestyle implications and health-promoting behaviour.	
		Collection of personal history, histological report.	
T1	Pedigree construction	Pedigree construction for at least three generations.	Oncologist counsellor
	Risk estimation	Analysis of pedigree acquired. The risk profile is defined as individual, familial and inherited (Claus, Modena and Frank models).	Oncologist counsellor; geneticist (when requested)
T2	Risk communication	Communication about individual and/or familial and/or inherited risk.	Oncologist counsellor; psychologist (psychiatrist at the Catanzaro unit)
		Communication about the implication of the risk estimation for the user and for the user's relatives.	
	Genetic testing considered	Genetic test offered in case of suspected inherited risk.	
		Discussion about advantages and limits of genetic testing.	
T3	Genetic test result communication	Communication of the results and discussion about implications.	Oncologist counsellor; psychologist (psychiatrist at the Catanzaro unit)
	Genetic results disclosure to relatives	The proband informs his/her relatives about genetic test results and informs them about counselling.	
	Counselling for relatives	Relatives interested in counselling contact the unit for an appointment.	Oncologist counsellor; psychologist (psychiatrist at the Catanzaro unit)
	Surveillance	Surveillance measures modelled on different levels of risk. Discussion of preventive measures available, including chemoprevention and/or prophylactic surgery.	Oncologist; surgeon; gynaecologist; radiologist

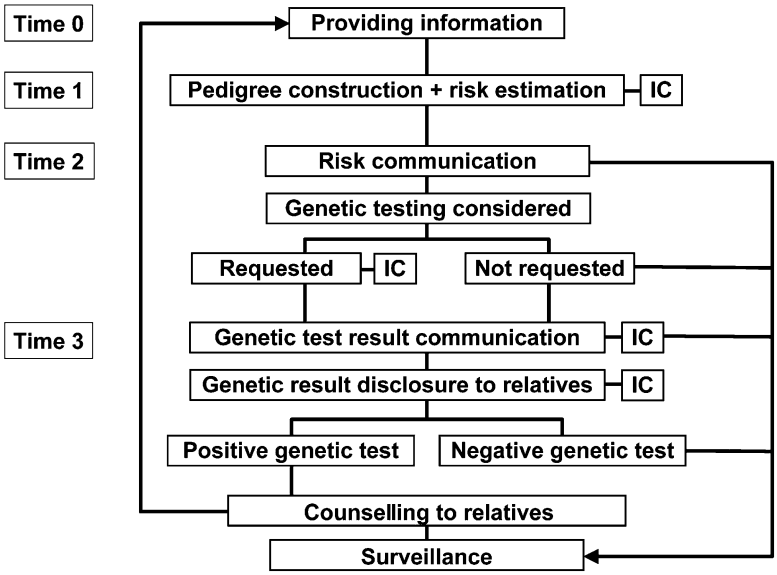

Figure 1. The multistep cancer genetic counselling model. IC, informed consent.

oncologist counsellor, and the user's motivations and expectations with regard to counselling are elicited. In this information-giving process the subject learns about the hereditary, familial and sporadic forms of breast cancer, and about the methods available to identify the risk of developing these forms of cancer (i.e. pedigree construction and analysis, personal history collection and susceptibility gene testing) [17–21]. The counsellor then discusses the implications of cancer risk in general terms, and the strategies available for risk management [20], i.e. surveillance [22–24] and prevention [25–29, 30]. During counselling, the user is repeatedly encouraged to ask questions and seek explanations; the user's responses also allow the counsellor to verify the user's understanding. Lastly, users are instructed to collect information about their family in preparation for step T1 (pedigree construction and risk estimation). After information-giving by the counsellor, subjects have a session with a psychologist to define, by way of a semi-structured interview, their cognitive level and the presence or not of psychological distress, evaluated by self-administered questionnaires. A low cognitive level and psychological distress preclude continuation of counselling. The psychologist becomes familiar with the subject's medical condition, and explores his/her socio-cultural background, relationship with the medical team, family members and others, personality profile and ability to adapt to changing situations.

At T1 (Figure 1 and Table 1), the proband is required to give written informed consent (IC) to allow the counsellor to acquire information about the family and, eventually, to disclose the results of pedigree analysis to other family members should they request counselling in the future. Information about the subject's ethnic background is recorded. The proband's family history going back at least three generations (maternal and paternal), is collected. The diagnosis is verified from the histological notes of the affected proband and his/her family. Each pedigree is assigned a code, which is used throughout the counselling process to guarantee privacy [31].

Risk is established according to Frank et al. [18], whereby the *a priori* risk of being a carrier of the susceptibility genes *BRCA1* and/or *BRCA2* is calculated. Risk estimation is also determined according to the criteria of Modena University [17] considering breast or ovarian cancer clustering within the family and within generations, the degree of relationship (first and second degree), vertical transmission, skipping a generation in case of interposition of a male due to incomplete BRCA1 and/or BRCA2 penetrance, mono or bilateral tumour and onset age of cancer, breast and ovarian cancer in the same subject, and multiple cancers other than breast or ovarian in the same subject. Pedigree analysis was performed by the oncologist and discussed with the geneticist in the more complex cases, in uncertain cases and when the pedigree did not contain a known cancer syndrome. At T2, the counsellor informs the user about the presence or not of a hereditary or familial risk, or, in the case of a disease-free proband, about an individual risk exceeding that found in the general population. If a hereditary risk is identified, the advantages and limits of genetic testing in defining the risk are illustrated and discussed. The user is encouraged to ask questions to ensure that the information given has been fully understood. The genetic test notwithstanding, the counsellor explains surveillance and prevention measures for the proband and disease-free relatives who could be at an increased risk with respect to the general population. Subjects who are contemplating a genetic test have another session with the psychologist in order to clarify further the psychological aspects related to genetic testing. Users then return to counselling and give written informed consent to blood withdrawal for *BRCA1*/*BRCA2* gene analysis. Gene analysis was performed at each unit by molecular biologists with whom the counsellor discussed the test results. The network laboratories use a standardised procedure and periodically verify testing proficiency. The costs of genetic testing are covered, at present, by an MIUR grant. Only the affected proband or, in the case of a disease-free proband, the youngest affected family member, has access to gene testing. As required by Italian guidelines, unaffected probands from families with no living affected relatives were not offered genetic testing [32].

When the test result becomes available, the user returns to counselling and is again required to give written consent to test result disclosure, and eventually to disclosure to relatives. Thus, if a relative requests counselling, the counsellor is free to use the pedigree information previously obtained for this family. At this time (T3), the counsellor explains the test results (positive or negative), taking care that the user understands all aspects and implications of the result with respect to relatives and progeny. The counsellor also explains the advantages of a positive test (i.e. preventive measures can be scheduled) and disadvantages of a negative result in cases of suspected hereditary risk (i.e. possible involvement of an unknown susceptibility gene) [33]. In the case of a positive test, the counsellor discusses with the gene carrier the possibility that first-degree disease-free relatives undergo the genetic test. Importantly, the user is instructed to vehicle the suggestions concerning surveillance to relatives at an increased risk with respect to the general population. The user also receives a written report that includes the test results, the procedure used for

the test, and an explanation of the significance of the test result, together with a copy of the pedigree. The risk information collected in the onco-genetic clinic is integrated into the medical management of the patient by the multidisciplinary counselling team. The user is also advised to contact a clinical oncological outpatients unit of the Network or a local oncological unit [15]. If a patient requests in writing, a report is sent to the general practitioner who referred the subject to counselling. The results of genetic testing are recorded on a separate chart that is kept in the Family Cancer Genetics Office.

The oncologist consults the gynaecologist, surgeon and radiologist as required to clarify aspects related to counselling. The proband decides whether or not to inform relatives that they belong to an at-risk family or to a *BRCA1*/*BRCA2*-carrying family, about taking surveillance measures and the possibility of genetic testing. The relatives so informed can request counselling and start the counselling cycle from T0. In such cases the contents of each counselling step are adapted to the user's level of information and to his/her expectations.

At the end of each step, the proband is given ample opportunity to discuss any questions or problems at length in order to clarify all aspects of their condition. In this regard, the inter-step interval must be sufficient so as to allow users to elaborate the contents of the previous step so that they can express a truly 'aware' consent, and not just 'informed' consent, to the various steps and actions selected during counselling. Consequently, the proband decides when he/she is ready for the subsequent counselling session based on appointments offered after 1 week, 2 weeks or longer. Each time informed consent is required, users are reminded that they have the right to rescind their decision at any time.

Results

Cancer genetic counselling was requested by 311 subjects, 21 (6.7%) of whom were referred by their physician, 243 (78.2%) were recruited from the clinical service of the participating departments, and the remaining 47 (15.1%) requested counselling spontaneously.

Of the 311 subjects who requested cancer genetic counselling in the five participating centres of the National Network for the Study of Hereditary Breast Cancer, 306 underwent step T0 (Figure 1). After information-giving by the oncologist, these subjects underwent an interview with a psychologist. Eleven subjects did not return to counselling or refused the psychologist interview or showed low motivation for counselling after referral by their physicians. The remaining 295 subjects (all Caucasian) returned to counselling and gave their informed consent for pedigree construction and risk estimation (step T1). Of these, 93 subjects were disease-free, 187 had primary breast cancer, 12 primary ovarian cancer and three primary breast cancer (BC) and ovarian cancer (OC). Patients were evaluated by counsellors at different stages of their oncological history: 146 (72.2%) during follow-up and 56 (27.8%) during advanced disease. Disease-free subjects were referred to counselling for various reasons: 54 (58.2%) for high familial clustering (at least three cases of BC and/or OC), 22 (23.6%) had at least one first-degree relative affected by BC and/or OC, and 17 (18.2%) with early onset BC or male breast cancer in the family. The age at diagnosis of breast cancer was <35 years in 28 subjects and ≥35 years in the remaining 159 breast cancer subjects (overall age range 27–80 years; median age 47 years). The age range of ovarian cancer patients was 29–63 years (median age 40 years). Sixty-six disease-free subjects were premenopausal and 23 postmenopausal, and four of the disease-free subjects were male.

Based on pedigree analysis, and personal history data in the case of disease-free individuals, we used the criteria of Modena University [17] and the Frank model [18] to divide the families into risk categories based on the hereditary and familial risk in all subjects.

A total of 292 (99.65%) subjects attended the T2 counselling session (risk communication). Of the three subjects who did not attend this session, one died and two decided not to proceed. At T2, the oncologist communicates the results of the pedigree analysis. In case of hereditary or familial risk or when a disease-free subject had a risk greater than that of the general population, information about surveillance and prevention measures was given to the subjects undergoing counselling and to their relatives if requested. Of these 292 subjects, 140 belonged to genetic at-risk families and were given details about identifying the risk by genetic testing.

At a subsequent appointment, 122 (87.71%) subjects from at-risk families gave written informed consent to blood withdrawal for genetic testing. Of these, 106 subjects were probands with primary breast cancer, eight had primary ovarian cancer, four had primary breast plus ovarian cancer, and four were relatives of disease-free probands who had participated in counselling from T0. Eighteen subjects decided not to undergo genetic testing. These subjects were encouraged to take disease surveillance and prevention measures. Of the 114 subjects informed that their test result was ready, 97 decided to learn the result (T3). As with the 18 subjects who did not take the genetic test, the 17 subjects who preferred not to know the result of their genetic test were informed of the importance of taking surveillance and prevention measures, and advised to contact a clinical oncological outpatients unit of the Network or their local oncological unit. They were also advised that they could request their test result at any time in the future should they change their mind.

Fifty-nine disease-free subjects, who were relatives of probands with a positive test, were informed by the proband that they belonged to an at-risk family. Thirty-four of these relatives requested counselling and underwent counselling starting at T0 (Figure 1); in these cases the contents of each step were modified depending on the user's level of information and on his/her expectations. Twenty-five of the 59 disease-free subjects did not undergo counselling, even though they had been informed by the proband that they belonged to an at-risk family.

Consent to the counselling model differed among the various steps of the model (Figure 2). The interstep interval was usually around 1–2 weeks. At T0, T1 and T2 (as regards risk communication), the percentage of consent was very high, with only a few cases of non-adhesion due to missed appointments (T0), a change of mind about pedigree construction and risk estimation (T1), and a change of mind about risk communication (T2). In contrast, the per cent of consent decreased in steps T2 (genetic testing) and T3. The drop-outs were: (a) subjects who, although they belonged to a family at genetic risk, did not undergo genetic testing at T2 (subjects who died and subjects who changed their mind about genetic testing); (b) subjects who underwent blood sampling for genetic

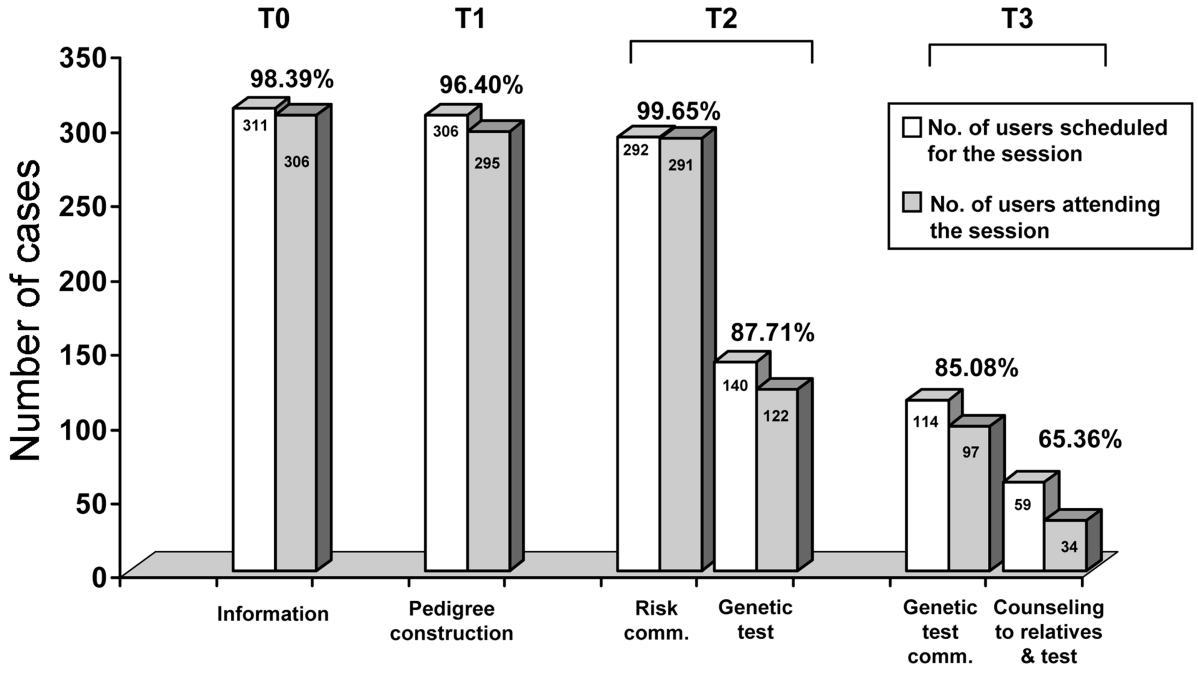

Figure 2. Consent to the multistep cancer genetic counselling model. The percentage of consent is calculated on the basis of the number of users scheduled/attending the counselling session.

testing but decided not to know the genetic test result, or who died (T3); and (c) subjects who, although they were informed by the proband that they belonged to an at-risk family, decided not to undergo genetic counselling (subjects who opted for surveillance measures only).

Discussion

Here we report the experience of five centres of the Italian Network for the Study of Hereditary Breast Cancer in applying a new model of cancer genetic counselling. This counselling service was available to cancer patients and to healthy subjects with a family history of cancer [15].

There is now general consensus that primary breast cancer exists in distinct forms: hereditary, familial and sporadic. The development of cancer genetics has led to a need for medical services, including cancer genetic counselling, for affected individuals and their families. In this regard and considering the complexities of cancer genetic counselling and the time required for the process, the oncologist involved in general oncology practice would be well advised to refer patients to an established oncogenetic service, if available [12, 25]. The oncologist counsellor is able to cover the whole spectrum of cancer genetic counselling, from verification of cases, risk assessment, genetic counselling and testing, and follow-up of at-risk subjects. The oncologist can refer users to other professional figures that can address the psychosocial needs of family members or that are involved in the educational and clinical management process.

It is difficult to compare our model of genetic counselling with others being applied nationally and internationally, particularly because, to our knowledge, data on adherence to the various models are lacking. The multistep counselling model described herein is based on the concept that information-giving is a dynamic process occurring over time because the individual needs time to assimilate new information and to adapt to a new reality. In particular, users must come to terms with the fear evoked by cancer, loss of functioning, and the possibility of transmitting cancer to progeny. Because the proband must give written informed consent at each crucial step of cancer genetic counselling, and because he/she has ample time to assimilate the contents of the previous counselling step, consent is not merely informed but is an aware consent. With the awareness resulting from this step-by-step counselling, users probably have a correct perception of their risk.

An interesting bi-model profile emerged from the consent results (Figure 2). In fact, sessions from T0 to T2, which cover information-giving and risk communication, were characterised by a high level of consent, after which consent decreased. Interestingly, the crucial point occurred when the question of genetic testing became a reality, i.e. when the user must decide whether or not to take the test, and when it comes to deciding whether or not to know the test result. Consent decreased even further when the user had to decide whether or not to inform relatives that they belonged to a family bearing a predisposing cancer mutation. These results demonstrate that the users felt completely free to reconsider their decision at any time during the counselling process.

The model aims at identifying at-risk subjects (i.e. defining the risk as hereditary, familial or individual when the subject referred to counselling is disease-free), and directing subjects to surveillance [17–19] and prevention [25–29]. In fact, immediately after pedigree analysis, subjects are referred to surveillance and prevention as necessary regardless of consent or not to subsequent

counselling sessions. In the multistep model, through information-giving and the implication-counselling discussion, users probably become more aware of their risk, and are thus more likely to adhere to surveillance and prevention regimes. In fact, users were informed that effective preventive measures can significantly reduce the risk of breast and/or ovarian cancer in individuals at increased risk, and that surveillance modalities favour the early diagnosis of cancer so that the vast majority of patients diagnosed with early-stage breast cancer die from causes other than cancer [29]. This is important also in the light of the recent widespread advertising campaign for genetic testing in the USA, which may be open to criticism on the grounds that it is a predictive test for a condition for which there is no cure, namely predisposition to cancer. Our educational model of cancer genetic counselling is aimed not only at genetic testing, but also at surveillance and preventive measures not only in the proband but also in relatives at risk of both hereditary and familial forms of cancer, irrespective of the identification of the predisposing mutation in the family.

In accordance with the recent American Society of Clinical Oncology Policy Statement Update: Genetic Testing for Cancer Susceptibility [12], our model is based on the fact that 'many of the management decisions surrounding the care of cancer patients with inherited cancer-predisposing mutations require a level of clinical expertise that is most likely within the purview of the oncology practitioner or a multidisciplinary team of specialists.' Our model also incorporates other main features recommended by ASCO: educational opportunities, requirement for informed consent, and integration of cancer risk assessment and management into oncology practice and prevention. The costs of this type of cancer genetic counselling will probably be offset by a decrease in cancer patients because more patients and relatives are taking early surveillance and preventive measures.

Given the high rate of consent throughout the counselling process, we believe that this multistep model might represent one of the strategies for the management of subjects at risk of hereditary and familial breast and/or ovarian cancers.

Acknowledgements

We are grateful to Dr J. E. Garber (Dana Farber Cancer Institute, Boston, MA, USA) for her input to the final version of the manuscript. Our thanks also to Professor A. R. Bianco (Department of Molecular and Clinical Endocrinology and Oncology, University of Naples 'Federico II') for having read the article and for his comments, and to J. A. Gilder for revising the text. This study was supported by grants from MURST-Cofin 1999 and MIUR-Cofin 2001, and by an unconditional educational grant from Teva.

References

1. Weber BL. Update on breast cancer susceptibility genes. Recent Results. Cancer Res 1998; 152: 49–59.
2. Hofmann W, Schlag PM. BRCA1 and BRCA2-breast cancer susceptibility genes. J Cancer Res Clin Oncol 2000; 126: 487–496.
3. Offit K, Brown K. Quantitating familial cancer risk: a resource for clinical oncologists. J Clin Oncol 1994; 12: 1724–1736.
4. Weber BL, Garber JE. Familial breast cancer: recent advances. In Harris JR, Lippman ME, Morrow M, Hellman S (eds): Diseases of the Breast. Philadelphia, PA: Lippincott-Raven 1998; 1–19.
5. Miki Y, Swensen J, Shattuck-Eidens D et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 1994; 266: 66–71.
6. Wooster R, Neuhansen S, Mangion J et al. Localization of a breast susceptibility gene, BRCA2, to chromosome 13q12–13. Science 1994; 265: 2088–2090.
7. Lynch HT, Tinely ST. Integration of family history and medical management of patients with hereditary cancers. Cancer 1999; 86: 1705–1712.
8. Srivastava A, McKinnon W, Wood ME. Risk of breast and ovarian cancer in women with strong family histories. Oncology 2001; 15: 889–913.
9. Peters JA, Stofer JE. Role of the genetic counselor in familial cancer. Oncology 1996; 10: 159–182.
10. American College of Medical Genetics. Genetic Susceptibility to Breast and Ovarian Cancer: Assessment, Counseling and Testing Guidelines. New York State Department of Health 1999; http://www.health.state.ny.us
11. Hoskins KF, Stopfer JE, Calzone KA et al. Assessment and counseling for women with a family history of breast cancer. A guide for clinicians. J Am Med Assoc 1995; 273: 577–585.
12. American Society of Clinical Oncology Policy Statement Update: Genetic Testing for Cancer Susceptibility. J Clin Oncol 2003; 21: 2397–2406.
13. Hopwood P. Genetic risk counseling for breast cancer families. Eur J Cancer 1998; 34: 1477–1479 (editorial).
14. Pasini B, Pierotti MA. Familial breast and ovarian cancer: genetic counseling and clinical management in Italy. Epidemiology 1999; 10: 747–751.
15. Italian Network for the Study of Hereditary Breast Cancer; http// www.hereditarycancer.it (5 September 2003, date last accessed).
16. Olopade OI, Pichert G. Cancer genetics in oncology practice. Ann Oncol 2001; 12: 895–908.
17. Federico M, Maiorana A, Mangone L et al. Identification of families with hereditary breast and ovarian cancer for clinical and mammographic surveillance: the Modena Study Group proposal. Breast Cancer Res Treat 1997; 55: 213–221.
18. Frank TS, Manley SA, Olopade OI et al. Sequence analysis of BRCA1 and BRCA2: correlation of mutation with family history and ovarian cancer risk. J Clin Oncol 1998; 16: 2417–2425.
19. Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. Cancer 1994; 73: 643–651.
20. Armstrong K, Eisen A, Weber B. Primary care: assessing the risk of breast cancer. New Engl J Med 2000; 342: 564–571.
21. Claus EB, Schildkrault J, Iversen ES et al. Effect of BRCA1 and BRCA2 on the association between breast cancer risk and family history. J Natl Cancer Inst 1998; 90: 1824–1829.
22. Vasen HFA, Haites NE, Evans DGR et al. Current policies for surveillance and management in women at risk of breast and ovarian cancer: a survey among 16 European family breast clinics. Eur J Cancer 1998; 34: 1922–1926.
23. Eisenger F, Alby N, Bremond A et al. Recommendation for medical management of hereditary breast and ovarian cancer. The French National Ad Hoc Committee. Ann Oncol 1998; 9: 939–950.
24. Burke W, Daly M, Gaber J et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. BRCA1 and BRCA2 Cancer Genetics Studies Consortium. J Am Med Assoc 1997; 277: 997–1003.
25. King MC, Wieand S, Hale K et al. National Surgical Adjuvant Breast and Bowel Project: Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. J Am Med Assoc 2001; 286: 2251–2256.

26. Narod SA, Bruner JS, Ghadirian P et al. Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a case–control study. Hereditary Breast Cancer Clinical Group. Lancet 2000; 356: 1876–1881.
27. Hartmann LC, Schaid DJ, Seller T et al. Bilateral prophylactic mastectomy (PM) in BRCA1/2 mutation carriers. Proc Am Assoc Cancer Res 2000; 41: 222–223.
28. NIH Consensus Conference. Ovarian Cancer. Screening, treatment and follow-up. NIH Consensus Development Panel on Ovarian Cancer. J Am Med Assoc 1995; 273: 491–497.
29. Rebbeck TR, Lynch HT, Neuhausen SL et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med 2002; 23: 1616–1622.
30. Lerman C, Narod S, Schulmann K et al. BRCA1 testing in families with hereditary breast–ovarian cancer. A prospective study of patient decision-making and outcomes. J Am Med Assoc 1996; 275: 1885–1892.
31. Bennett RL, Steinhaus KA, Uhrich SB et al. Recommendations for standardized human pedigree nomenclature. Am J Hum Genet 1995; 56: 745–752.
32. Comitato nazionale per la biosicurezza e le biotecnologie. Istituto Superiore di Sanità (ISS). Linee guida per test genetici. http://www.iss.it/scientifica/pubblica/lineguida/genetici.htm
33. Seitz S, Roche K, Bender E et al. Strong indication for breast cancer susceptibility gene on chromosome 8p12-p22: linkage analysis in German breast cancer families. Oncogene 1997; 14: 741–743.